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Recent advancements in synthetic methodologies of 3-substituted phthalides and their application in the total synthesis of biologically active natural products

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We have provided a critical review that focuses on key developments in the area of 3-substituted phthalides and their role in the development of important biologically active natural products. 3-Substituted phthalides are vital molecules owing to their fascinating biological activity. The scope, isolation, and characterization of various naturally occurring racemic and chiral 3-substituted phthalides have been covered. We have put significant emphasis on recently developed research methodologies for the synthesis of racemic and chiral 3-substituted phthalides. These newer approaches are essential for the development of newer and elegant strategies for the synthesis of phthalide-based or similar molecular architecture with broader substrate scope and higher stereoselectivities. Also, we have discussed the application of 3-substituted phthalides as a precursor for the synthesis of natural products and their analogs.

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1. Introduction

One of the prime areas of research in organic chemistry has been concerned with the development of small-molecule natural products. A considerable number of modern-day drug developments are inspired by various sets of natural products, such as amino acids, flavonoids, alkaloids, terpenoids, quinonoid, and steroids. This area of research has paved the way for an important class of chemistry, known as medicinal chemistry.

An extensive series of biologically important natural products consist of phthalide frameworks.² Phthalides are a prominent branch of natural products due to their biological

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 $R_1 = H$, OH, OMe, alkyl, halogen $R_2 = H$, alkyl, aryl

Fig. 1 1(3H)-Isobenzofuranones 1 (phthalides) and their derivatives.

importance. The fundamental core structure of phthalide consists of a benzene ring fused with a γ -lactone between carbons 1 and 3 (Fig. 1). All the known phthalide compounds have been recognized as derivatives of 1(3*H*)-isobenzofuranone. Mainly, phthalides have been found commonly in plant genera and also in fungi, bacteria, and liverworts.

More than 180 naturally occurring phthalide derivatives have been identified. Among them, nearly 140 phthalides were isolated from a wide variety of plant species. These isolated phthalides have shown a broad spectrum of important clinical properties, such as anti-platelet accumulation, anti-smooth proliferation, anti-thrombosis, protection against cerebral ischemia, anti-angina, and cardiac function modulation and actions on the central nervous system.³

In ancient times, many phthalide-containing plants were used as herbal medicines. In China, phthalide-containing herbs have been recognized as some of the most commonly used natural medicines in traditional medicinal practice. Rhizoma Chuanxiong (Chinese name Chuanxiong) and Radix *Angelicae sinensis* (Chinese name Danggui) have been used for the

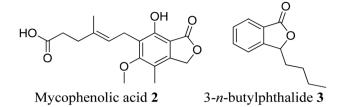


Fig. 2 Structure of mycophenolic acid 2 and 3-n-butylphthalide 3.

treatment of cerebral- and cardiovascular diseases and female irregular menstruation for more than 2000 years.⁴

Phthalide containing drugs have gained worldwide popularity because of the wide range of pharmacophore activities of the moiety. For example, a significant problem during organ transplantation is a rejection of the transplanted organ. Mycophenolic acid (mycophenolate) 2 is a phthalide-containing immunosuppressant drug given to facilitate organ transplantation. It was the first antibiotic synthesized in a pure crystalline state. The US Food and Drug Administration has also approved this for use in kidney transplantation. Similarly, *n*-butylphthalide (NBP) 3 also became a successful anti-platelet drug for ischemia-cerebral apoplexy (Fig. 2). The Chinese government had approved this as an anti-ischemic stroke drug in 2002. Taking these facts into consideration, we can state that phthalide moiety has been used as a valuable framework in synthesizing many pharmaceutical drugs.

Some phthalide-containing natural products are also reported in the literature. Phthalide plays a vital role as a building block⁸ in the synthesis of many natural products. For example, fuscinarin 4 is a potent human CCR5 antagonist, used to block the entry of HIV into host cells.⁹ However, the bioactivities of



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Fig. 3 Naturally occurring 1(3H)-isobenzofuranones 4-7.

(-)-typhaphthalide 5,¹⁰ (+)-spiroxaline 6,¹¹ and monascodilone 7¹² are still not known (Fig. 3).

There are several available reactive sites of phthalides which have been explored, i.e., a nucleophilic attack on C₁ carbonyl group, nucleophilic substitution reactions at C₃ position carbanion, and reactions on the C₄, C₅, C₆ and C₇ positions of the phthalide.13 The 1(3H)-isobenzofuranone was initially synthesized in 1922 by Perkin and coworkers, via thermal decomposition of ethyl 2-(bromomethyl)benzoate.14 Later in 1955, Eliel and coworkers performed the reduction of methyl phthalate to phthalide in good yield using LiAlH₄.15 In 1989, Watanabe and coworkers utilized a Diels-Alder reaction between substituted furanones and silyloxydienes to provide substituted phthalides in moderate to excellent yields. 16 Recently, directed ortho-metallation, the reaction between homophthalic anhydride and benzil,17 the Heck-Matsuda reaction,18 and many more methods have been introduced to synthesize substituted phthalides.

1.1 Scope for 3-substituted phthalides

As we have already discussed, phthalide moiety is present in many natural products. Phthalides that are substituted at the C-3 positions possess an extensive range of biological and physiological activities. This moiety has been an essential intermediate to synthesize versatile natural products. This fact has led extensive efforts in the field of 3-substituted phthalides in the past two decades (Fig. 4). Different synthetic methodologies of selected natural products using 3-substituted phthalides as intermediates are described in the later part of the review.

Statistically, more than 60% of the drugs currently available on the market are chiral molecules. As a result, asymmetric synthesis of chiral phthalides introducing C-3 chirality has also achieved considerable attention. Subsequently, an extensive number of asymmetric synthetic methodologies have been established for a variety of naturally occurring molecules with the potential treatment of different kinds of diseases.

The attention of this review is primarily on the synthesis and reactivity of the active methylene compounds, *i.e.*, 1(3*H*)-isobenzofuranones. Previously, Mal *et al.* and Renoux *et al.* published two excellent reviews on the chemistry of phthalides.^{5,19}

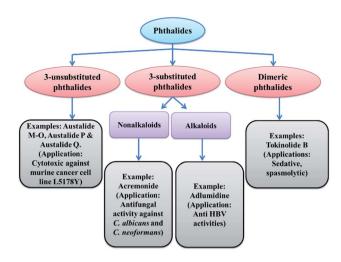


Fig. 4 Classification of phthalides and their examples.

However, as per our knowledge, in previous literature reviews, the chemistry of racemic and chiral 3-substituted 1(3H)-isobenzofuranones and its application in total synthesis of important natural products was not discussed in detail. In this review, the synthetic methodologies for racemic and chiral 3-substituted 1(3H)-isobenzofuranones are discussed with particular emphasis on recent advances. Also, the application of racemic and chiral 3-substituted 1(3H)-isobenzofuranones as precursors for the synthesis of other critical molecular moieties are discussed.

The work presented here can benefit researchers in developing newer efficient strategies. This review paper contributes to ongoing efforts in seeking to develop and expand the utility of 3-substituted phthalides as precursors for much broader objectives.

1.2 Sources of a different kind of phthalides

Plants, fungi, bacteria, and liverworts have been different sources for phthalides. More than 180 naturally occurring phthalides appear in the literature. Most of these (~137) are extracted from 202 diverse species of plants; as a result, phthalide-containing plants were long used as herbal medicines. Most naturally occurring phthalides are obtained from two plant species, *Ligusticum* and *Angelica*, in the Umbelliferae family. Some of the isoquinoline type phthalides such as noscapine 8 and bicuculine 48 are isolated from the poppy family. From the genus *Ligusticum*, more than 53 naturally occurring phthalides have been isolated from *Ligusticum*, and 38 biologically phthalides have been isolated from *Angelica*. 20,23

1.3 Extraction, isolation, and characterizations of phthalides

The extraction of naturally occurring biologically active phthalides is one of the critical steps of analysis. It involves techniques such as pre-washing, grinding, and drying of plant materials to obtain a homogenous sample. It should be taken care that potential plant constituents are not degraded during

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Table 1 Important biologically active natural products encompassing 3-substituted phthalide framework

S. no.	Natural products	Isolation sources	Biological activities
1 (ref. 30)	Noscapine 8	Cultivated opium poppy plants	Anti-tussive, anti-cancer, and potential antineoplastic activities
2 (ref. 31)	MeO OH OH OH OH	Aigialus parvus BCC 5311	Not known
3 (ref. 32)	HO OH O	Pestalotiopsis virgatula	Cytotoxic against HeLa (cervical epithelium) cells
4 (ref. 17)	(i) Virgatolide B (C3 = α) 11 (ii) Virgatolide C (C3 = β) 12	Pestalotiopsis virgatula	Cytotoxic against HeLa (cervical epithelium) cells
5 (ref. 33)	HO OH 4 Cytosporone E 13	<i>Cytosora</i> sp. CR200	Anti-microbial
6 (ref. 34)	MeO OMe OMe OMe OMe OMe OMe OMe OMe OMe	Penicillium vermiculatum DANG	Cytotoxic against tumor cells

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Table 1 (Contd.)

S. no.	Natural products	Isolation sources	Biological activities
7 (ref. 35)	MeO OMe OOMe OOMe OOMe OOMe OOMe OOMe O	Corydails stricta	Anti-paclitaxel – resistant anti- cancer (ovarian) activity
8 (ref. 36)	Rubiginone 16 (Stereochemistry at C-3 position unknown)	Streptomyces sp.	Anti-bacterial activity, prevents the growth of specific Gram- positive bacteria and cytotoxic against diverse tumor cells
9 (ref. 37)	MeO MeO Colletotrialide 17	Collectotrichum sp.	Anti-oxidant and chemo preventive properties
10 (ref. 38)	Me O N [±] O· Alcyopterosin E 18	Alcyonium paessleri	Cytotoxicity toward human larynx carcinoma
11 (ref. 39)	OR_2 O R_1 O $R_1 = R_2 = H$ 19 (ii) $R_1 = OMe$, $R_2 = H$ 20 (iii) $R_1 = OMe$, $R_2 = Me$ 20	Pittosporum illicioides	<i>In vitro</i> inhibitory activity on neutrophil pro-inflammatory response
12 (ref. 40)	Catalpalactone 22	Catalpa ouata G.	Anti-tumor promoting activity

Table 1 (Contd.)

S. no.	Natural products	Isolation sources	Biological activities
13 (ref. 41)	HO HO OH COOH Cryphonectric acid 23	Cryphonectria parasitica	Anti-fungal activity, (inhibits the formation of tomato seedings)
14 (ref. 42)	R = H, Isoochracinic acid 24 R = OH, Herbaric acid 25	Alternaria kikuchiana (isoochracinic acid), Cladosporium herbarum (herbaric acid)	Anti-bacterial and anti-biotic
15 (ref. 43)	MeO O O O	Xanthoxylum arnottianum	Not known
16 (ref. 44)	(-)-Arnottin II 26 OH MeO Me COOH Altenuic acid 27	Alternaria tenuis	Not known
17 (ref. 45)	Tilifodiolide 28	Salvia tiliaefolia and Salvia puberula	Plant growth stimulator
18 (ref. 46)	H ₂ N — HN — COOMe Dermacozine D 29	Dermacoccus abyssi	Cytotoxic against different tumor cells lines
19 (ref. 47)	OH O (CH ₂) ₅ CH ₃ Corollosporine 30	Corollospora maritima	Anti-bacterial activity against Staphylococcus

Table 1 (Contd.)

S. no.	Natural products	Isolation sources	Biological activities
20 (ref. 48)	n-Butylphthalide 2	Apium graveolens, Angelica sinensis	Anti-convulsant, anti-stroke and anti-proliferative
21 (ref. 49)	Alcyopterosin E 31	Subantarctic soft coral Alcyonium paessleri	Toxic towards Hep-2 (human larynx carcinoma) cell line
22 (ref. 50)	OMe O (CH ₂) 5	Fungus Sporotrichum laxum	Anti-tumor and active against Helicobacter pylori, also, lower the cholesterol level in the body
23 (ref. 51)	OH OF Spirolaxine 6 Paecilocin A 32	Fungus Paecilomyces variotii	Anti-bacterial activity against pathogenic bacteria including Staphylococcus aureus 3089 and Vibrio parahaemolyticus 7001
24 (ref. 52)	Isopestacin 33	Pestalotiopsis microspora	Anti-fungal activity
25 (ref. 53)	HO Ph Matteucen C 34	Chineses medicinal herb <i>Matteuccia</i> orientalis for the treatment of hemostatics and reliving ostalgia	Not reported
26 (ref. 54)	(3S)- Pestaphthalides A 35a (3R)- Pestaphthalides A 35b	Solid culture of an isolate of <i>Pestalotiopsis</i> foedans	Anti-fungal

Table 1 (Contd.)

S. no.	Natural products	Isolation sources	Biological activities
27 (ref. 55)	Paecilomycin C (R ¹ = H, R ² = OH) 36 Paecilomycin D (R ¹ = OH, R ² = H) 37	Solid culture of Paecilomyces sp. SC0924	Anti-fungal
28 (ref. 56)	HOH ₂ C HO OH Celephthalide A 38	Celery seed	A diuretic for bladder and kidney complaints and adjuvant in arthritic conditions
29 (ref. 57)	Concentricolide 39	Ascomycete Daldinia concentrica	Anti-HIV-1
30 (ref. 58)	Danshenspiroketallactone 40	Traditional Chinese medicine consisting of Salvia miltiorrhiza	Immunosuppressants and anti- stroke
31 (ref. 59)	OH O S Chrycolide 41	Leaves and stem of a popular vegetable Chrysanthemum coronarium	Anti-feeding activity
32 (ref. 60)	OH O OH O	Rhizomes of <i>Typha</i> capensis	Anti-bacterial activity against diarrhea and dysentery

Typhaphthalide 42

Table 1 (Contd.)

S. no.	Natural products	Isolation sources	Biological activities
33 (ref. 61)	3a- [4'- Methoxy-4',5'- methyllenedioxybenzyl]-5,7- dimethoxyphthalide 43	<i>Frullania</i> sp.	Cytotoxic against human promyelocytic leukemia
34 (ref. 62)	Colletotrialide 44	Euryops hebecarpus	Not known
35 (ref. 63)	(R)-3-acetyl-7-hydroxy-5-methoxy-3,4-dimethylisobenzofuran-1(3H)-one 45	Endophytic fungus	Anti-oxidant activity
36 (ref. 64)	OH OHO HO Chrysoarticulin C 46	<i>Leptosphaeria</i> sp.	Anti-fungal activity
37 (ref. 65)	Z-Ligustilide 47	Ligusticum porteri	Anti-proliferative activity (sedative and relaxant)
38 (ref. 66)	(+)- Bicuculine 48	Fumaria capreokzta L and Fumaria bella	Potent GABa receptor antagonist and used to block Ca ²⁺ activated potassium channels

extraction. The selection of solvent also plays a crucial role in the extraction of phthalides, and it largely depends upon the nature of the phthalides. Most phthalides are non-polar, so for the extraction of such molecules, hexane or petroleum ether can be used as an initial extraction solvent. To extract polar phthalides, we use polar solvents, such as ethanol, chloroform, Review

methanol, and ethyl-acetate.21,24 The extraction process for phthalides has remained mostly unchanged over the years; however, some upgraded extraction procedures have been

reported.25,26

Phthalides are usually isolated via column chromatography, thin layer chromatography (TLC), and HPLC, with column chromatography being the most common. Silica, alumina, and LH-20 are frequently used adsorbents for column chromatography.27,28 Other techniques that have been used for some specific phthalides include preparative TLC (PTLC), centrifugal circular TLC (CCTLC), medium-pressure liquid chromatography (MPLC), high-speed countercurrent chromatography (HSCCC), droplet-countercurrent chromatography (DCCC), and high-vacuum low-temperature distillation.29

Initially, the characterization of naturally occurring phthalides was carried out through melting points, boiling points, saponification, UV spectroscopy, and hydrolysis techniques. After the development of NMR, IR, GC-MS, and X-ray crystallography, characterizing phthalides has become much easier.

Isolated natural products encompassing 3-substituted phthalide framework

Table 1 summarises examples of isolated natural products encompassing 3-substituted phthalide framework

Synthetic routes for 3-substituted 1(3H)-isobenzofuranones

We have classified synthetic routes to access 3-substituted (\pm) -1(3H)-isobenzofuranones in two major titles. First, we have emphasized recent approaches to generate racemic 3substituted (\pm) -1(3H)-isobenzofuranones, and later we have described recent approaches to generate optically pure 3substituted 1(3H)-isobenzofuranones.

3.1 Recent methodologies for the synthesis of 3-substituted (\pm)-1(3H)-isobenzofuranones

3.1.1 Metal catalyzed synthesis of 3-substituted (\pm)-1(3H)isobenzofuranones. Fan and co-workers⁶⁷ have reported 3substituted phthalides 51 via a ruthenium-catalyzed intermolecular cascade reaction of aromatic acids 49 with aromatic aldehydes 50. The synthesis involves the direct insertion of the C-H bond of the aromatic acids into a polar C=O bond of aromatic aldehydes, which is followed by the consecutive

intramolecular nucleophilic substitution. The polarity (electrophilicity) of the C=O bond in aromatic aldehydes was increased by having electron-withdrawing groups (NO2, CF3, F, Cl, Br) on the aromatic ring (Scheme 1).

Nguyen and co-workers⁶⁸ demonstrated a direct route to obtain phthalides 53 via carboxylation of benzoxasiloles 52 with carbon dioxide, using CuI as a catalyst. Several advantages of this methodology are the use of copper salt as a catalyst, economical starting materials and convenient reaction setup (Scheme 2). The main challenge of this methodology was the unexplored reactivity of organosilanes with CO₂.

Arcadi and co-workers⁶⁹ have described a palladiumcatalyzed hydroarylation and hydrovinylation reaction of ypropargylic alcohols 54 with aryl iodides 55 to afford crude γ,γdisubstituted allylic alcohols 56. Allylic alcohols 56 were treated with NaOH followed by acidification afforded 3,3-disubstituted phthalides 59 in good to moderate yields (Scheme 3).

Matsuda and co-workers70 described an oxidative cyclization of phthalaldehydes 60 and alcohols catalyzed by rhodium(III) catalyst and copper acetate to afford 3-alkoxyphthalides 61 in good to moderate yields (Scheme 4). The reaction is believed to be proceeding via Rh-Cu relay catalytic system.

The work was further extended to explore the utility of 1,3dicarbonyl compounds 63 as nucleophiles for the reaction with phthalaldehydes 62 under similar conditions. This led to the synthesis of 3-alkylphthalides 64 in excellent yields (Scheme 5).

Gandeepan and co-workers71 demonstrated rhodium(III)catalyzed regio- and stereoselective synthesis of disubstituted Ephthalides 67 from aryl acids 65 and allenes 66. The reaction proceeded via ortho C-H bond activation followed by an annulation pathway. The scope of the methodology was further investigated on a variety of aryl acids 65 and allenes 66 (Scheme

3.1.2 Hydroiodination-triggered synthesis of 3-substituted (\pm) -1(3*H*)-isobenzofuranones. Hydroiodination-triggered cascade reaction is demonstrated by Kawaguchi and coworkers72 by using I2, PPh3, and H2O in CDCl3 to furnish 3substituted phthalides 69 in excellent yields. The reaction proceeds via a four-step sequence, i.e., desilylation, hydroiodination, cyclization, and reduction, in one pot (Scheme 7). The present method eliminates the need for a metal catalyst to form phthalides.

The substrate scope of 2-ethynylbenzoates 70 was also studied by using cyano, chloro, phenyl, and ester groups on the side chain. They were tolerated during the four-step sequence to provide 3-substituted phthalides 71 (Scheme 8).

$$R^{1} = Alkyl$$

$$R^{1} = Alkyl$$

$$Ar$$

$$R^{1} = Alkyl$$

$$Ar$$

$$Ar$$

$$R^{1} = Alkyl$$

$$R^{2} = Alkyl$$

$$R^{2} = Alkyl$$

$$R^{3} = Alkyl$$

$$R^{4} = Alkyl$$

$$R^{2} = Alkyl$$

$$R^{3} = Alkyl$$

$$R^{4} = Alkyl$$

$$R^{4} = Alkyl$$

$$R^{5} = Alkyl$$

$$R^{4} = Alkyl$$

$$R^{5} = Alkyl$$

$$R^{5} = Alkyl$$

$$R^{5} = Alkyl$$

$$R^{7} = Alky$$

Scheme 1 Ruthenium catalyzed the synthesis of 3-substituted phthalides.

Scheme 2 Synthesis of benzoxasiloles via copper-catalyzed direct carboxylation

3.1.3 Synthesis of 3-substituted (\pm) -1(3H)-isobenzofuranones using β -keto acids as a nucleophile center. Jia and co-workers⁷³ developed a one-pot cascade aldol/cyclization reaction of 72 wherein β -keto acids 73 were directly employed as a nucleophilic center, and glycerol was used as a solvent. Here, β -keto acids functioned as ketone enolate equivalents. An extensive substrate scope for β -keto acids was explored, affording a wide variety of 3-substituted phthalides in good to excellent yields (Scheme 9).

3.1.4 Synthesis of 3-substituted (\pm) -1(3H)-isobenzofuranones using Schiff base. Perillo and co-workers⁷⁴ developed cascade reaction of glycine Schiff base 77 with 2-carbomethoxy benzaldehyde 76, which involved aldol condensation followed by cyclization under the acidic conditions to provide α -amino ester 3-substituted phthalides 80 in good yield (Scheme 10). The methodology was further extended to develop an enantioselective version of the reaction to obtain chiral 3-substituted phthalides in high ee's. 73

A variety of bifunctional phase-transfer catalysts (PTC) were examined to obtain 3-substituted phthalides in excellent enantioselectivity. Bifunctional PTC 75 (Fig. 5) gave the desired product in moderate ee's (51–71%).⁷³

3.1.5 Oxa-Michael addition reaction to generate 3-substituted (±)-1(3*H*)-isobenzofuranones. Youn and coworkers⁷⁵ have developed NHC-catalyzed domino oxidation of 2-alkenylbenzaldehydes 81, followed by oxa-Michael addition reaction to afford 3-substituted phthalides 83. The protocol developed has a broad substrate scope and wide functional group tolerance. The success of the domino process could be achieved in two ways; by exploiting atmospheric oxygen as an oxygen atom source and by adding an electron-deficient olefin bearing hetero atom with lone pair of electrons. Also, molecular oxygen in air could play an essential role in transformation, as similar NHC-catalyzed reactions of the same substrates under inert atmosphere produce follow different reaction pathways (Scheme 11).

 $R^1 = 6$ -Me, $R^2 = H (77 \%)$

 $R^1 = 4$ -OMe, $R^2 = Me$ (79 %)

 $R^1 = 4$ -Me, $R^2 = OH (68 \%)$

3.1.6 Friedel–Crafts alkylation reaction to generate 3-substituted (±)-1(3*H*)-isobenzofuranones. Tang and coworkers⁷⁶ have developed an efficient methodology to synthesize 3-indolyl-substituted phthalides **86** *via* Friedel–Crafts alkylation of indoles **85** with 3-hydroxy phthalide **84** using TsOH as the catalyst. The usefulness of the process was studied with variously substituted indoles which reacted efficiently at room temperature to afford phthalides in excellent yields (Scheme 12).

OMe
$$+$$
 R-X $+$ R-X

Scheme 3 Synthesis of 3-vinyl phthalides

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Scheme 4 Synthesis of 3-alkoxy phthalides

CHO

CHO

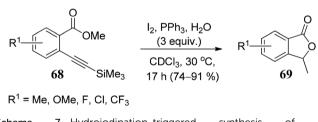
$$R^1 = H, R^2 = R^3 = OMe$$
 $R^1 = H, R^2 = R^3 = OMe$
 $R^1 = H, R^2 = R^3 = OEt$
 $R^1 = H, R^2 = R^3 = OEt$

Scheme 5 Synthesis of 3-alkyl phthalides.

$$R = H, 4-Me, 4-OMe, 4-F, \\ 4-CI, 4-Br, 4-I, 4-NO2, 4-CN, \\ 2-Me, 2-CI, 3-Me, 3-CI, 3-Br \\ R = R, R^2 = C = -R^3$$

$$R = R^3 = H \\ R^1 = 3-Me-Ph, R^2 = R^3 = H \\ R^1 = 3-Me-Ph, R^2 = R^3 = H \\ R^1 = 3-Me-Ph, R^2 = R^3 = H \\ R^1 = 1-napthyl, R^2 = R^3 = H \\ R^1 =$$

Scope of arenecarboxylic acids and allenes (synthesis of disubstituted phthalides)



7 Hydroiodination-triggered synthesis Scheme methylphthalides.

3.1.7 NBS mediated free-radical bromination to generate 3substituted (\pm)-1(3*H*) isobenzofuranones. Li and co-workers⁷⁷ have devised a four-step strategy for the synthesis of 3substituted phthalide. The condensation reaction of 3-ethoxyphthalide 89 with diethylmalonate carbanion followed by decarboxylation and hydrolysis gave 3-substituted phthalides 92 in 44% overall yield over four steps (Scheme 13). NBS mediated free-radical bromination of phthalide 87 gives 88. The crude 88 was treated with hot ethanol, then cooled to give 89 as white solid.

3.1.8 Photochemical catalyzed synthesis of 3-substituted (\pm) -1(3*H*)-isobenzofuranones. Tatsugi and co-workers78 demonstrated that the degassed alcoholic solution of indane-1,2,3-trione 93 could be photochemically irradiated to afford 3-alkoxycarbonylphthalides 94 as the major product. During the process, 3-alkoxyphthalide 95 was also obtained in minor quantities (Scheme 14).

The initial step of the photochemical process could be the cleavage of a C-O bond to form semidione radical 93a, which under rearrangement forms 93b. Thus, 93b can follow two pathways: (i) it can form the compound 93c, which on reaction with ROH forms 93d followed by protonation to give 3-alkoxyearbonylphthalides 94 or (ii) 93f rearranges to 93g followed by decarbonylation gave phthalides carbene which on quenching with ROH gave 3-alkoxyphthalide 95 (Scheme 15).

R¹ = Me, OMe

$$R^2$$
 R^2
 R^3
 R^4
 R^2
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 R^4

Scheme 8 Synthesis of 3-substituted phthalides triggered via hydroiodination.

Scheme 9 Synthesis of 3-substituted phthalides using β -keto acids as a nucleophile center.

Scheme 10 Synthesis of α -amino ester 3-substituted phthalide

3.2 Recent methodologies to synthesize enantiomerically pure 3-substituted 1(3*H*)-isobenzofuranes

In this section, we have described recent approaches to synthesize enantiomerically pure 3-substituted 1(3H)-isobenzofuranes.

3.2.1 Synthesis of 3-substituted 1(3*H*)-isobenzofuranones using diverse organozinc reagents. Huang and co-workers⁷⁹ demonstrated a new protocol for the synthesis of chiral 3-substituted phthalides 99 by carrying out catalytic asymmetric 1,2-addition of methyl 2-formylbenzoates 98, followed by lactonization, using diverse organozinc reagents (Scheme 16).

They developed a chiral phosphoramide ligand–Zn(π) complex, which was synthesized from (1R,2R)-diphenylethyelendiamine **100** as catalyst. The efficiency of the process is highlighted by the fact that the enantiopure phthalide **99** was obtained in excellent yields (\sim 95%) and good enantioselectivities (\sim 89%).

Carlos and co-workers⁸⁰ carried out the asymmetric catalytic synthesis of 3-aryl phthalides **102** *via* sequential asymmetric arylation–lactonization pathway. In the presence of a chiral amino naphthol ligand, the reactive arylating agents, generated by boron–zinc exchange, were reacted with 2-formylbenzoates **101**, which was followed by lactonization to yield the corresponding chiral phthalides **102** in excellent yields and

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Fig. 5 Bifunctional phase-transfer catalyst.

enantioselectivities (\sim 87–90% ee) (Scheme 17). The place of the substituent at the aryl ring was found to have a slight effect on the efficiency of the arylation reactions. The asymmetric addition of an aryl zinc reagent to the 2-formylbenzoate is the enantio determining step.

3.2.2 Synthesis of chiral 3-substituted phthalides *via* palladium-catalyzed Heck–Matsuda arylation of arenediazonium salt. Kattela and co-workers⁸¹ have described an enantioselective synthesis of chiral 3-substituted phthalides *via* palladium-catalyzed Heck–Matsuda arylation of arenediazonium salt 104 with 2,3-dihydrofurans 105, followed by NaBH₄ mediated reduction and lactonization pathway to give chiral phthalides 107 in overall yields and excellent enantioselectivities (up to 98% ee). The strategy was further extended for the synthesis of medicinally important chiral lactones, amines, and olefins (Scheme 18).

3.2.3 Novel derived metal complex ligand as a catalyst for the synthesis of chiral 3-substituted phthalides. Ge and coworkers⁸² have developed the first asymmetric hydrogenation of 3-alkyl/arylidenephthalides 108 to furnish an extensive range of 3-substituted chiral phthalides 109 in admirable enantiomeric excesses (~98% ee). The hydrogenation process was catalyzed by a novel derived Ir^I complex of a spiro-[4,4]-1,6-nonadiene-based phosphine-oxazoline ligand (SpinPHOX) 110 as a catalyst. The effectiveness of the protocol further extended for the asymmetric synthesis of enantioselective drugs as well as the bioactive natural products (Scheme 19).

Zhang and co-workers⁸³ demonstrated a novel route for the reductive cyclization of 2-acylarylcarboxylate **111** via asymmetric transfer hydrogenation. The reaction was promoted by a new Ru(π)-diamine complex **113**, which catalyzes asymmetric transfer hydrogenation and *in situ* lactonization to provide enantiomerically pure 3-substituted phthalides **112** (Scheme 20).

The observed excellent enantioselectivity can be explained by a preferable transition state of the Ru–TsDBuPEN complex and ethyl 2-acylarylcarboxylate substrates, which determines the chirality. Hydrogen bonding with the neighboring ester function group of the 2-acylarylcarboxylate substrate might also be accountable for the observed selectivity (Fig. 6).

Kumbhar and co-workers⁸⁴ synthesized bipyridyl ligands. These chiral ligands were applied in the synthesis of chiral phthalides. The reaction sequence involved chromium-catalyzed enantioselective Nozaki-Hiyama-Kishi allylation of

Scheme 11 NHC-catalyzed domino oxidation/oxa-Michael addition of 2-alkenylbenzaldehydes.

Scheme 12 Synthesis of 3-indolyl-substituted phthalides

91

Scheme 13 Synthesis of 3-substituted phthalides.

90

Scheme 14 Photochemical reactions of indane-1,2,3-trione.

substituted benzaldehydes **114**, followed by lactonization gave enantiopure phthalides **116** with an optimal ee of 99%. Chiral $Cr(\Pi)$ complex developed using bipyridine alcohol and $CrCl_3$. This utility of the protocol was further extended by accomplishing the synthesis of (S)-cytosporone E in three steps (Scheme 21).

Lu and co-workers⁸⁵ established an extremely effective and enantioselective approach towards the synthesis of bioactive 3-substituted chiral phthalides **119**. The protocol involved ruthenium-catalyzed hydrogenation followed by lactonization of 2-acylarylcarboxylates **117** to furnish 3-substituted chiral phthalides. Different chiral phosphine ligands were employed to obtain good enantioselectivity, the best among them was (S)-SunPhos **118**, which helped in the induction of enantioselectivity >99% ee (Scheme 22).

3.2.4 Chiral bifunctional cinchonine as an organocatalyst for the synthesis of chiral 3-substituted phthalides. Youn and co-workers⁸⁶ developed an asymmetric domino oxidation/oxa-Michael addition reaction wherein an N-heterocyclic carbene (NHC) 121 and a chiral bifunctional cinchonine organocatalyst 122 work cooperativity to furnish the chiral 3-substituted phthalides 123. The use of a bifunctional cinchonine catalyst helps in achieving excellent enantioselectivity, where it functions both as a base (quinuclidine) and hydrogen bond donor, thus activating nucleophile and electrophile, respectively. Cinchonine works both as a Brønsted base for the generation of

NHC as well as a bifunctional catalyst for asymmetric induction (Scheme 23).

92

3.2.5 Synthesis of chiral 3-substituted phthalides *via* a nucleophilic addition reaction. Zhang and co-workers⁸⁷ described a two-step asymmetric route for 3-substituted phthalides 130. The chiral amide 126 was subjected to the treatment with isopropyl magnesium chloride followed by reaction with various aldehydes 128 (Scheme 24). Intramolecular cyclization of the substrate allowed the synthesis of 3-substituted phthalides 130 (\sim 88% ee).

Davis and co-workers⁸⁸ developed an enantioselective approach towards the synthesis of 3-substituted phthalides by the addition of phthalide anions **133** to chiral-sulfinimines (*N*-sulfinyl imines) **132**. The present approach was extended for the synthesis of chiral 3-substituted isoquinolones and 3-substituted 4-hydroxy isoquinolines, respectively (Scheme 25).

3.2.6 Tandem aldol-lactonization reactions for the synthesis of chiral 3-substituted phthalides. Ray and coworkers⁸⁹ carried out chiral Brønsted acid 140 catalyzed, tandem mannich-lactamization, and aldol-lactonization reactions to achieve the enantioselective synthesis of phthalides 143 in good to excellent enantioselectivities (Scheme 26). The developed protocol has broad substrate scope, and a variety of substituted aromatic aldehydes and aromatic amine were used.

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Scheme 15 Proposed mechanistic pathway.

 $\textbf{Scheme 16} \quad \text{Asymmetric 1,2-addition/lactonization tandem reaction of methyl 2-formylbenzoate}.$

4. Application of 3-substituted 1(3*H*)-isobenzofuranones for the construction of crucial molecular architecture

As discussed in Table 1, we can state that phthalide moiety is present in various biologically active natural products. In this section, we aim to provide some of the examples of 3-

substituted 1(3H)-isobenzo furanones for the construction of important molecular architecture.

4.1 Annulation of stabilized phthalide anions with Michael acceptors

Annulation with stabilized phthalide anions along with Michael acceptors is a powerful and convenient tool for obtaining the quinoid natural products. Many natural products consist of a standard quinone unit. The exciting structures and vital

R = Ph. 80% vield (91% ee) RB(OH)2, Et2Zn R = o-tolyl, 86% yield (83% ee) 103 (20 mol%) R = p-tolyl, 90% yield (91% ee) $R = 4-PhC_6H_4$, 71% yield (81% ee) toluene, -5 °C, 5 h $R = 4-CIC_6H_4$, 58% yield (85% ee) ÓМе $R = 4-BrC_6H_4$, 95% yield (83% ee) 3-aryl phthalide 2-formylbenzoate $R = 4-MeOC_6H_4$, 71% yield (91% ee) (103)102 101

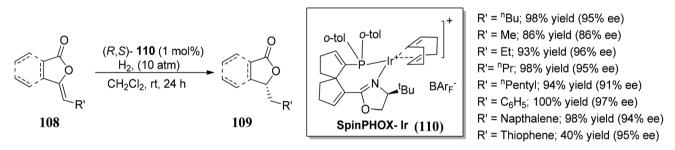
Scheme 17 Asymmetric arylation-lactonization sequence.

R = 2-Me; 66% yield (99% ee); R = 3-OMe; 62% yield (98% ee); R = 3-NO₂; 55% yield (98.5% ee);

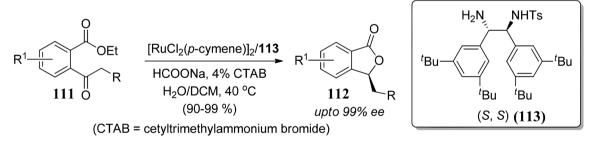
R = 3-Cl; 60% yield (98.5% ee); R = 3-Br; 55% yield (98.5% ee); R = 3-Br & 4^{-i} Pr; 58% yield (98.5% ee);

R = 3-OMe & 4-OMe; 56% yield (98.5% ee); R = 2-OMe & 4-OMe; 58% yield (98.5% ee)

Scheme 18 Heck-Matsuda arylation of dihydrofurans



Scheme 19 Asymmetric hydrogenation of the 3-alkyl/arylidenephthalides.



 $R = R^1 = H$; 97% yield (98% ee)

 $R = Me, R^1 = H; 95\% \text{ yield } (98\% \text{ ee})$

 $R = CICH_2(CH_2)_2$, $R^1 = H$; 95% yield (99% ee)

 $R = Ph, R^1 = H; 96\% \text{ yield } (99\% \text{ ee})$

 $R = 4-CIC_6H_4$, $R^1 = H$; 98% yield (99% ee)

 $R = 4-MeC_6H_4$, $R^1 = H$; 93% yield (99% ee)

 $R = 4-MeOC_6H_4$, $R^1 = H$; 96% yield (99% ee)

 $R = 4-MeSC_6H_4$, $R^1 = H$; 99% yield (99% ee)

 $R = 4-CF_3C_6H_4$, $R^1 = H$; 96% yield (99% ee)

 $R = 3.5 - (MeO)_2 C_6 H_3$, $R^1 = H$; 93% yield (99% ee

R = 2-thienyl, $R^1 = H$; 97% yield (99% ee)

R = 1-napthyl, $R^1 = H$; 98% yield (99% ee)

R = 4-quinolyl, $R^1 = H$; 94% yield (98% ee)

R = 4-Cl-phenoxyl, $R^1 = H$; 94% yield (99% ee)

R = 4-Cl-phenylthio, $R^1 = H$; 97% yield (98% ee)

 $R = Ph, R^1 = 4-Br; 90\% \text{ yield } (99\% \text{ ee})$

 $R = Ph, R^1 = 5-Br; 93\% \text{ yield } (99\% \text{ ee})$

 $R = Ph, R^1 = 4,5-Cl_2; 98\% \text{ yield } (98\% \text{ ee})$

 $R = Ph, R^1 = 4.5 - C_6 H_4$; 97% yield (98% ee)

Scheme 20 Asymmetric synthesis of 3-substituted phthalides by ruthenium-catalyzed transfer hydrogenation.

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Fig. 6 Proposed transition state

biological activities⁹⁰ of these natural products have provided an influential forum for organic chemists to explore this area of research. The general protocol for this reaction was discovered in the late 1970s simultaneously by Hauser⁹¹ and Kraus.⁹²

The phthalide annulation involves the deprotonation of a stabilized phthalides **144** by a strong base and *in situ* capture of anion by a suitable Michael acceptor **145** followed by Dieckmannlike condensation to afford a bicyclic compound **148** (Scheme

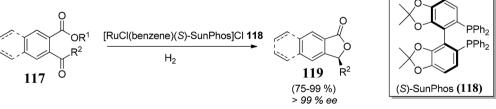
27). Compound **148** undergoes mild oxidation to form biphenol derivatives **149**. This methodology presents an elegant way to synthetic naphthol derivatives *via* phthalide chemistry.

Chaturvedi and co-workers⁹³ developed a novel route to utilize unsaturated phosphonates for annulation reaction as Hauser acceptors. Good yields of phosphorylated 1,4-dihydroxynaphthalenes **153** are obtained, which on further oxidation results in their corresponding 1,4-naphthoquinones **154**. The reaction is successful in providing an efficient, straightforward, and powerful approach for synthesizing disubstituted naphthalene-1,4-diols **153**. Naphtha-1,4-diones **154** consist of a various (hetero) aryl groups positioned at 3 and a phosphonate group positioned at 2 (Scheme 28).

4.1.1 Metal-free catalytic annulation to develop enantioriched highly functionalized dihydronaphthoquinones. A metalfree catalytic annulation is developed by Zhuang and coworkers, ⁹⁴ which involves Lewis base-mediated asymmetric allylic alkylation and a novel asymmetric intramolecular acyl cyanation of alkenes. This route provides a novel method to obtain enantioriched highly functionalized dihydronaphthoquinones 160 and chiral 3,3-disubstituted phthalides **158** having quaternary

 R^1 = H, R^2 = OCH₃, R^3 = H, R^4 =OCH₃; 87% yield (97% ee) R^1 = H, R^2 = OCH₃, R^3 = OCH₃, R^4 =H; 85% yield (94% ee) R^1 = OCH₃, R^2 = OCH₃, R^3 = OCH₃, R^4 =H; 89% yield (99% ee) R^1 = H, R^2 = H, R^3 = H, R^4 =H; 86% yield (96% ee) R^1 = H, R^2 = H, R^3 = OCH₃, R^4 =H; 90% yield (97% ee) R^1 = H, R^2 = H, R^3 = N(CH₃)₂, R^4 =H; 70% yield (96% ee) R^1 = H, R^2 = Br, R^3 = N(CH₃)₂, R^4 =H; 90% yield (98% ee)

Scheme 21 Enantioselective Nozaki-Hiyama-Kishi allylation.



 $R^1 = Me$, $R^2 = Me$; 95% yield (99.6% ee) R^1 = Me, R^2 = C_6H_5 ; 95% yield (98.2% ee) $R^1 = Et$, $R^2 = Me$; 98% yield (99.6% ee) $R^1 = H$, $R^2 = C_6H_5$; 95% yield (96.2% ee) $R^1 = {}^{i}Pr$, $R^2 = Me$; 98% yield (99.2% ee) $R^1 = Me$, $R^2 = o-CH_3C_6H_4$; 75% yield (99.2% ee) $R^1 = H$, $R^2 = Me$; 92% yield (99.4% ee) $R^1 = Me$, $R^2 = p-CH_3C_6H_4$; 87% yield (33.8% ee) $R^1 = Me$, $R^2 = Et$; 94% yield (99.6% ee) $R^1 = Me$, $R^2 = o$ - $CF_3C_6H_4$; 98% yield (99.4% ee) $R^1 = Me$, $R^2 = {}^nPr$; 94% yield (99.2% ee) Methyl 2-acetyl-5-methylbenzoate; 98% yield (99.0% ee) $R^1 = Me$, $R^2 = {}^nBu$; 96% yield (99.4% ee) Methyl 2-acetyl-5-chlorolbenzoate; 98% yield (99.4% ee) $R^1 = Me$, $R^2 = {}^tBu$; 58% yield (99.6% ee) Methyl 3-acetyl-2-napthoate; 98% yield (99.4% ee)

Scheme 22 Asymmetric hydrogenation of 2-acylarylcarboxylate

```
R^1 = R^2 = R^3 = H, R^4 = CO_2Et; 72% yield (96% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2Me; 70% yield (95% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 71% yield (95.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 71% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 71% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 71% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (95.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (95.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (94.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (94.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (94.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^4 = CO_2^nBu; 70% yield (96.5% ee) R^1 = R^2 = R^3 = H, R^2 = R^3 = H, R^3 = R^3 = H, R^4 = R^3 = R
```

Scheme 23 Asymmetric oxidative cyclization of 2-alkenylbenzaldehydes.

Scheme 24 Direct asymmetric synthesis of 3-substituted phthalides.

Scheme 25 Reaction of phthalide anion with enantiopure sulfinimines.

Scheme 26 Tandem aldol-lactonization reactions.

Scheme 27 Annulation of stabilized phthalide anions with Michael acceptors

carbon centers (Schemes 29 and 30). The reaction involves the use of chiral bifunctional thiourea organocatalyst.

- 4.1.2 Hauser-Kraus annulation to give naphthoquinolcarbohydrate hybrids. Chakraborty and co-workers95 described a regioselective approach to naphthoquinone/naphthoquinolcarbohydrate hybrids using 3-cyano phthalides 161 as one of the essential precursors. In this approach, anionic annulation of 3cyano phthalides 161 takes place with an acrylate appended sugar moiety 162 (Scheme 31).
- 4.1.3 Total synthesis of uncialamycin via Hauser-Kraus annulation. Nicolaou and co-workers⁹⁶ described the total synthesis of uncialamycin, and a Hauser-Kraus annulation was employed as one of the critical reactions for the synthesis of uncialamycin core (Scheme 32).
- 4.1.4 Total synthesis of the griseusin B scaffold (bioactive natural product) via Hauser-Kraus annulation. Naysmith and co-workers97 developed a convergent route for the synthesis of the griseusin B scaffold (bioactive natural product). The main steps of the synthetic journey include the highly effective onepot Hauser-Kraus annulation followed by methylation and

double deprotection-spirocyclization sequence that directly results in the target tetracyclic ring system (Scheme 33).

4.2 Total synthesis of (-)- α -noscapine

(-)-α-Noscapine (narcotine), which was initially isolated from Papaver somniferum L.,98 is a non-addictive anti-tussive agent with little to no significant toxicity.99 (-)-α-noscapine also displays other probable scientific utilities 100 for the treatment of life-threating diseases. Naturally occurring noscapine consists of two adjacent chiral centers: one at C-5' position of tetrahydroisoquinoline ring and another at the C-3 position of phthalide framework.

Xu and co-workers¹⁰¹ commenced with the synthesis of meconine-3-carboxylic acid 173, which could be synthesized from pure 2,3-dimethoxybenzoic acid 171 and glyoxylic acid 172 in the presence of a conc. H₂SO₄. While the amine functionality 174 could be easily prepared from gallic acid over a nine-step sequence. The amide bond (C5'-C3 bond formation) was formed from the acyl chloride derivative of 173 and free amine 174 to give compound 175 in 89% yield (Scheme 34). The next step of the sequence was Bischler-Napieralski reaction in the

Scheme 28 Hauser-Kraus annulation of 3-substituted phthalides.

Scheme 29 Lewis base-catalyzed asymmetric allylic alkylation of 3-cyano phthalides.

presence of POCl₃. The cyclization took place efficiently to give imine, which was further reduced to afford tetrahydroisoquinoline **176**. After extensive optimization of NaBH₄/NaBH₃CN mediated reduction, it was concluded that low reaction temperature was critical for the high diastereoselectivity and moderately high yields. Subsequently, Eschweiler–Clarke reaction was used to obtain an *N*-methylated compound, **177** in 75% yield. RANEY® Ni was used for hydrogenation of 177 to

produce target compound **8.** Further recrystallization of the crude sample gave pure (\pm) - α -noscapine **8.**

4.3 Total synthesis of olaparib

Olaparib is an FDA approved targeted therapy for the treatment of cancer. It is a PARP inhibitor, inhibiting poly ADP ribose polymerase (PARP), an enzyme that plays a role in DNA repair. It targets

Scheme 30 Annulation reaction of 3-substituted phthalides.

R = H, R² = H; 71% yield (95% ee) R = 4-Me, R² = H; 67% yield (97% ee) R = 4-OMe, R² = H; 55% yield (99% ee) R = 3-Me, R² = H; 52% yield (86% ee) R = 3,4-Me, R² = H; 64% yield (95% ee) R = 4,5-OMe, R² = H; 55% yield (59% ee) R = 2-OMe, R² = H; 52% yield (52% ee) R = 4-F, R² = H; 48% yield (95% ee) R = 4-Cl, R² = H; 47% yield (86% ee) R = 4-Br, R² = H; 48% yield (83% ee) R = 3-F, R² = H; 48% yield (83% ee)

Scheme 31 Hauser-Kraus annulation to give naphthoquinol-carbohydrate hybrids

Scheme 32 Total synthesis of uncialamycin.

cancer cells in people with hereditary BRCA1 or BRCA2 mutations, which include some ovarian, breast, and prostate cancers. 102

Lou and co-workers¹⁰³ demonstrated an effective protocol for the synthesis of olaparib. The synthesis initiated by 3-phosphonophthalide 178, which on further reaction with aromatic aldehyde 179 gave 180, which further on reaction with hydrazine hydrate underwent ring expansion to give **181**. **181** on amide coupling with **182** gave the desired drug, olaparib (Scheme 35).

4.4 Synthesis of cytogenin (a bioactive natural product)

Gadakh¹⁰⁴ and co-workers developed a route for the synthesis of 3-carbethoxy-isocoumarins **184**. The reagent system used in this

Scheme 33 Total synthesis of the griseusin B scaffold.

Scheme 34 Total synthesis of (\pm) - α -noscapine.

Scheme 35 Synthesis of FDA approved the anti-cancer drug olaparib.

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$$R^{1} = R^{2} = R^{3} = H (94 \%)$$

$$R^{1} = H, R^{2} = OMe, R^{3} = H (96 \%)$$

$$R^{1} = H, R^{2} = OMe, R^{3} = H (96 \%)$$

$$R^{1} = R^{2} = OMe, R^{3} = H (96 \%)$$

$$R^{1} = R^{2} = OMe, R^{3} = H (96 \%)$$

$$R^{1} = R^{2} = OMe, R^{3} = H (96 \%)$$

$$R^{1} = R^{2} = OMe, R^{3} = H (96 \%)$$

$$R^{1} = R^{2} = OMe, R^{3} = OMe (90 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (90 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = R^{3} = H (94 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = R^{3} = H (94 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = R^{3} = H (94 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = R^{3} = H (94 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = R^{3} = H (94 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (92 \%)$$

$$R^{1} = H, R^{2} = R^{3} = H (94 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (90 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (90 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (90 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (90 \%)$$

$$R^{1} = H, R^{2} = OBn, R^{3} = OMe (90 \%)$$

Scheme 36 Intramolecular ring expansion of 3-substituted phthalides to isocoumarins

Scheme 37 Synthesis of cytogenin'.

Scheme 38 InBr₃ catalyzed Friedel-Crafts reaction between indole and 3-indolyl-substituted phthalides.

methodology is DEAD/PPh₃/TBHP through 1,2-shift intramolecular ring expansion, or we can say that the simple elimination is dependent on the various functional groups present on 3-substituted phthalides (Scheme 36).

The methodology is also used to synthesize cytogenin (a bioactive natural product) (Scheme 37).

4.5 InBr₃-catalyzed Friedel-Crafts reaction on 3-indolylsubstituted phthalides to develop unsymmetrical bis(indolyl) methanes (BIMs)

Lin and co-workers¹⁰⁵ developed a convenient, efficient, and novel synthetic route for synthesizing the unsymmetrical bis(indolyl)methanes (BIMs) 189 via InBr3-catalyzed Friedel-Crafts reaction by reacting indoles 188 with 3-indolylsubstituted phthalides 187 in water to obtain 189 in excellent yields (Scheme 38). These BIMs compounds present have excellent anti-Alzheimer's disease activity.

5. Conclusions

In the past decade, there has been considerable attention in the area of phthalides (more specifically 3-substituted phthalides) due to the development of various phthalides-based drugs. This has led to the development of elegant research methodologies with diverse applications in academic and industrial laboratories on micro- and macroscale operations. In light of the continued research in the area of 3-substituted phthalides, we have made an effort to present a critical review on the chemistry of 3-substituted phthalides. The chemistry of phthalides has been reviewed, but an independent and detailed review on the chemistry of 3-substituted phthalides is unavailable.

We have reviewed the isolation and biological activities of various 3-substituted phthalides. We have presented pivotal research methodologies for the synthesis of racemic and chiral 3-substituted phthalides. These newer approaches are essential for the development of newer and elegant strategies for the synthesis of phthalide-based or similar molecular architecture with broader substrate scope and higher stereoselectivities. Also, we have reviewed the application of 3-substituted phthalides as a precursor for the synthesis of natural products and their analogs. Through this review, we have provided enough contextual information on the chemistry of 3-substituted phthalides, which can inspire organic chemists to develop methodologies for the synthesis of biologically and medicinally important molecules.

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Conflicts of interest

The authors declare no conflict of interest.

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