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Preparation of 3-Alkylidenephthalides: Recent Advances

Julien Petriguet,^[a] Jérôme Thibonnet,^[a] Laurent Commeiras,^[b] and David Gueyraud^{*[c]}

3-Alkylidenephthalides represent an important class of natural compounds which are also valuable synthetic precursors for the preparation of phthalides. While recent reviews reported the great interest of the phthalides in the field of medicinal chemistry, few reports are mentioning the recent progress for

the synthesis of their unsaturated homologous in the position 3. So, the aim of this report is to present the latest progresses (since 2010 and until 2021) in the synthesis of 3-alkylidenephthalides.

1. Introduction

3-Alkylidenephthalides (or 3-alkylideneisobenzofuran-1(3*H*)-one), fused-ring aromatic γ -lactones containing natural products or pharmaceutically designed compounds, represent a large class of structurally diverse molecules exhibiting a wide range of biological activities (Figure 1).^[1] For example, 3-alkylidenephthalides are known to exhibit cytotoxic, antioxidant, antiplatelet, anticonvulsive, antifungal, antibacterial, anti-HIV activities and many more. In addition, these five-membered heterocyclic moieties are useful synthetic intermediates, in the field of synthetic and medicinal chemistry, enable to undergo various post-functionalization for the preparation of phthalide-based natural products derivatives and therapeutics. In light of these aspects, many groups have contributed to the development of synthetic methods to prepare these fused-ring aromatic γ -lactone privileged structures. Surprisingly and to best of our knowledge, while recent reviews covered the synthetic aspect of phthalides,^[1,2] no recent report for the synthesis of unsaturated homologous in the position 3 has been reported. The purpose of this minireview is to highlight recent advances (since 2010 and until 2021) in the synthesis of 3-alkylidenephthalides. The discussion is structured in the following strategies: olefination reactions, intramolecular cyclizations, tandem cross-coupling and oxacyclization reactions and C–H cross coupling reactions. It is not intended to give here, a comprehensive inventory, but provide the reader with a multifaceted and global vision.

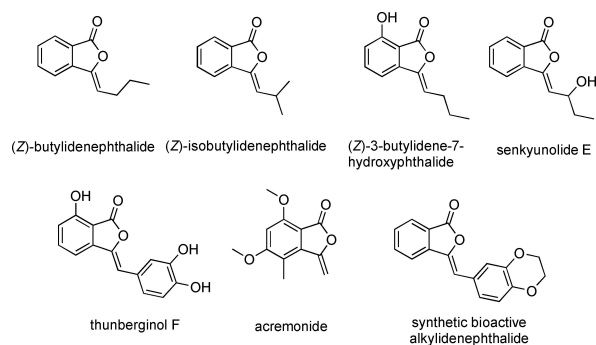


Figure 1. Examples of naturally or pharmaceutically designed 3-alkylidenephthalides.

2. Olefination reactions

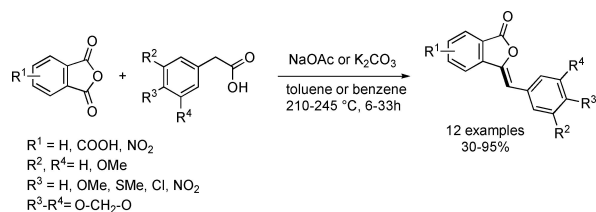
During their course of the biological evaluations of several alkylidenephthalides or related heterocyclic compounds, the group of del Olmo recently reported the condensation at high temperature of phthalic anhydride with several mono-, di- or trisubstituted phenylacetic acids or naphthylacetic acids leading to the corresponding (Z)-alkylidenephthalides from moderate to good yields (Scheme 1).^[3] The lowest yields were obtained when the starting phthalic anhydride is substituted by a carboxylic acid or a nitro function.

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Scheme 1. Condensation of phenylacetic acids for the preparation of (Z)-alkylidenephthalides.

In 2020, Deng and co-workers reported a more classical approach based on a Wittig reaction^[4] between 5,6-dimethoxy-3-triphenyl phosphonium bromide phthalide and several aminoalkaldehydes for the synthesis and the evaluation of alkylidene-phthalides as acetylcholinesterase inhibitors against Alzheimer's disease.^[5] The desired phthalides are obtained in moderate yields and in a separable mixture of diastereoisomers (Scheme 2a). Even these phthalide alkyltertiary amine derivatives exhibited good Acetylcholinesterase (AChE) inhibitory activities and blood-brain barrier permeabilities, moderate results were observed as antioxidant and MAO inhibitory activities. Since it is known that phenolic Mannich bases containing an aminoalkyl moiety present various biological activities, the same group decided to synthesize and evaluate phthalide alkyltertiary amine-phenolic Mannich base hybrids as a new potential multifunctional agent for the treatments of Alzheimer's disease. In this case, the desired alkylidene-phthalides

were prepared thanks to a Horner-Wadsworth-Emmons reaction^[6] as a mixture of *E* and *Z*-isomers. (Scheme 2b).^[7]

Recently, Gueyrard and co-workers described an effective modified Julia olefination from the preparation of benzal-phthalides from phthalic anhydrides and tetrazolyl sulfone (Scheme 3).^[8] In optimized conditions, the *E*-configured heterocycles (*E/Z*: from 80/20 to 95/5) were generally obtained in good yields whatever the nature of the tetrazolyl sulfone. For examples, alkyls and terminal alkenes groups as well as protected alcohols are well tolerated. The limit of the reaction is reached by using a cyano group on sulfone partner. It is worth noted that this methodology could be extended to others symmetrical phthalic anhydrides and was found to be regioselective (steric hindrance effect) when the reaction is performed with 3-nitrophthalic anhydride.

As a part of the ongoing work on the reactivity of 3-sulfonylphthalide with various acceptors, the group of Nambu-



David Gueyrard was born in Bobigny (France) in 1974. He received his Ph.D. degree (2000) from the University of Orléans under the supervision of Prof. P. Rollin on the synthesis of natural and synthetic glucosinolates. After his Ph.D. he was appointed as a postdoctoral researcher with Prof. C. M. Marson at University College London working on the stereoselective synthesis of organofluorine compounds, before returning to the University of Orléans to join the group led by Prof O. R. Martin and Dr. P. Compain to work on the synthesis of iminosugars. A year later, he moved to the University of Rennes 1 to work on the preparation of synthetic models of cytochrome C oxidase in the group of Dr. B. Boitrel. In September 2003, he was appointed as a Lecturer at the University Claude Bernard Lyon 1 and became Reader in 2008. His research interests consist of the development of new synthetic methodologies to prepare carbohydrate mimics, the extension of the modified Julia olefination on carboxylic acid derivatives and its application in total synthesis.



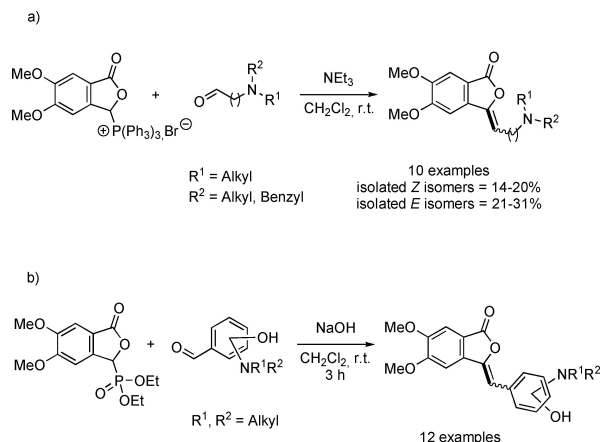
Laurent Commeiras was born in Marseille (France). He received his PhD degree in organic chemistry in 2002 from Aix-Marseille University under the guidance of Dr Jean-Luc Parrain on the total synthesis terpenes isolated from *Caulerpa taxifolia*. He then joined the group of Prof. Sir Jack E. Baldwin at the University of Oxford as post-doctoral researcher, working on the total synthesis of panephenanthrin. In 2003, he went back to Aix-Marseille University to start his independent career first as an associate professor then as a full professor. His research interests concern the total synthesis of natural and biologically active compounds and the development of new methodologies including the formation of hetero-, poly- and spirocyclic complex structures.



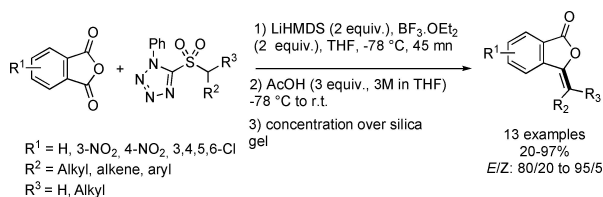
Julien Petrignet was born in Epinal (France) in 1981. He received his PhD degree in 2007 from the University of Rennes under the supervision of Dr. R.Grée on the intramolecular version of the isomerization-aldolization reaction. After his PhD, he was appointed as a postdoctoral researcher with Prof. O. Riant at University of Louvain-La-Neuve (Belgium), working on asymmetric copper-catalyzed silylation reactions. He joined the University of Strasbourg for a second postdoctoral stay with Dr. J. Suffert working on palladium domino-reactions applied to the synthesis of Taxol skeleton. In September 2010, he was appointed as a Lecturer at the University of Tours. His research interests consist of the development of new synthetic methodologies to prepare natural lactones and analogs as new antibiotics drugs.



Jérôme Thibonnet was born in Joinville (France). He received his Ph.D. from the University of Tours in 2000 under the supervision of Prof. A. Duchêne on the total synthesis of retinoids. After post-doctoral studies with Prof. P. Knochel at University of Munich on the highly functionalized organomagnesium reagents prepared through halogen-metal exchange, he joined the CEA-Le Ripault of Monts for a second postdoctoral stay with Dr. A. Balland-Longeau on the deuterated monomers and polymers. In September 2000, he was appointed as "ingénieur de recherche" at the laboratory of Prof. M. Santelli on the development of transition metal catalysis and total synthesis of natural products. In October 2003, he became Lecturer at the University of Tours and full professor in 2009. His research focuses on the synthesis of heterocycles using reactions catalyzed by copper or palladium, in order to produce natural biologically active compounds or analogues.

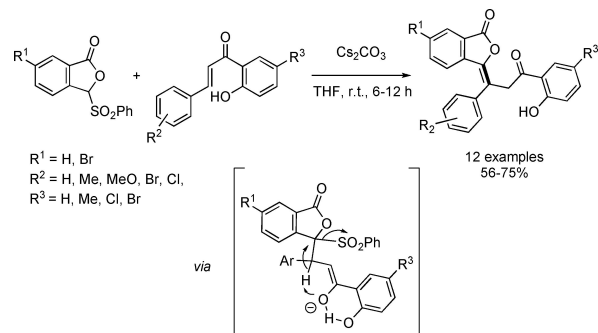


Scheme 2. Wittig and Horner-Wadsworth-Emmons strategies for the preparation of alkylidene-phthalides.



Scheme 3. Modified Julia olefination strategy for the preparation of alkylidene-phthalides.

thi investigate, in 2021, the behavior of *o*-hydroxybenzoyl derived chalcones (Scheme 4).^[9] In basic conditions, they established an olefination protocol based on sequence including a Michael addition followed by an elimination reaction to afford the corresponding alkylidene-phthalides in good yields and as a single isomer. From the mechanistic point of view, the first step would be a base mediated Michael addition of phthalide to chalcone resulting in the formation of the corresponding enolate. This latter which is stabilized by the phenolic OH *via* H-bonding would undergo the intramolecular



Scheme 4. Michael addition - Elimination process of sulfonylphthalide with hydroxychalcone for the preparation of alkylidene-phthalides.

elimination step to afford the benzaphthalides. Interestingly, when the chalcones possess a weakly electron withdrawing (4-Br or 4-Cl) aryl groups, unexpected indanedinones side products arising from (4+1) annulated process were observed up to 15%. The authors took the advantage of such reactivity to prepare useful indanedinones derivatives from styrenyl *o*-hydroxychalcones.

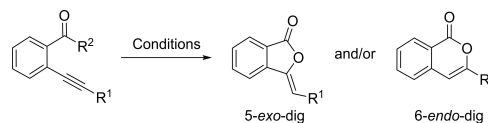
3. Intramolecular cyclizations

Among the strategies for the synthesis of 3-alkylidene-phthalides, the direct 5-*exo*-dig cycloisomerization of nucleophilic carboxylic function on alkyne was extensively explored before the 2010's.^[10] This pathway often requires the use of a transition metal in order to activate the triple bond to promote the cyclization, but recent works has shown the possibility to do without. It is noteworthy that the reaction conditions have a notable impact on the pathway of the cyclization, since the isocoumarines resulting from 6-*endo*-dig cyclization can be obtained among (or as single product) with the 3-alkylidene-phthalides resulting from the 5-*exo*-dig cyclization (Scheme 5). The development of conditions allowing full regioselectivity in favor of the five- or six- membered ring is thus challenging.

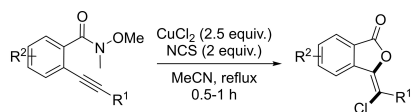
3.1. Cu-mediated reactions

In 2011, Miyata and co-workers reported a CuCl_2/NCS mediated chlorocyclization of *N*-alkoxy-*ortho*-alkynylbenzamides in acetonitrile (Scheme 6).^[11] A large scope of the corresponding chlorinated phthalides were obtained after hydrolysis, with good to excellent yields as single stereoisomers with *E* configuration. The copper(II) chloride plays an essential role for the regioselective formation of the 5-membered-ring: the 6-*endo*-dig compound was mainly obtained when the same reaction was performed without the latter. The Weinreb amide functionality is also crucial: the yield and the regioselectivity dropped dramatically when the reaction was performed with other carbonyl derivatives (amides, esters). A possible mechanism pathway would involve a regioselective 5-*exo*-dig cyclization, followed by an oxidation, which afforded a Cu(III) specie which allowed the formation of the C-Cl bond after the reductive elimination step.

In 2017, Shen *et al* reported a regioselective sequence iodolactonization/acyloxycyanation starting from potassium 2-alkynylbenzoate catalyzed by copper(II) acetate in presence of silver acetate (Scheme 7).^[12] The authors demonstrated herein that the choice of the carboxylate nucleophile and the



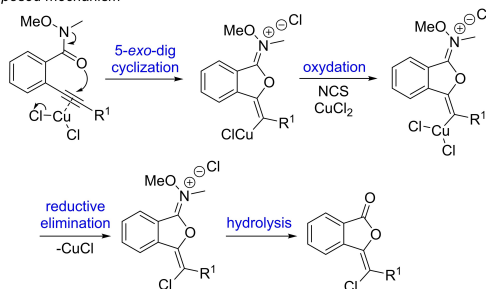
Scheme 5. 5-*exo*-dig and 6-*endo*-dig pathways in cycloisomerization.



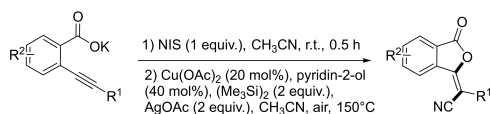
R¹ = aryl, alkyl, CH₂OH, TMS
R² = Me, OMe, F, Cl, NO₂, alcylnyl

19 examples
42-99%

Proposed mechanism



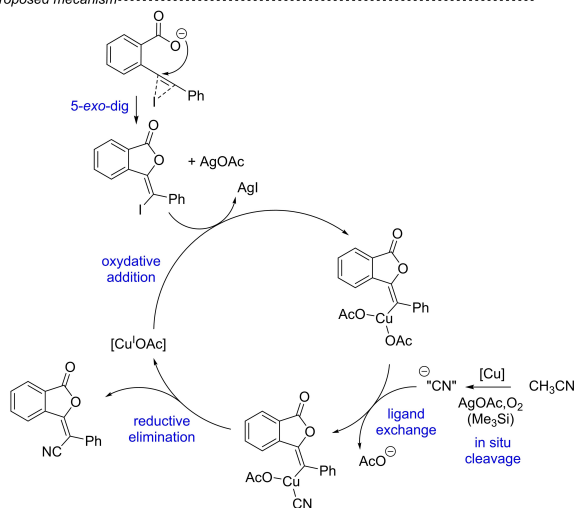
Scheme 6. Synthesis of (*E*)-3-ylidene-phthalides via Cu(II) mediated cyclization of *N*-alkoxy-*ortho*-alkynylbenzamides.



R¹ = aryl, heteroaryl, alkyl
R² = Me, OMe

8 examples
29-77%

Proposed mechanism



Scheme 7. Preparation of 3-ylidene-phthalides by iodolactonization/ acyloxycyanation of potassium 2-alkynylbenzoate.

iodinated agent allowed to control the regioselectivity, as the 6-*endo*-dig compounds were obtained in different conditions. The corresponding cyanated phthalides were thus obtained with average to good yields as single diastereoisomers and with a good substrate scope.

The reaction would proceed first with a 5-*exo*-dig iodolactonization promoted by *N*-iodosuccinimide. The iodinated lactone would be directly engaged in the second step and underwent the oxidative addition with copper(I) specie assisted by silver salt. Acetonitrile was used as solvent and cyanide source, which would allow the ligand exchange. The reductive elimination would finally afford the expected phthalide and regenerated the catalytic specie.

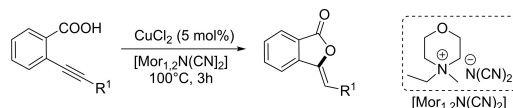
In 2018, Gabriele and co-workers reported a Cu(II)-catalyzed synthesis of 3-alkylidene-phthalides in ionic liquids, starting from 2-alkynylbenzoic acids (Scheme 8).^[13] Various ionic liquids were tested and the nature of the latter was directly linked to the 5-*exo*/6-*endo* regioselectivity. Thus, *N*-ethyl-*N*-methylmorpholinium dicyanide afforded the best results in favor of the phthalides, which were obtained with good yields as *Z* isomers. The author also emphasized the potential recyclability of the catalytic/ionic liquid system.

3.2. Pd and Fe- mediated reactions

One year after, the same group reported an oxidative carbonylation of 2-alkynylbenzoic acids catalyzed by Pd(II) in presence of carbon monoxide and aliphatic alcohol (Scheme 9).^[14] The corresponding phthalides were obtained with excellent yields using different 2-[(trimethylsilyl)ethynyl]benzoic acids and alcohols. A possible mechanism pathway for this reaction involved a ligand exchange between the substrate and PdI₂ leading to a palladium carboxylate complex. The latter underwent a stereospecific 1,2-*syn* insertion, then a 1,1-insertion of carbon monoxide. The reductive elimination and the concomitant desilylation afforded the product, and the Pd(II) was regenerated under the aerobic conditions. It is noteworthy that this reaction could be achieved without TMS protection on the alkyne but a dramatic drop of the yields was observed in this case.

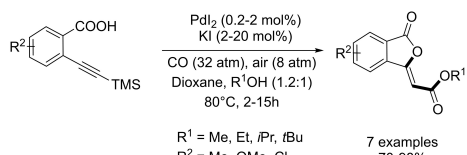
In 2020, Baire and Gandhi reported a domino-double cyclization of methyl 2-alkynylbenzoate catalyzed by Fe(III) to prepare the polycyclic alkylidene-phthalides as a mixture of diastereoisomers (Scheme 10).^[15] This strategy proceeds through a domino double cyclization and exhibits a very high substrate scope (16 examples reported) with good to excellent yields.

The role of the iron (III) chloride would be the activation of the benzylic alcohol to generate a carbocation intermediate, which allowed 5-*exo*-dig/6-*endo*-trig domino cyclizations. Conformational equilibrium on such intermediate would explain

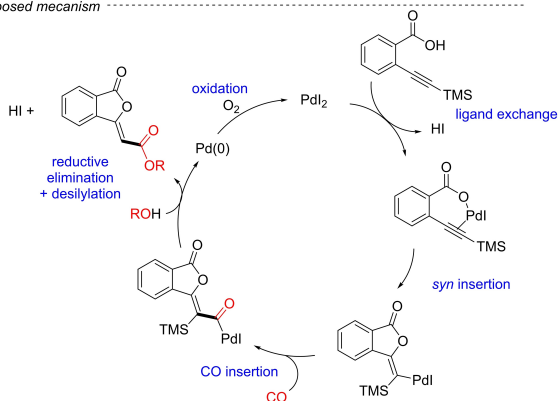


R¹ = aryl, H
4 examples
70-82%

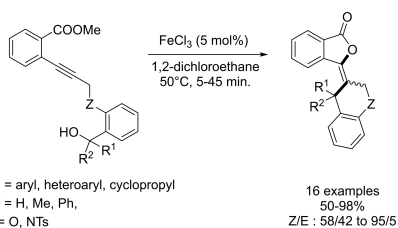
Scheme 8. Synthesis of 3-ylidene-phthalides by Cu(II) catalyst cycloisomerization in ionic liquid.



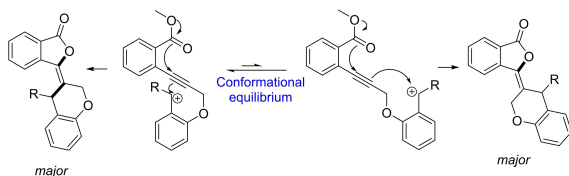
Proposed mechanism



Scheme 9. Synthesis of (Z)-3-ylidene-phthalides via a Pd(II)-catalyzed oxidative carbonylation.



Proposed mechanism

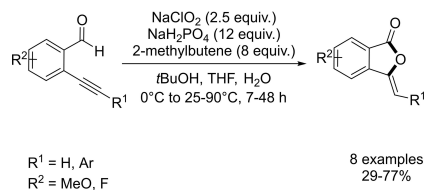


Scheme 10. Synthesis of 3-ylidene-phthalides by Fe(III) intramolecular domino-cyclative coupling.

the diastereoisomeric mixture obtained during this transformation.

3.3. Metal-free reactions

In 2010, Li and co-workers reported an oxidative cyclization of 2-alkynylbenzaldehydes for the preparation of phthalides with Z configuration (Scheme 11).^[16] Pinnick-like conditions ($\text{NaClO}_2/\text{NaH}_2\text{PO}_4$) in presence of 2-methylbutene allowed the oxidation into the corresponding carboxylate which cyclized *in situ* on the

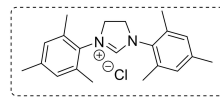
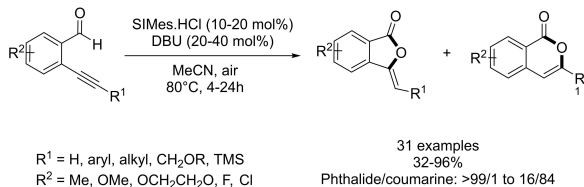


Scheme 11. Synthesis of (Z)-3-ylidene-phthalides by Pinnick oxidation of 2-alkynylbenzaldehydes.

alkyne. Substrates including aryl substituents on R^1 provided good yields.

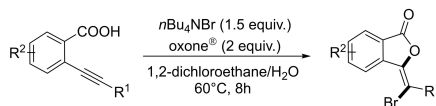
The next year, Youn group reported a similar method using catalytic amount of NHC (SImes) under aerobic conditions. The scope was extended to a large diversity of substrates, including aliphatic moieties on R^1 . The latter provided however lower regioselectivity as the corresponding coumarines were obtained in significant proportions (Scheme 12).

In 2019, the group of Wu published a regioselective bromocyclization of 2-alkynylbenzoic acids (Scheme 13).^[17] The reaction proceeds smoothly in presence of oxone[®] and tetrabutylammonium bromide to afford a large scope of ylidene-phthalide as single *E* isomers with good yields. The mechanistic pathway was not clearly established but could involve a radical specie. During this work, these brominated adducts were successfully functionalized *via* palladium cross-coupling reactions.



SImes.HCl

Scheme 12. Synthesis of 3-ylidene-phthalides by NHC-catalyzed oxidation of 2-alkynylbenzaldehydes.



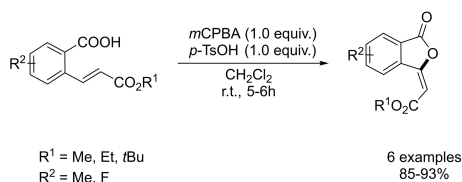
Scheme 13. Synthesis of 3-ylidene-phthalides through regioselective bromocyclization of 2-alkynylbenzoic acids.

3.4. Miscellaneous cyclizations

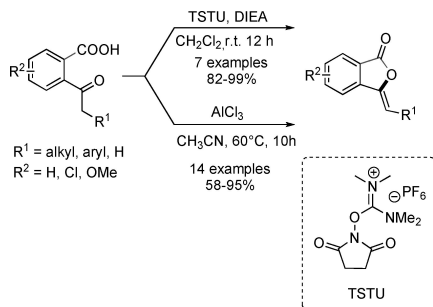
Intramolecular cyclizations of nucleophilic carboxylic adducts were also explored using different electrophiles than alkynes.

In 2013, Ray and Yasmin reported a one-pot preparation of (*E*)-alkylidenephthalides starting from 2-alkenylbenzoic acids (Scheme 14).^[18] This method involved a domino sequence epoxidation-intramolecular cyclization - dehydration under acidic conditions.

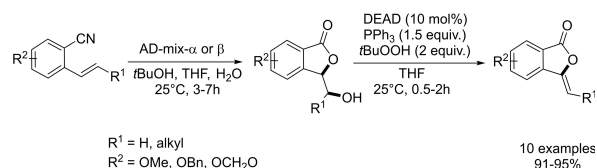
Xue *et al.* reported in 2014 an efficient method for the preparation of (*Z*)-3-ylidenephthalides.^[19] Thus, starting from 2-acylbenzoic acids, an intramolecular cyclization mediated by TSTU at room temperature generates the phthalides with total *Z* selectivity in good to excellent yields (Scheme 15). This method has been used for the gram scale preparation of *n*-butylphthalide, an antiplatelet drug. It is noteworthy that Zhang *et al.* reported in 2020 a similar strategy in which TSTU was replaced by AlCl₃.^[20] This method afforded the 3-alkylidenephthalides with good yields and stereoselectivities, the scope was extended to 14 examples.



Scheme 14. Synthesis of (*E*)-3-ylidenephthalides via domino epoxidation - cyclization - dehydration sequence.



Scheme 15. Preparation of (*Z*)-3-ylidenephthalides by cyclization of 2-acylbenzoic acids in presence of coupling agent or a Lewis acid.



Scheme 16. Preparation of (*Z*)-3-ylidenephthalides by E₂ elimination of hydroxyphthalides.

In 2014, Sudalai and co-workers reported an elimination reaction of hydroxyphthalides whose preparation is based on previous work published earlier by the same team.^[21] Compounds were obtained by a domino sequence dihydroxylation - cyclization of cyanocinnamates and was followed by the E₂ elimination performed with DEAD/PPh₃ (Scheme 16). This two-step sequence afforded the 3-ylidenephthalides with *Z* configuration with good yields and a broad scope.

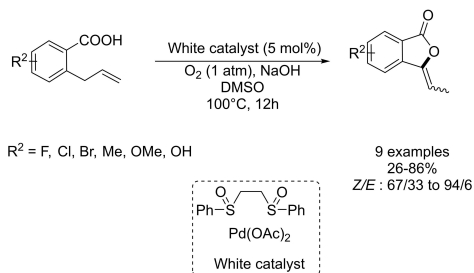
In 2020, Hou *et al.* reported an allylic oxidation of 2-allylbenzoic acids in presence of White catalyst (Scheme 17).^[22] Nine examples of 3-ethylidenephthalides were obtained with average to good yields as a mixture of *Z* and *E* stereoisomers.

4. Tandem cross-coupling and oxacyclization reaction

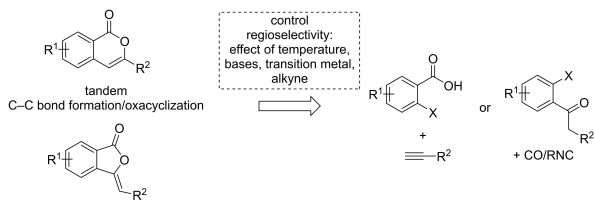
Generate regio- and stereo-chemically defined heterocycles is an important concept and vital importance for both academic and industrial researches. Regarding economy and diversity, it is important to construct 3-ylidenephthalides and isocoumarins from single starting materials through the control of the regioselectivity. Consequently, a number of methods have been reported to study the mode of 5-*exo*-dig or 6-*endo*-dig cyclization on 2-alkynylbenzoic acids derivatives principally, which can be generated *in situ* from the Sonogashira cross-coupling reaction of 2-halobenzoic acids and terminal alkynes. In this section, different approaches to obtain phthalides or isocoumarins such as (a) transition-metal-catalyzed coupling-oxacyclization of 2-halogen substituted benzoic acids with terminal alkynes; (b) Pd-catalyzed CO or RNC insertion-cyclization reactions of 2-halo or 2-triflyloxy-acetophenones (Scheme 18) are reported.

4.1. Pd catalyst

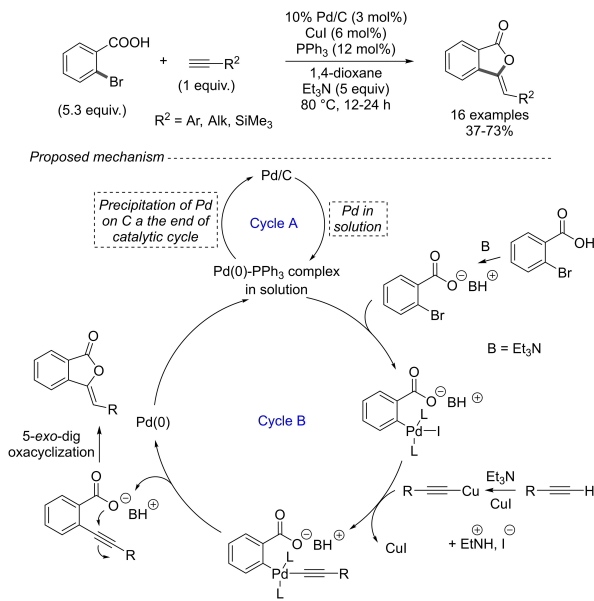
In 2013, Pal and co-workers reported an efficient synthesis of (*Z*)-3-alkylidenephthalides which involved the use of Pd/Cul as a catalyst system (Scheme 19).^[23] The reaction proceeded in 1,4-dioxane at 80 °C in the presence of Et₃N, using relatively inexpensive starting material and catalyst (*o*-bromobenzoic acid



Scheme 17. Synthesis of 3-ylidenephthalides via Pd catalyzed allylic oxidation of 2-allylbenzoic acids.



Scheme 18. Representative approaches for the regioselective one-pot synthesis of isocoumarins and phthalides.

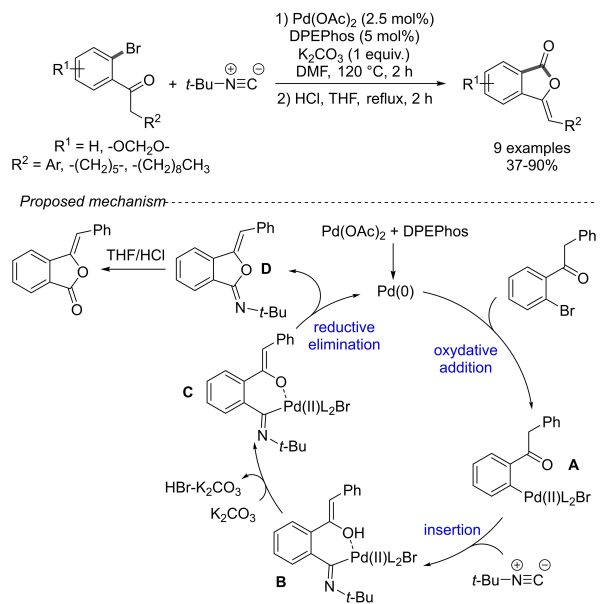


Scheme 19. Pd/C–Cu mediated synthesis of (*Z*)-3-alkylidenephthalides.

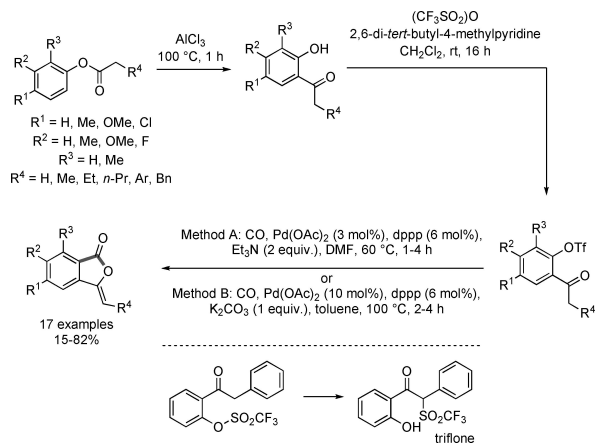
and 10% Pd/C–CuI–PPh₃ system). This methodology showed greater selectivity toward phthalides through a coupling-cyclization reaction sequence of *o*-bromobenzoic acid derivatives with a range of terminal alkynes. (*Z*)-3-Alkylidenephthalides were obtained in 37–73% yield. The reaction would proceed according to two catalytic cycles A and B. Initially, the bound palladium (Pd/C) generates an active Pd(0) specie via a Pd leaching phenomenon into the solution. Then, this palladium reacts with triphenylphosphine as a ligand to afford a dissolved Pd(0)–PPh₃ complex. The *o*-bromobenzoic acid reacts with Et₃N to give the carboxylate A followed by the oxidative insertion of Pd(0) in the C–Br bond, creating a Pd(II) intermediate B. *Trans* organometallation of B with copper acetylide generated *in situ* from CuI and a terminal alkyne, followed by reductive elimination of Pd(0) would provide the 2-(1-alkynyl)benzoic acid salt C. Finally, an intramolecular 5-*exo*-dig oxacyclization, probably due to the activation of the triple bond by palladium, would provide (*Z*)-3-alkylidenephthalide. Interestingly, some of these compounds showed biological activities when tested *in vitro* against the cyclooxygenase (COX) enzyme.

Recently, molecular insertion of *tert*-butyl isocyanide similar to carbon monoxide, has emerged to construct a library of heterocyclic compounds including azaindole, quinazoline, indoloquinoline for example. Ji and co-workers reported in 2012 the preparation of phthalides or isocoumarins by a palladium(0) catalyzed reaction incorporating *tert*-butyl isocyanide (Scheme 20).^[24] The reaction was performed using various 1-(2-bromophenyl)ethan-1-ones in DMF at 120 °C in the presence of 2.5 mol% Pd(OAc)₂ and DPEPhos as catalyst systems. Phthalides were obtained in 37–90% yields. A plausible mechanism for this reaction is outlined in Scheme 20. Oxidative addition of 1-(2-bromophenyl)ethan-1-one to the Pd(0) catalyst would lead to a palladium(II) complex A. Then, the reaction would proceed by insertion of *tert*-butyl isocyanide to form palladium(II) complex B wherein the oxygen atom of the hydroxyl group coordinates with the palladium. This coordination promotes the formation of C, allowing the elimination of Pd(0) to give the imine intermediate D, which would yield phthalide by acid hydrolysis. When the 2-(2-bromophenyl)ethan-1-ones derivatives were used as partner for the insertion of *tert*-butyl isocyanide the formation of isocoumarins are observed. The same procedure has subsequently been reported but using nickel(II) salts.^[25]

Considering the importance of 3-ylidenephthalides endowed with a wide range of biological and pharmacological activities, De Petrocellis and co-workers reported in 2013 the preparation of a series of 3-ylidenephthalides as a class of transient receptor potential channels TRPA1 and TRPM8 modulators (Scheme 21).^[26] The reaction sequence starts by the preparation of 1-(2-hydroxyaryl)alkyl-1-ones by a AlCl₃-promoted Fries rearrangement of aryl esters. These phenols were then engaged in a triflation reaction. A palladium-catalyzed cyclocarbonylation of trifluoromethanesulfonate derivatives



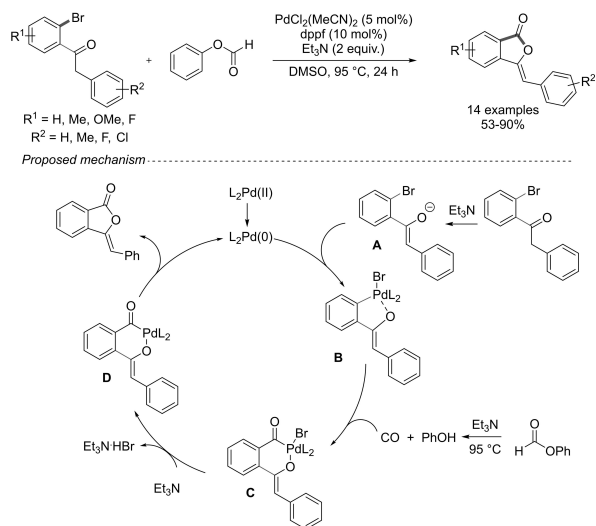
Scheme 20. Pd-catalyzed synthesis of phthalides via *tert*-butyl isocyanide insertion on 1-(2-bromophenyl)ethan-1-one derivatives.



Scheme 21. Synthesis of 3-ylidene-phthalides by a palladium-catalyzed cyclo-carbonylation of 2-triflyloxyacetophenone derivatives.

affording the 3-ylidene-phthalides in 15–82% yield. The cyclo-carbonylation was successfully accomplished in DMF or toluene as solvent, at either 60 °C or 100 °C using 3 mol% or 10 mol% Pd(OAc)₂ catalyst, 6 mol% of 1,3-bis(diphenylphosphino)propane (dppp) as ligand, and Et₃N or K₂CO₃ as base. These variations in operating conditions prevent the formation of triflone.

Zhu and co-workers developed the preparation phthalides by an efficient one-pot palladium-catalyzed intramolecular carbonylative reaction from 2-bromophenylketones by employing phenyl formate as a carbon monoxide source (Scheme 22).^[27] This methodology is more convenient, environmentally friendly, tolerant of a wide range of substrates and applicable to library of phthalides. This strategy involves

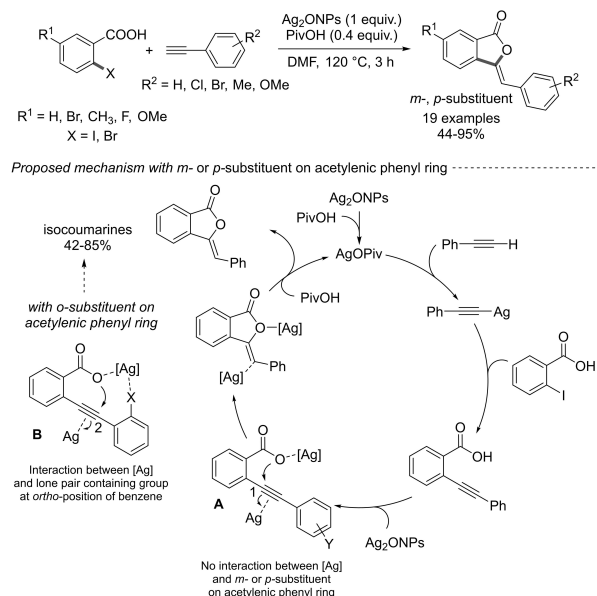


Scheme 22. Palladium-catalyzed carbonylative synthesis of phthalides by using phenyl formate as a carbon monoxide source.

palladium-catalyzed intramolecular carbonylative annulation at 95 °C in the presence of 5 mol% PdCl₂(MeCN)₂ and 10 mol% dppf in DMSO. When the reaction was conducted with 1-(2-bromophenyl)-2-phenylethan-1-ones, phthalides were obtained in 53–90% yield. Moreover, the reaction showed a good functional-group compatibility. The proposed reaction mechanism is shown in Scheme 22. Initial palladation of enolate **A** with Pd(0) would provide the palladium complex **B**. Then, phenyl formate decomposes into one molecule of CO and phenol in the presence of a base at 95 °C. An insertion of CO with palladium complex **B** form acyl palladium species **C**. Finally, phthalide was achieved *via* an intramolecular attack of the nucleophile on acyl palladium intermediate **C** and reductive elimination in the presence of the base to generate the Pd(0) species. Interestingly, when 2-(2-bromophenyl)-1-phenylethan-1-ones were engaged in the reaction, isocoumarins were produced in 55–91%.

4.2. Ag catalyst

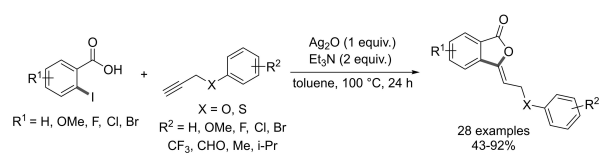
The controlled regioselectivity is an important concept to direct the synthesis towards the formation of phthalides or isocoumarins. Kumar and co-workers developed in 2018, a practical and regioselective access of phthalides or isocoumarins by a judicious choice of substituents present on the phenyl acetylenic ring (Scheme 23).^[28] The reaction was catalyzed by silver oxide nanoparticle (Ag₂ONPs) in the presence of pivalic acid in DMF at 120 °C by using substituted 2-halobenzoic acid with *o*-, *m*-, or *p*-substituted terminal alkynes. This one pot reaction involves C–C Sonogashira coupling followed by substrate-controlled 5-*exo*-dig or 6-*endo*-dig cyclization reac-



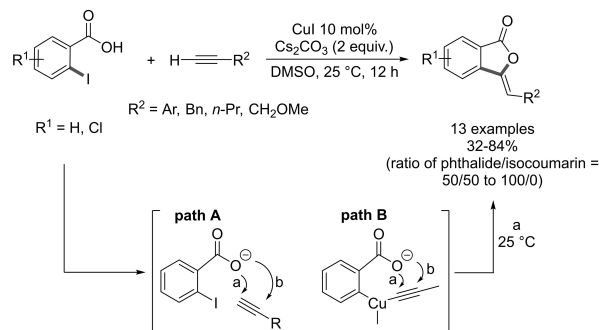
Scheme 23. Ag₂O nanoparticle catalyzed Sonogashira coupling followed 5-*exo*-dig cyclization.

tion. When the substituent is *meta* or *para* to the aromatic system, a 5-*exo*-dig type cyclization is observed and phthalides are obtained with 44–95% yield. In this specific case, there is no interaction between [Ag] and *m*-/*p*-substituent on acetylenic phenyl ring. The carboxylate oxyanion formed (intermediate A) is then attacked at the C-1 position of the acetylenic bond *via* 5-*exo*-dig cyclization to yield phthalides. When the *ortho*-group having lone pair of electrons *e.g.*, Cl, Br and OMe as well as the *ortho*-group without having lone pair of electrons *e.g.*, Me furnished isocoumarins exclusively in 42–85% yield. Presumably, the formation of isocoumarin was due to a significant electronic interaction between the [Ag] and the group at *o*-substituted acetylenic phenyl ring (intermediate B). Then, a 6-*endo*-dig cyclization occurs between the carboxylate oxyanion and the carbon 2 of acetylenic bond to give isocoumarin. Soon afterwards, the same group reported the preparation of functionalized (*Z*)-3-benzylideneisobenzofuran-1(*3H*)-ones as highly potent antioxidants and antiplatelet agents.^[29]

Furthermore, in 2022, Yin and co-workers demonstrated an efficient regioselective preparation of 3-ylidene-phthalides by a tandem reaction between aryl propargyl ether and *o*-iodobenzoic acids mediated by Ag₂O and Et₃N as base at 100 °C in toluene (Scheme 24).^[30] This efficient mild transformation produced a wide range of phthalides with moderate to good yields and diverse substituent groups could be tolerate in the reaction. Under alkaline conditions, an Ag(I)-mediated coupling sequentially followed by intramolecular cyclization would be disclosed.



Scheme 24. Ag₂O-mediated tandem reaction between terminal alkynes and *o*-iodobenzoic acids.

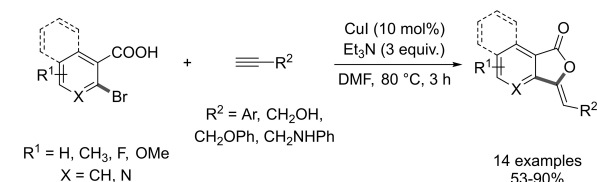


Scheme 25. Synthesis of phthalides from the coupling reaction of *o*-iodobenzoic acids and terminal alkynes.

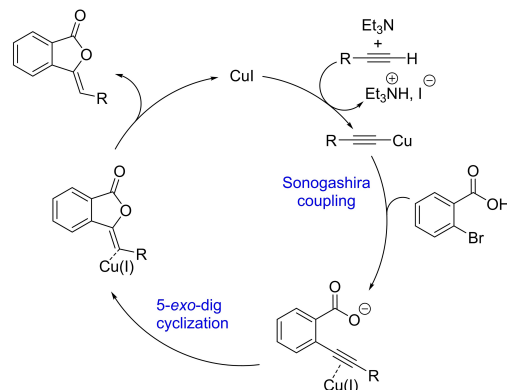
4.3. Cu catalyst

To investigate the effect of regioselectivity in the formation of phthalides and isocoumarins, Lee and co-workers was investigated in 2013 a straightforward method to access to these compounds (Scheme 25).^[31] This practical route based on the copper(I)-catalyzed regioselective one-pot synthesis of phthalides or isocoumarins from 2-iodobenzoic acids and terminal alkynes was successfully accomplished in DMSO using 10 mol% CuI catalyst and Cs₂CO₃ as base without additives or ligands by temperature control. The isocoumarins were obtained at 100 °C, and the phthalides were obtained at 25 °C. Moreover, at 25 °C, the copper(I)-catalyzed one-pot procedure is more tolerant to the electronic properties of different substituents on the aryl rings and phthalides were obtained in yields up to 84% and up to 100:0 regioselectivities. A mechanism was proposed by the authors to explain these divergent annulation pathways. This study shows that the addition of the carboxylic acid of 2-iodobenzoic acid to the alkyne would proceed first (**path A**) or at the same time with the Sonogashira-type coupling reaction (**path B**). Between these two pathways, cyclization along path B might be the predominant route at 100 °C, and cyclization along path A might be the predominant route at 25 °C.

In 2014, Ray and co-workers reported the synthesis of phthalides through copper-catalyzed domino Sonogashira coupling and 5-*exo*-dig cyclization between suitable substituted *ortho*-bromobenzoic acids and terminal alkynes (Scheme 26).^[32] The reaction was performed with diversely substituted alkynes in the presence of CuI (10 mol%) and Et₃N (3 equiv.) in DMF at 80 °C to provide phthalide derivatives in 53–90% yield. A mechanistic rationale was proposed to explain the regioselectivity.



Proposed mechanism

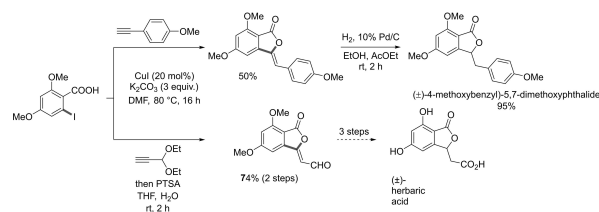


Scheme 26. One pot regioselective synthesis of 3-substituted phthalides by a copper(I) process.

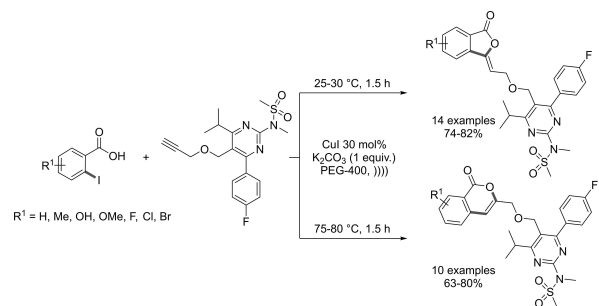
tivity in Scheme 26. The reaction would proceed *via* domino reaction of Cu-mediated Sonogashira coupling and intramolecular 5-*exo*-dig cyclization. It involves deprotonation of alkyne furnishes the Cu-acetylide *in situ*. Then, Cu-acetylide undergoes a Sonogashira type coupling with the C–Br bond to afford the *o*-alkynylcarboxylate **A**. Finally, an intramolecular 5-*exo*-dig oxacyclization, probably due to the coordination of the triple bond by Cu(I), would provide the intermediate **B**. The intermediate **B** would produce the phthalide and Cu(I) which again enters the catalytic cycle.

In 2014, Petriguet *et al.* reported the total regioselective synthesis of two natural phthalide products isolated from Australian liverwort *Frullania falciloba*,^[33] (\pm)-herbaric acid and (\pm)-(4-methoxybenzyl)-5,7-dimethoxyphthalide starting from 2-iodo-4,6-dimethoxybenzoic acid (Scheme 27).^[34] The key step of the sequence included a copper-catalyzed tandem cross-coupling and oxacyclization reaction of terminal alkynes and 2-iodo-4,6-dimethoxybenzoic acid *via* 5-*exo*-dig cyclisation with high stereo-, regio- and chemoselectivity. The reaction proceeded in the presence of the CuI catalyst (20 mol%) and K₂CO₃ (2.0 equiv) in DMF at 80 °C with 4-methoxyphenylacetylene or 3,3-diethoxyprop-1-yne to yields phthalides in a very regioselective manner. These reactions provide a rapid synthetic route for the preparation of biologically interesting phthalide derivatives.

In 2020, Kumar *et al.* described the syntheses of 3-substituted isocoumarins or 3-alkylidenephthalides *via* a Pd/C-catalyzed Suzuki–Miyaura coupling of alkyne with a range of 2-iodo benzoic acid derivatives (Scheme 28).^[35] This C–C bond



Scheme 27. Synthesis of two natural phthalides (\pm)-herbaric acid and (\pm)-(4-methoxybenzyl)-5,7-dimethoxyphthalide by a copper-catalyzed tandem cross-coupling and oxacyclization.



Scheme 28. Synthesis of rosuvastatin based 3-substituted isocoumarins/3-alkylidenephthalides *via* the ultrasound assisted Cu-mediated coupling-cyclization.

forming reaction was facilitated by ultrasound irradiation to afford the desired products in good yields. Temperature control plays a vital role in regioselectivity issues. A number of 3-alkylidenephthalides and 3-substituted isocoumarins were subsequently tested for their cytotoxic properties against different cancer cells.

In 2012, Hwang and Sagadevan report that simple copper(I) chloride salt, in the absence of Pd and ligands, can catalyze domino Sonogashira reaction of phenylacetylene with substituted aryl iodides under blue LED light irradiation (Scheme 29).^[36] 2-Iodobenzoic acid and 2-iodo-*N*-methoxybenzamide could be coupled with phenylacetylene, leading to the formation of 5-*exo*-dig cyclization products, *via* the domino Sonogashira Cross-coupling reaction with good yields (94% and 90%, respectively). However, this reaction provides a mixture of stereoisomers.

5. C–H cross coupling

5.1. Rh catalyst

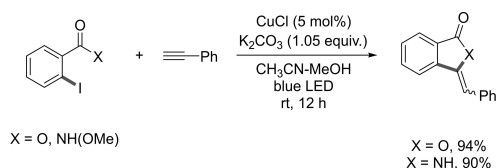
Since the *ortho* C–H activation of benzoic acid was well-known, different groups envisioned the possibility to synthesize ylidene-phthalides *via* a tandem C–H activation-cyclization process.

In 2013, Goossen *et al.* reported a Rh catalyst system to promote the synthesis of diverse alkylidenephthalides from benzoic acids and aliphatic acids or anhydrides through a one-pot C–H acylation/acylalation/elimination process.^[37]

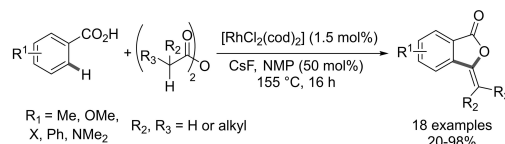
In all cases, the *Z*-configured products were formed with high selectivities. (Scheme 30)

In 2016, Yang and You described a Rhodium catalyzed oxidative coupling /annulation of benzoic acids with terminal alkynes *via* C–H activation (Scheme 31).^[38]

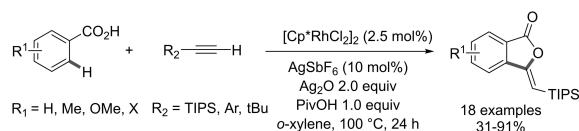
This procedure shows a fairly wide substrate scope and an excellent *Z*-selectivity.



Scheme 29. Domino Sonogashira reaction of phenylacetylene with 2-iodobenzoic acid and 2-iodo-*N*-methoxybenzamide.



Scheme 30. One-pot synthesis of 3-ylidenephthalides *via* a Rh-catalyzed C–H acylation/acylalation/elimination cascade.



Scheme 31. Preparation of 3-ylideneephthalides *via* a Rh-catalyzed oxidative coupling of benzoic acids with terminal alkynes.

Next year, Shi *et al.* reported a Rh(III)-catalyzed intermolecular tandem C–H olefination and oxidative cyclization of aromatic acids with acrylates (Scheme 32).^[39]

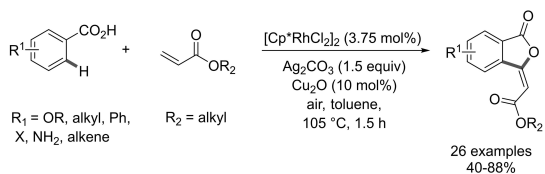
This method afforded an efficient synthesis of (*E*)-ylideneephthalides with an ester group in a short reaction time.

More recently, Su and Shang developed a rhodium-catalyzed protocol for cascade C–H acylation/intramolecular nucleophilic acyl substitution of benzamides with a large range of available carboxylic acids using 8-aminoquinoline as directing group (Scheme 33).^[40] Aliphatic acyl fluorides were generated *in situ* from the corresponding acids using fluoro-dipyrroli-dinocarbenium-hexafluorophosphate (BTFFH) as fluorinating reagent.

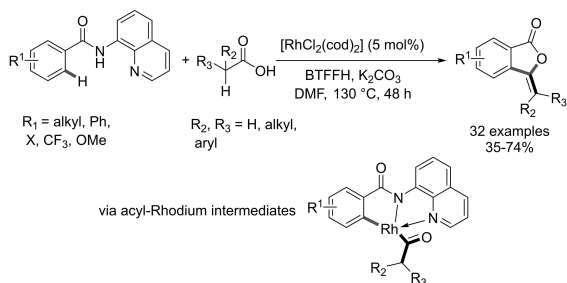
This method shows high stereo-selectivity for *Z*-isomer products, and tolerates a variety of functional groups and aliphatic carboxylic acids with various structural skeletons.

5.2. Pd catalyst

In 2013, Lee *et al.* described a one-step procedure for the preparation of isocoumarins and 3-benzylideneephthalides *via* a



Scheme 32. Synthesis of 3-ylideneephthalides *via* a Rh-catalyzed C–H olefination and oxidative cyclization of benzoic acids with acrylates.



Scheme 33. Synthesis of 3-ylideneephthalides *via* a Rh-catalyzed cascade C–H acylation/intramolecular nucleophilic acyl substitution of benzamides.

palladium catalyzed C–H olefination and oxidative coupling of benzoic acids and vinyl arenes (Scheme 34).^[41] When *ortho*-substituted benzoic acids were used, the 3-benzylideneephthalides were obtained in good yields as a unique product.

The authors proposed that the dependence of the preferential formation of 3-benzylideneephthalides is related to the steric effect between the *ortho* substituent and the carboxylate which restricts the cyclization. The authors applied this methodology to the total synthesis of Thunberginol F in two steps.

More recently, Liu and Zeng reported a similar approach using a palladium catalyzed synthesis of phthalides from benzoic acids and TIPS protected bromoalkynes *via* *ortho*-alkynylation – annulation reaction (Scheme 35).^[42]

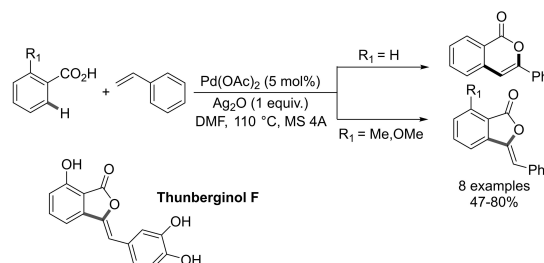
The reaction displays a broad substrate scope. In addition, the authors demonstrate that the reaction can be performed on a gram-scale in good yield and that the removal of the silyl-protecting group provides an access to unsubstituted 3-ylideneephthalides.

5.3. Ru catalyst

In 2018, Jeganmohan *et al.*^[43] described a Ru(II) catalyzed C–H bond activation of aromatic acids with allylic acetates to produce (*Z*)-3-ylideneephthalides. The C–H activation occurred at the *ortho* position of the aromatic acid (Scheme 36).

From a mechanistical point of view, the reaction would proceed through an allyl insertion, acetate elimination, isomerization of the double bond of *ortho*-allylated benzoic acid into the vinylated benzoic acid followed by intramolecular Wacker type addition and then β -hydride elimination. The proposed mechanism was supported by DFT studies.

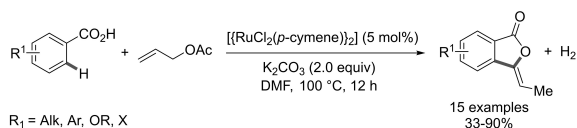
Baidya *et al.* developed an efficient annulative coupling of benzoic acid with vinyl sulfones catalyzed by Ru(II) to produce



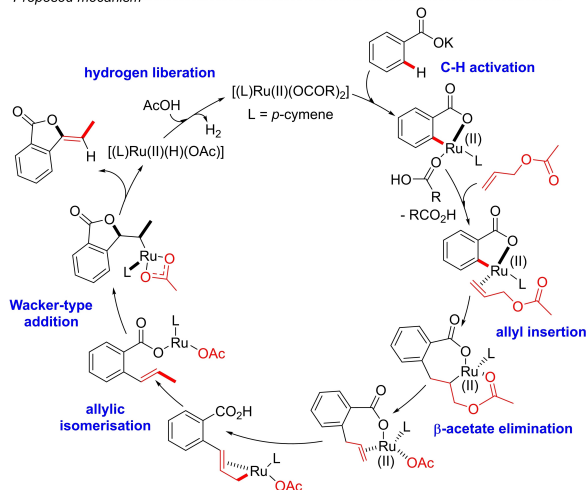
Scheme 34. One-pot synthesis of 3-benzylideneephthalides *via* a Pd(II)-catalyzed C–H olefination-oxidative coupling of aromatic acids with vinyl arenes.



Scheme 35. Preparation of 3-ylideneephthalides *via* a Pd(II)-catalyzed *ortho*-alkynylation – annulation reaction of aromatic acids with bromoalkynes.

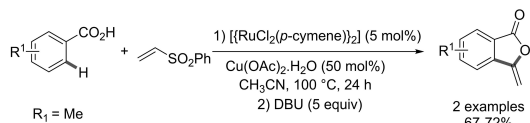


Proposed mechanism

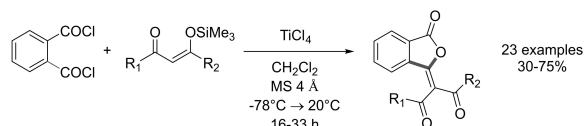


Scheme 36. Synthesis of (Z)-3-ylidenephthalides via a Ru(II)-catalyzed redox-neutral reaction of aromatic acids with allylic acetates.

phthalides in high yields (Scheme 37).^[44] They showed on two examples that the exposure of the crude reaction to DBU led to the corresponding 3-ylidenephthalide through elimination of the sulfonyl group in one-pot. This method is useful to provide an access to unsubstituted 3-ylidenephthalides.



Scheme 37. One-pot synthesis of 3-ylidenephthalides via a Ru(II)-catalyzed annulative coupling-elimination reaction of aromatic acids with vinyl sulfones.



Scheme 38. Preparation of 3-ylidenephthalides by reaction of silyl enol ethers with phthaloyl dichloride.

6. Miscellaneous

6.1. Reaction of enol ethers with phthaloyl derivatives

In 2011, Langer *et al.* described the preparation of alkylidenes phthalides by reaction of silyl enol ethers with phthaloyl dichloride with good to excellent *E*-selectivity (Scheme 38).^[45]

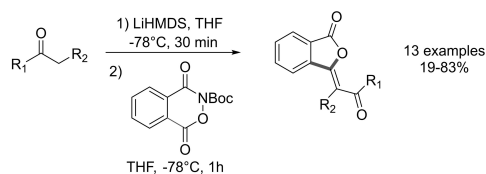
Satisfactory yields are obtained for products derived from 1,3-dicarbonyl compounds. In contrast, poor yields were obtained from silyl enol ethers formed from esters.

A similar approach has been reported by Tomkinson *et al.* in 2016 (Scheme 39).^[46] The reaction of lithium enolate with *N,O*-phthaloylhydroxylamine led to the formation of alkylidene phthalides.

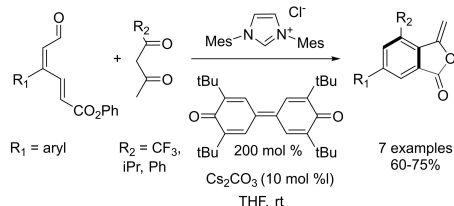
The selectivity observed can be modified by varying the polarity of the reaction medium. Isomerization of the products was also demonstrated under acidic conditions to give access to both stereoisomers.

6.2. NHC activation of unsaturated aldehydes

Song and Chi developed an original synthesis of 3-ylidenephthalide through the construction of the benzene ring (Scheme 40).^[47] An *N*-heterocyclic carbene (NHC) catalyzed domino reaction triggered by a δ -LUMO activation of γ,δ -unsaturated α,β -enal has been developed for the construction of 3-ylidenephthalide.



Scheme 39. Preparation of 3-ylidenephthalides by reaction of lithium enolate with *N,O*-phthaloylhydroxylamine.



Scheme 40. Preparation of 3-ylidenephthalides by NHC activation of unsaturated aldehydes.

6.3. Copper catalyzed Sonogashira type coupling-cyclization of 1-phenyl-1,2-benziodoxol-3-(1H)-one with acetylene derivatives

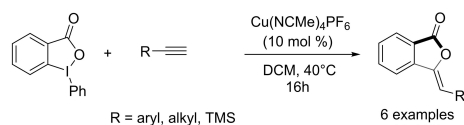
1-Phenyl-1,2-benziodoxol-3-(1H)-one is known as a benzyne precursor. In 2018, Mejia *et al.* reported the first synthetic application of 1-phenyl-1,2-benziodoxol-3-(1H)-one for the preparation of phthalides using copper catalyst (Scheme 41).^[48]

Z Isomers were observed in all cases but, however, the desired product is accompanied by the corresponding isocoumarins as minor product.

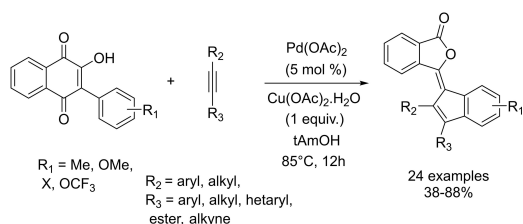
6.4. Palladium catalyzed decarbonylative C-H/C-C activation and annulation reaction

Gogoi *et al.* described recently a novel Pd(II)-catalyzed decarbonylative alkyne insertion reaction (Scheme 42).^[49]

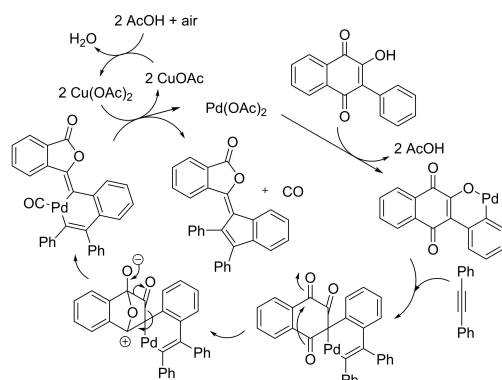
The proposed mechanism proceeds *via* C-H/C-C activation, alkyne insertion, intramolecular cyclization, and decarbonyla-



Scheme 41. Pd-catalyzed carbonylative synthesis of 3-ylidenephthalides.



Scheme 42. Pd catalyzed decarbonylative C-H/C-C activation and annulation reaction.



Scheme 43. Proposed mechanism.

tion, affording good yields of alkyldene phthalides (Scheme 43).

7. Conclusion

3-Ylidenephthalides or [3-ylidene-1(3H)-isobenzofuranones] constitute an important group of natural products and synthetic compounds with a large range of biological activities. We presented several synthetic methods for the construction of this scaffold. We discussed about the scope and limitations of each reaction conditions. During the last decade, the preparation of 3-ylidenephthalides was mainly performed by cyclization of products obtained by C-H activation or C-X coupling. We also reported different original methods using *N*-heterocyclic carbenes and the extension of classical olefination methods. We also tried to find some uncommon but useful methodologies. These different methods generally allow to control the stereochemistry of the exocyclic C=C bond and to prepare a large range of diversely functionalized 3-ylidenephthalides. We hope this review will be helpful for readers working in this field.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkyldienephthalide · Cross-coupling · Cyclization · Olefination

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