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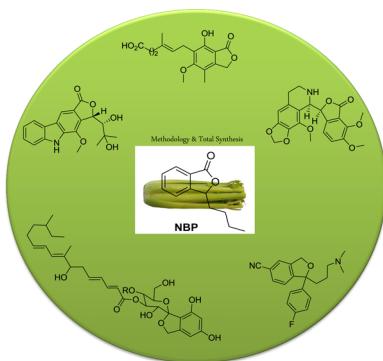
Phthalides and Phthalans: Synthetic Methodologies and Their Applications in the Total Synthesis

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1. PHTHALIDES

1.1. Introduction

Small molecule natural products have been the mainstay of research in organic chemistry since its early development.^{1a} The established classes of natural products, like alkaloids, amino acids, flavonoids, quinonoids, steroids, and terpenoids, have played vital roles in the discovery of new drugs. Random and diverse screening of crude natural sources such as plant extracts and fermentation broths, according to their therapeutic activity, has proven to be an important aspect of modern drug development. These processes have led to the discovery of different classes of lead compounds with bioactivities against a wide range of diseases and infections. More than 60% of marketed medicines have their origins in the natural products.^{1b} They are either natural product-based or natural product-inspired. Research on the chemistry of natural products is continuing to generate new leads in medicinal chemistry. A case in point is the emerging class of compounds called isobenzofuranones, commonly termed as phthalides. Phthalides (**1**), also known as 3*H*-isobenzofuran-1-ones, are characterized by a bicyclic nucleus (Figure 1) derived from the fusion of a γ -lactone (ring A) with a benzene (ring B). They are considered internal esters of the corresponding γ -hydroxy carboxylic acids. Although the parent phthalide (**1**, R = H) has been known for 100 years, its occurrence in natural products dates back to the 18th century. Phthalide isoquinolines, hydrastine, or noscapine could be considered the first phthalide natural product.^{1c}

Phthalides are frequently found in naturally occurring substances, and exhibit a broad spectrum of biological

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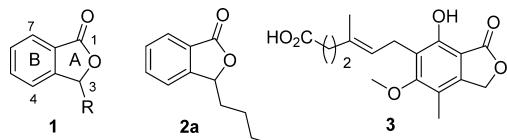


Figure 1. Structure of a phthalide (**1**), 3-*n*-butylphthalide (**2a**), and mycophenolic acid (**3**).

activities.² They have proven to be useful in the treatment of circulatory and heart diseases. They also act as versatile building blocks³ in organic synthesis, particularly in the synthesis of functionalized naphthalenes, anthracenes, and naphthacene natural products. The total synthesis of tetracycline antibiotics (eq 1), as well as the synthesis of pharmacologically active synthetic molecules (eq 2), as shown in Scheme 1, have been realized with the use of phthalide synthons.⁴

Although phthalides are components of traditional and folk medicines from ancient times, the diverse range of their therapeutic activities has only recently made an impact among the scientists. The success story of *n*-butylphthalide (NBP, **2a**, Figure 1),^{5a} which is currently in the market as an antiplatelet drug for ischemia-cerebralapoplexy,^{5b} has led to the development of phthalides as a class of pharmaceutically important natural products. It was also approved by the state food and drug administration of China in 2002 as an anti-ischemic stroke drug. It inhibits platelet aggregation, improves microcirculation, and mitigates ischemic brain injury. Between the two enantiomers, the (*S*)-isomer has been found more effective in certain cases.^{5c} NBP is a viscous oil and occurs as the major component of celery oil. It also exhibits antibacterial, antiviral, and antihypertensive activity. Mycophenolic acid (**3**, Figure 1) is in clinical trial for the prevention and reversal of transplant rejection and anticancer.^{5d-f} Such bioactivities and structural diversities of this class of synthetic targets have aroused interests in their syntheses, which have been marginally reviewed earlier.^{2a} Further, the obtention of NBP from the natural sources is not cost-effective. As a consequence, its laboratory synthesis by either chemical or biochemical means has been an active area as is evident from recent reviews.^{2b,c}

The earlier reviews^{2a-d} provide overviews of the methods of investigations, structural diversity, the bioactivities and the synthetic methods for 3-*n*-butylphthalide (**2a**). The recent

review^{2e} has mainly focused on the chemistry of active methylene compounds for the 3-substituted phthalides. Herein, we intend to develop a compendium of the significant synthetic strategies employed for the synthesis of phthalides and the total synthesis of naturally occurring phthalides. As a prelude to the topic, an overview of salient aspects of sources, isolation, characterization, biological activities, biosynthetic studies, and classification of phthalides is presented as far as practicable. As a complementary note, the synthesis of phthalans⁶ including phthalan natural products has been covered in the second section.

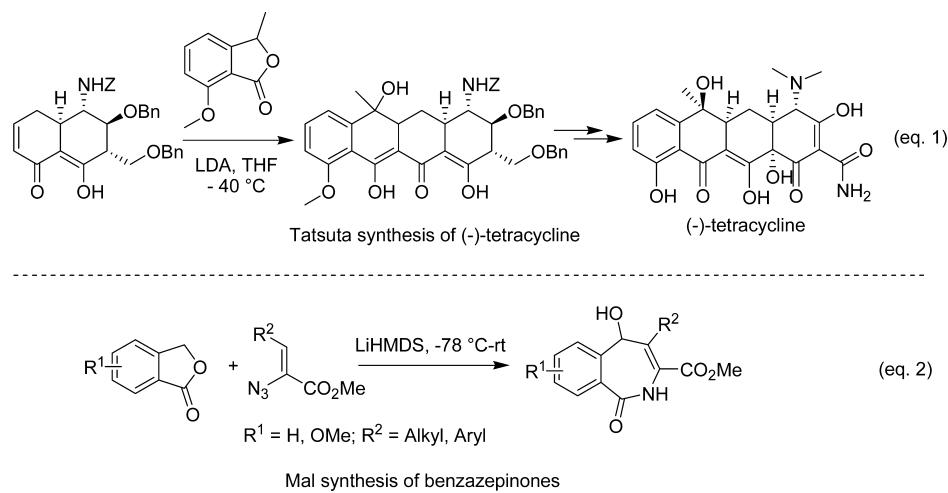
1.1.1. Sources, Isolation, and Characterization. Plants are the main sources of phthalide natural products. According to a recent review,^{2a} there are approximately 180 naturally occurring phthalides isolated to date from about 137 plant species. They are obtained mainly from two genera *Ligusticum* and *Angelica* of the *Apiaceae* family, except the isoquinolyl phthalides.^{7a} A few of them also have been identified from several species of *Apium* genus. Isoquinolyl phthalides are obtained from two genera, *Corydalus* and *Fumaria*. Phthalides are also obtained as secondary metabolites from different microorganisms, for example, fungi, bacteria, liverworts, etc.

In a typical process, phthalides are extracted from the air-dried parts of the plants by different extraction techniques.^{7b} In recent times, super critical CO₂ or biomembranes are utilized for the purpose of extraction. In addition to the typical purification processes, high-speed counter-current chromatography (HSCCC) and droplet-counter-current chromatography (DCCC) techniques are prevalent.^{7c}

The structural characterizations of phthalide natural products are accomplished by analysis of IR, NMR, and X-ray crystallographic data. IR frequencies at \sim 1750 cm⁻¹ indicate the presence of γ -lactone unit of the basic skeleton. In ¹H NMR spectrum, characteristic singlets at $\sim\delta$ 5.3 ppm typically correspond to the benzylic protons. The ¹³C NMR signals at $\sim\delta$ 70–80 ppm and $\sim\delta$ 164–174 ppm correspond to C-3 and lactone carbonyl, respectively.

1.1.2. Biological Activities. Since ancient times, phthalide-containing plants have been used worldwide as traditional medicines, dietary supplements, and food flavoring agents etc.^{2a} While earlier reports focused mainly on the biological activities of phthalide isoquinoline alkaloids like noscapine, most of the recent studies have dealt with other 3-substituted phthalides

Scheme 1. Examples of Synthetic Applications of Various Phthalides



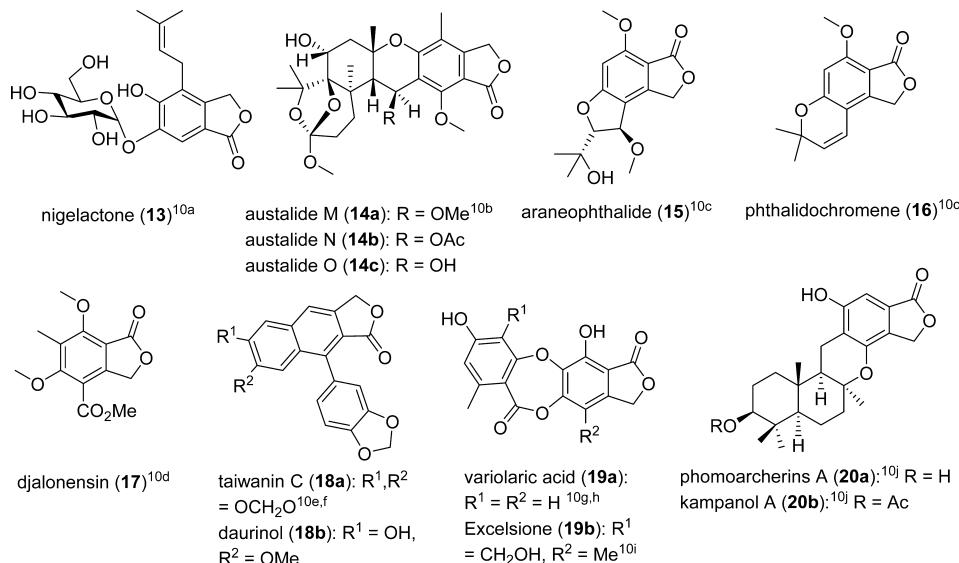
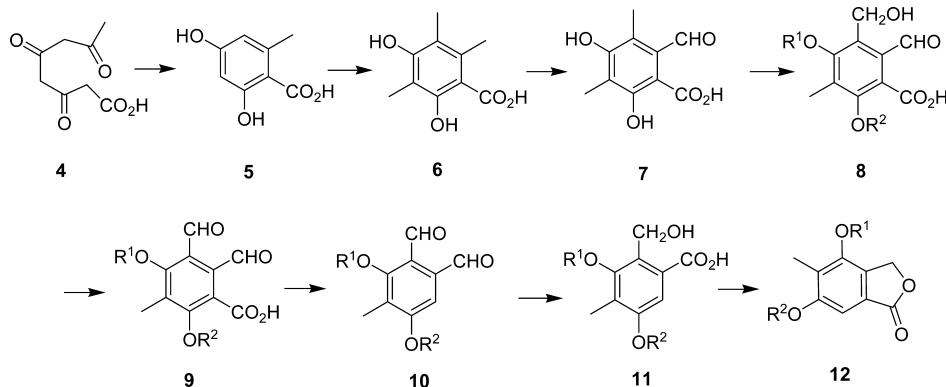


Figure 2. Representative examples of 3-unsubstituted natural phthalides.

Scheme 2. Representative Scheme of Biosynthesis for Isobenzofuranones



due to their wide range of pharmacological applications. The biological activities of this group of molecules are attributed to the lactone ring of the phthalide unit.⁸ In their work on synthetic monocyclic analogues of mycophenolic acid (3, Figure 1), Anderson et al. have shown that compounds lacking the lactone moiety are much less cytotoxic.⁸ To date, studies on the structure and activity relationships have been limited to NBP (2a).

1.1.3. Biosynthetic Studies. The biosynthesis of phthalides has been studied by different groups of scientists from time to time. The pathways for mycophenolic acid (3, Figure 1)^{9a} and vermistatin (28, Figure 2)^{9b} have been elucidated by labeling experiments, and isolation of different intermediates. In general, the biosynthesis of phthalide skeleton begins with tetraketide 4 (Scheme 2), which, in turn, is formed by the condensation of four acetic acid units by the iterative action of polyketide synthases (PKSs).^{9c} The tetraketide chain 4 then condenses to orsellinic acid 5 by various ketoreductases (KR), cyclases (CYC), and aromatases (ARO). Methylation, regiospecific oxidation, followed by decarboxylation produces dialdehyde 10 via 6–9. Phthalide 12 is thought to arise from 10 via 11 by an intramolecular Cannizzaro reaction.^{9d}

1.2. Classification and Bioactivities

The phthalide natural products, isolated between 1960 and early 2014, are presented below. The majority of them differ

from one another in the nature and pattern of substitutions, and their level of oxidations in the B ring. Dimeric forms of this core structure feature a few natural products. On the basis of the structural characteristics of phthalide units, they are generally classified into three categories:^{2a} (i) 3-unsubstituted phthalides, (ii) 3-substituted phthalides, and (iii) dimeric phthalides. In addition to these 3-categories, allied natural products and synthetic analogues are also appropriately presented.

1.2.1. 3-Unsubstituted Phthalides. Phthalides without a substituent at C-3 of the phthalide unit belong to this group. Some of the represented examples (13–20) are shown in Figure 2.

1.2.2. 3-Substituted Phthalides. (*S*)-3-Butylphthalide (2b, Figure 3) is the simplest and representative member of this group. Most of the natural phthalides belong to this group. Depending upon the nature of substituents at C-3, they are further classified into two groups, nonalkaloid phthalides (Figure 3) and alkaloid phthalides (Figure 4).

1.2.2.1. Nonalkaloid Phthalides. These constitute the most important subgroup (21–32, Figure 3) not only due to their abundance in nature, but also due to their potent pharmacological activities. There are about 80 natural products that have substituents at C3.

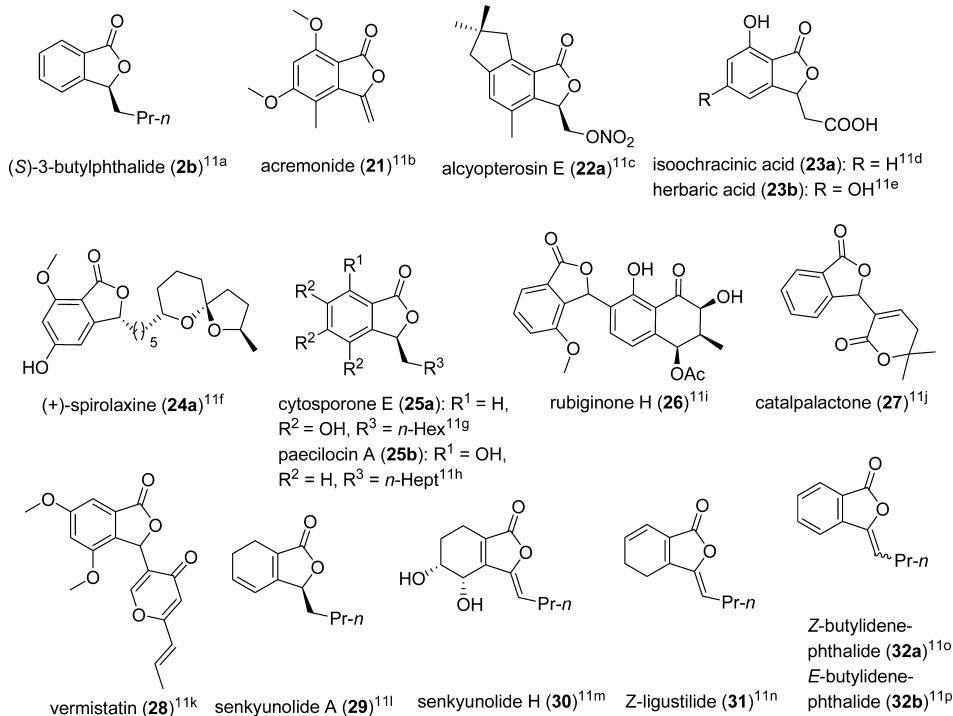


Figure 3. Representative examples of naturally occurring 3-substituted nonalkaloid phthalides.

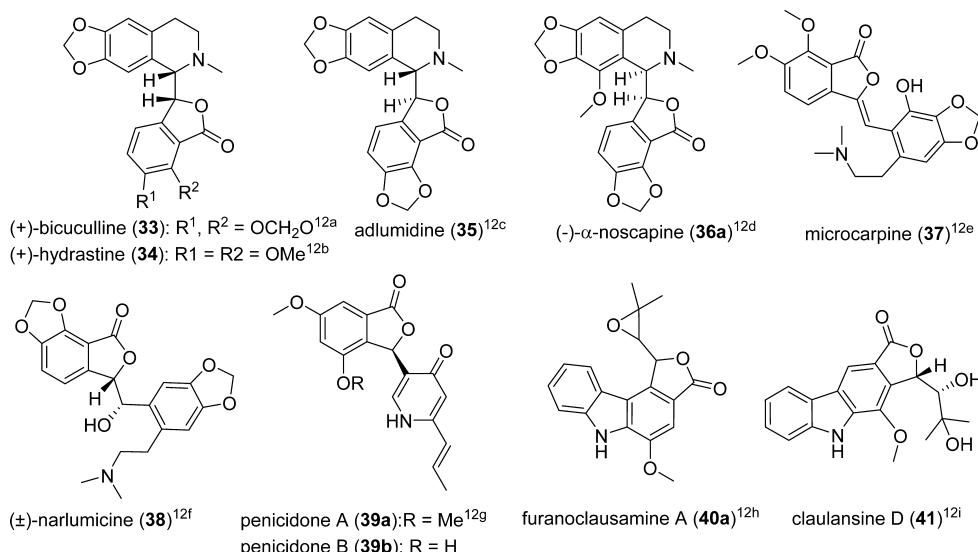


Figure 4. Representative members of alkaloid phthalides.

1.2.2. Alkaloid Phthalides. Phthalides containing isoquinoline moieties or nitrogen atom in their side chains, perhaps oldest in literature, belong to this group (33–41, Figure 4). The rare and recently isolated phthalide carbazoles, furano-clausamine A (**40a**) and claulansine D (**41**), are also included in this category.

1.2.3. Dimeric Phthalides. These members are viewed as Diels–Alder adducts or [2+2] cycloadducts products of monomeric 3-alkylidene phthalides. Selected dimeric phthalide natural products (**42**–**46**) are shown in Figure 5. For instance, sinaspriolide (**45**) and ansaspriolide (**46**) are dimeric derivatives of the monomeric ligustilide (**31**) and 3-butylidenephthalide (**32**), respectively.

1.2.4. Allied Natural Products. The 3-hydroxyphthalides (e.g., **47**–**49**, Table 1) are structurally similar to phthalides.

1.2.5. Synthetic Analogues. There have been reported a large number of synthetic phthalides, which have potential to be lead compounds in medicinal chemistry. Their chemical modifications are conceivable to enhance the promising pharmacological activities. The structures of such selected phthalides **51**–**55** along with their biological activities are presented in Table 2.

The structures of the naturally occurring phthalides isolated during 1960–2014 are presented in Table 3. Their sources and biological activities are also included in the table.

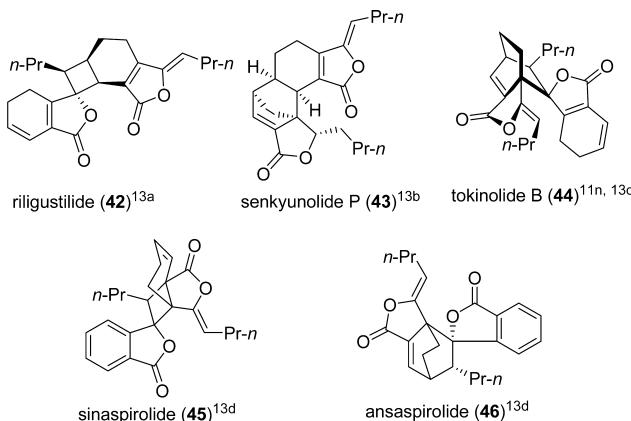


Figure 5. Representative examples of dimeric phthalides.

1.3. Synthetic Routes

From the synthetic perspective, phthalides have been studied in detail since 1980, and their chemistry has been reviewed in several publications.⁴⁶ Because of the wide range of biological activities as well as usefulness as important synthetic intermediates, many methods have been developed for the synthesis of isobenzofuranones, after the pioneering work by Wislicenus.^{46g} Although most of the industrial syntheses of simple phthalides rely on the oxidation of *o*-xylenes, the quest

for the synthesis of more complex phthalides and 3-substituted enantiopure phthalides has led to the development of newer methodologies. From an atomistic view, the strategies can be categorized into three groups. The first group consists of building the γ -lactone on a benzene ring or a cyclohexane ring. In the second category, the benzene ring of the phthalides is constructed on a γ -lactone. In the third group, both of the rings are concomitantly fabricated. Herein, we categorized them into nine different classes according to the key reactions utilized for accessing the phthalide framework. These are (i) lactonization, (ii) reduction of phthalic anhydrides and phthalaldehydic acids, (iii) oxidation, (iv) nucleophilic addition, (v) condensation, (vi) electrophilic and nucleophilic aromatic substitution, (vii) cyclocarbonylation, (viii) benzannulation/cycloaddition, and (ix) thermal and photochemical rearrangements and named reactions.

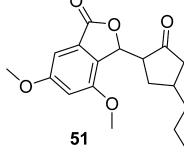
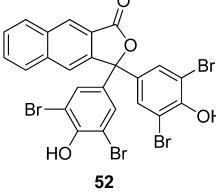
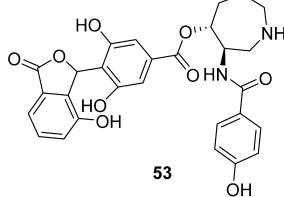
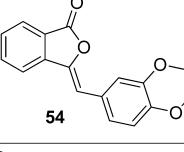
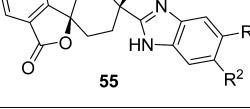
1.3.1. Cyclization of *ortho*-Functionalized Benzoic Acids and Derivatives. Lactonization of 2-(hydroxymethyl)-benzoic acids or their analogues is probably the most easily conceivable mode of formation of phthalides. In addition to the acid/base-catalyzed and thermal lactonization, several tandem methods are known, which we have termed oxidative lactonization and reductive lactonization. They are described in sections 1.3.1.1–1.3.1.3.

1.3.1.1. Redox-Neutral Lactonization. This category includes methods involving no change in oxidation levels^{47a} between the starting materials and phthalide products. The *o*-

Table 1. Structurally Analogous Natural Products

Sl. No	Structure and / or Trivial names	Sources	Bioactivity
1 ^{14a}	 (±)-Hypodermin B (47)	Isolated from the culture of the basidiomycete <i>Hypoderma radula</i> .	A potential drug leads for the treatment of asthma and chronic bronchitis as well as of heart and CNS illnesses.
2 ^{14b}	 Corollosporine (48)	Isolated from the marine fungus <i>Corollospora maritima</i> .	Shows antibacterial activity against <i>Staphylococcus aureus</i> and other microorganisms
3 ^{14c}	 Betolide (49)	Isolated from the above ground parts and roots of <i>Stachys</i> species and <i>Betonica</i> species	Not reported
4 ^{14d}	 Rubralide A (50a): R ¹ = Me, R ² = CHO Rubralide B (50b): R ¹ = H, R ² = CHO Rubralide C (50c): R ¹ = R ² = Me	Isolated from <i>Penicillium rubrum</i> .	Inhibits plant growth

Table 2. Synthetic Phthalides

Sl. No.	Structure	Bioactivity
1 ^{15a}		Strong inhibitor of RNA synthesis of P-388 leukemia cells
2 ^{15b}		Antibacterial activity with no in vitro toxicity
3 ^{15c}		Potent inhibitory activity against protein kinase C
4 ^{15d}		Anti-HIV activity
5 ^{15e}		Y5 receptor antagonists

hydroxymethyl benzoates readily undergo lactonization under weakly acidic or basic conditions. As an example, the Mukaiyama aldol-type condensation of *t*-butyldimethylsilyloxypyrrole **91** (Scheme 3) with methyl 2-formylbenzoate (**92**) furnished the aldol adduct **93** with high yield and stereoselectivity.^{47b} The adduct **93**, when subjected to treatment with SiO₂, preceded by hydrogenation transformed into enantioselectively pure phthalide **94**, an analogue of bicuculline alkaloids.

Intramolecular cyclization of *o*-alkynylbenzoic acid **95** is a useful route for the synthesis of 3-alkylenephthalides (Scheme 4). Different transition metal salts for example, Pd,^{48a} Ag,^{48b} Cu,^{48c} and I₂-complexes,^{48d} are reported to catalyze the reaction. Yet, the processes suffer from the formation of isomeric isocoumarins (e.g., **97**) as side products arising from 6-*endo* cyclization. The cyclization is regioselective in favor of phthalides furnishing **96**, when organic bases, for example, DBU, are used.^{48e,f} This trend is quite general for a large number of substrates. It is to be noted that, in this reaction, the starting materials **95** and the products **96** are of the same oxidation level.

Alkylidene phthalides can also be prepared from *o*-iodobenzoic acids (**98**) by reaction with monosubstituted alkynes in the presence of a palladium catalyst (Scheme 5).^{49a} The reaction produces isocoumarins only as minor products. The heteroannulation process was found to be general and stereospecific in favor of the Z-isomers **99**. Very recently, a similar transformation was reported for *o*-bromobenzoic acids

by the use of Pd/C–CuI–PPh₃ as a catalyst system in the presence of Et₃N in dioxane.^{49b}

When Stille coupling is used for the synthesis of *o*-alkynyl benzoates from tributylstannyll-2-iodobenzoate (**100**) utilizing tributylstannylacetylene (**101**), (*E*) - 3-(tributylstannylmethylidene)phthalide (**102**) is formed in situ (Scheme 6).⁵⁰ A second Stille coupling of the product **102** with different vinyl or aryl halides provides a range of alkylidene phthalides **103** with 58–77% yields.

Aryl alkynes **104** with *ortho*-Weinreb amide functionality, when activated by CuCl₂–NCS, allowed regioselective synthesis of 3-(chloroalkylidene)phthalides **105** via intramolecular cyclization (Scheme 7).⁵¹ A broad range of substituents and functional groups are tolerated under the reaction conditions. For the selective formation of the phthalides through 5-*exo*-dig cyclization, the Cu(II) catalyst plays a crucial role, where chlorocyclization was facilitated by NCS. However, the use of only NCS resulted in exclusive formation of six-membered products.

The only report on the phthalide formation from a nonactivated alkene was due to Washer et al.^{52a} *o*-Alkenylbenzoic acids **106**, when treated with Pd(hfacac)₂ and benziodoxolone-derived hypervalent iodine compound **107**, afforded 3,3-disubstituted phthalides **108** in high yields (Scheme 8). A similar reaction in the presence of I₂–KI–NaHCO₃ yielded 3,3-disubstituted phthalides via iodolactonization.^{52b}

Table 3. List of Phthalide Natural Products Isolated during 1960–2014

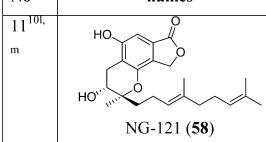
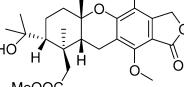
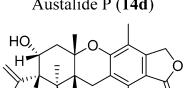
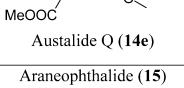
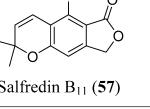
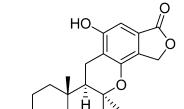
Sl. No	Structure and / or Trivial names	Sources	Bioactivity	Sl. No	Structure and / or Trivial names	Sources	Bioactivity
1 ^{10f}	Mycophenolic acid (3)	Species of <i>Penicillium</i> , including <i>P. brevicompactum</i> , <i>P. stoloniferum</i> , <i>P. viridicatum</i> etc.	Antineoplastic, antiparasitic, antiviral and immunosuppressive, anti-HIV activity. Potential drug to control prostate cancer.	11 ^{10l, m}		<i>Stachybotrys parvispora</i> F-4708	Effective against Alzheimer's disease
2 ^{10a}	Nigelactone (13)	Seeds of <i>Nigella glandulifera</i>	Not reported	12 ^{5a}	<i>n</i> -Butylphthalide (2a)	Plant species such as <i>Apium graveolens</i> , <i>Angelica sinensis</i> , <i>Levisticum chuanxiong</i> etc.	Anti-convulsant, anti-stroke and anti-proliferative activities. Inhibits arachidonic acid and collagen-induced aggregation of platelets. Reduces blood pressure.
3 ^{10b}	Australide M-O (14a-e)  Australide P (14d)  Australide Q (14e) 	Fungus <i>Aspergillus</i> sp., isolated from the mediterranean sponge <i>Tethya aurantium</i>	Cytotoxic against murine cancer cell line L5178Y	13 ^{11a}	(S)-3-Butylphthalide (2b)	<i>Cnidium officinale</i>	Adulticidal activity
4 ^{10c}	Araneophthalide (15) Phthalidochromene (16) 	<i>Anaphalis araneosa</i>	Not reported	14 ^{11b}	Acremonide (21)	Culture broth of endophytic fungus <i>Acremonium</i> sp. PSU-MA70, isolated from mangrove <i>Rhizophora apiculata</i> .	Antifungal activity against <i>C. albicans</i> and <i>C. neoformans</i>
5 ^{10k}		Fermentation broth of <i>Crucibulum</i> sp. RF-3817	Aldose reductase inhibitory activity	15 ^{11c}	Alcyopterosin E (22a)	Subantarctic soft coral <i>Alcyonium paessleri</i>	Toxic towards Hep-2 (human larynx carcinoma) cell line
6 ^{10d}	Djalonensin (17)	<i>Anthocleistu djalonensis</i>	Not reported	16 ^{11d}	(±)-Isoochracinic acid (23a)	Fungus <i>Cladosporium</i> sp. and parasitic fungus <i>Akrnariukukuchiana</i>	Anti-bacterial activity
7 ^{10e,f}	Taiwanin C (18a) Daurinol (18b)	18a: Root of <i>Acanthopanax chiisanensis</i> , a Korean medicinal plant; 18b: <i>Haplophyllum dauricum</i> (L.) G. Don (Rutaceae)	Inhibited prostaglandin E ₂ (PGE ₂) production. 18b: Anticancer, antitumor, and antidepressant	17 ^{11f}	(+)-Spirolaxine (24a)	Fungus <i>Sporotrichum laxum</i> .	Antitumour and active against <i>Helicobacter pylori</i> . Shows cholesterol lowering activity
8 ^{10g,h}	Variolaric acid (19a)	<i>Lecanora rupicola</i> (L.) Zahlbr.	Not reported	18 ^{11g}	Cytosporone E (25a)	Endophytic fungi <i>Cytospora</i> sp. and <i>Diaporthe</i> sp.	Antibacterial activity
9 ¹⁰ⁱ	Excelsione (19b)	<i>Knightia excelsa</i>	Cytotoxic against P388 murine leukemia cells	19 ^{11h}	Paecilomin A (25b)	Fungus <i>Paecilomyces variotii</i> , derived from the jellyfish <i>Nemopilema nomurai</i> 3089 and <i>Vibrio parahemolyticus</i> 7001	Inhibits pathogenic bacteria including <i>Staphylococcus aureus</i> 3089 and <i>Vibrio parahemolyticus</i> 7001
10 ^{10j}	Phomoarcherin A (20a) Kampanol A (20b)  Phomoarcherin B (20c)	Endophytic fungus <i>Phomopsis archeri</i>	20a-c: Cytotoxic against different cholangiocarcinoma cell lines, weak cytotoxicity against the KB cell line. 20c: Antimalarial activity against <i>Plasmodium falciparum</i>	20 ¹¹ⁱ	Rubiginone H (26)	Cultures of <i>Streptomyces</i> sp.	Inhibits the growth of Gram-positive bacteria and different tumor cell lines.
21 ^{11j}	Catalpalactone (27)	Japanese tree <i>Catalpa ovata</i>	Antitumour-promoting activity	22 ^{11k}	Vermistatin (28)	<i>Penicillium vermiculatum</i>	Antibiotic and antifungal. Suppresses the proliferation of leukemia P388 and EAC tumor cells.
23 ^{11l, m,q}	Senkyunolide A (29) Senkyunolide H (30)	<i>Cnidium Officinale</i> and <i>Ligusticum chuanxiong</i> Hort.	Antifungal and smooth muscle relaxing activities				

Table 3. continued

Sl. No	Structure and / or Trivial names	Sources	Bioactivity	Sl. No	Structure and / or Trivial names	Sources	Bioactivity
24 ¹¹ⁿ 1	Z-Ligustilide (31)	<i>Ligusticum Porteri</i> and <i>Ligusticum chuanxiong</i> Hort.	Sedative and relaxant agent	40 ^{10l} 17		60a: <i>Juticia prostrata</i> (Acanthaceae); 60b: Root of <i>Acanthopanax chiisanensis</i> (Araliaceae), a Korean medicinal plant	60a: Anticancer, antitumor, and antidepressant 60b: Inhibitor of prostaglandin E ₂ (PGE ₂).
25 ^{2a,l} 2m-o	Z-Butylenephthalide (32a) E-Butylenephthalide (32b)	32a: Plant species like <i>Angelica glauca</i> , <i>Levisticum officinale</i> etc. 32b: Wild celery (<i>kelussia odoratissima</i>)	32a: Sedative and relaxant for various smooth muscle cells. Shows anti-anginal and insecticidal activity. 32b: Wild celery (<i>kelussia odoratissima</i>)				
26 ^{12a}	(+)-Bicuculine (33)	<i>Fumaria capreokzta</i> L. and <i>Fumaria bella</i>	Potent GABA _A receptor antagonist, and used to block Ca ²⁺ -activated potassium channels	41 ^{18a}		<i>Aspergillus silvaticus</i>	Not reported
27 ^{12b}	(+)-Hydrastine (34)	Plant species <i>Corydalis rutifolia</i>	γ-Aminobutyric acid A (GABA _A) antagonist	42 ^{18b}		Marine fungus <i>Epicoccum sp.</i>	Antioxidant
28 ^{12c}	Adlumidine (35)	<i>Corydalis saxicola</i>	Anti HBV (<i>hepatitis B virus</i>) activities	43 ¹⁹		Culture broths of the endophytic fungus <i>Pestalotiopsis microspora</i>	Antifungal activity and acts as an antioxidant toward both superoxide radical and hydroxyl free radicals
29 ^{12d}	(-)-α-Noscapine (36a)	Plant species <i>Fumaria parviflora</i> , <i>Rauwolfia heterophylla</i> etc.	Anti-tussive agent and involved in σ-opioid receptor antagonism (Under phase I trial by Cougar Biotechnology)	44 ²⁰		Cultures of a hypovirulent strain of <i>Cryphonectria parasitica</i>	Inhibits the formation of tomato seedlings
30 ^{12e}	Microcarpine (37)	<i>Fumaria microcarpa</i> Boiss	Not reported	45 ²¹		Rhizomes of <i>Matteuccia orientalis</i> , a Chinese medicinal herb for the treatment of hemostatics and reliving ostalgia.	Not reported
31 ^{12f}	(±)-Narlumicine (38)	Stems of <i>Fumaria indica</i>	Not reported	46 ²²		Solid cultures of an isolate of <i>Pestalotiopsis foedans</i>	Antifungal
32 ^{12g}	Pencidone A (39a) Pencidone B (39b)	Culture of an endophytic fungal strain <i>Penicillium</i> sp.	Moderate cytotoxicity	47 ^{23a}		Mycelia solid culture of <i>Paecilomyces</i> sp. SC0924	Antifungal activity against <i>Peronophthora litchii</i>
33 ^{12h} j	Furanoclausamine A (40a) Furanoclausamine B (40b): R = Me Harmandianamine A (40c): R = H	40a,b: Stems of <i>Clausena anisata</i> 40c: Twigs of <i>Clausena harmandiana</i>	40a,b: Not reported 40c: Antibacterial activity	48 ^{23b}		Sapwood of <i>Quercus crispula</i> .	Not reported
34 ¹²ⁱ	Claulansine D (41)	<i>Clausena lansium</i> (Lour.)	Not reported				
35 ¹¹ⁿ 13a	Riligustilide (42)	Rhizomes of <i>Ligusticum porteri</i>	Not reported				
36 ^{13b}	Senkyunolide P (43)	<i>Cnidium officinale</i> , <i>Ligusticum chuanxiong</i>	Not reported				
37 ¹¹ⁿ 13c	Tokinolide B (44)	Rhizomes of <i>Ligusticum porteri</i>	Sedative, spasmolytic				
38 ^{13d}	Sinaspirolide (45) and Ansaspirolide (46)	Roots of <i>Angelica sinensis</i>	Serotonergic activity				
39 ¹⁶		Lichens <i>Huemutomma coccineum</i> (Dicks.) Korb. and <i>H. porphyrium</i> (Pers.) Zopf.	Not reported				

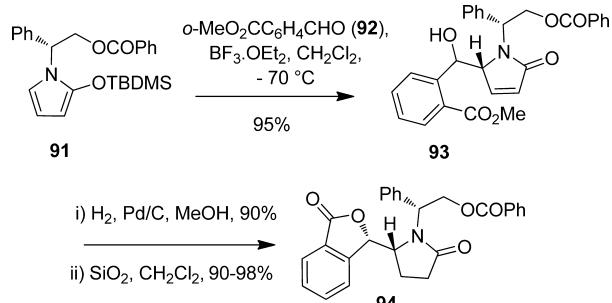
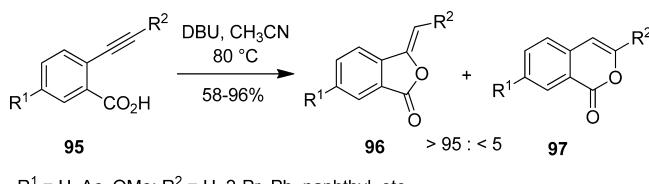
Table 3. continued

Sl. No	Structure and / or Trivial names	Sources	Bioactivity	Sl. No	Structure and / or Trivial names	Sources	Bioactivity
49 ²⁴		Endophytic fungus <i>Pestalotiopsis virgatula</i>	Cytotoxic against HeLa cells.	57 ^{22a,b}		<i>Streptomyces</i> sp. B-412	Inducers for fruiting-body formation of basidiomycete <i>Polyporus arcularius</i>
50 ²⁵		<i>Aigialus parvus</i> BCC 5311	Not reported	58 ³³		<i>Dermacoccus abyssi</i> sp.	Cytotoxic against K562 (human chronic myelogenous leukemia) cancer cell line
51 ²⁶		Celery seed (fruits of <i>Apium graveolens</i> L.)	A diuretic for bladder and kidney complaints and adjuvant in arthritic and rheumatic conditions.	59 ³⁴		<i>Ceropagia juncea</i>	Tranquillising, hypotensive and local anaesthetic activities
52 ²⁷		Ascomycete <i>Daldinia concentrica</i>	Anti-HIV-1	60 ³⁵		Bark of <i>Xanthoxylum arnottianum</i> maxim	Not reported
53 ²⁸		Ascomycete fungus <i>Cytospora</i> sp.	Not reported	61 ³⁶		<i>Alternaria tenuis</i>	Not reported
54 ²⁹		Soil fungus <i>Oidiodendron griseum</i> .	Anti-HIV	62 ³⁷		Danshen, a traditional Chinese medicine consisting of <i>Salvia miltiorrhiza</i> .	Used to treat renal failure, heart disease, and strokes
55 ³⁰		<i>Eleutherine bulbosa</i>	Not reported	63 ³⁸		Leaves and stem of a popular vegetable <i>Chrysanthemum coronarium</i>	Plant growth inhibiting activity
				64 ³⁹		Rhizomes of <i>Typha capensis</i>	Traditional medicine for venereal diseases, dysmenorrhea, diarrhoea, dysentery etc

Table 3. continued

Sl. No	Structure and / or Trivial names	Sources	Bioactivity	Sl. No	Structure and / or Trivial names	Sources	Bioactivity
65 ^{40a} ^b	 Isosalvipuberulin (84a): X ₁ = CH ₂ , X ₂ -X ₃ = CH=CH Dugesin B (84b): X ₁ -X ₂ = CH=CH, X ₃ = CH ₂ 	84a and 85 : <i>Salvia tiliifolia</i> and <i>Salvia puberula</i> 84b : <i>Salvia dugesii</i>	Not reported	67 ⁴²	 (+)-3a-[4'-methoxybenzyl]-5,7-dimethoxyphthalide (87a) (-)-3a-[3'-Methoxy-4',5'-methylenedioxybenzyl]-5,7-dimethoxyphthalide (87b)	<i>Frullania</i> sp.	Cytotoxic against human promyelocytic leukemia (HL-60) and human pharyngeal squamous carcinoma (KB) cell lines.
66 ⁴¹	 Marilone A (86a): R ¹ = P ¹ Marilone B (86b): R ¹ = H Marilone C (86c): R ² = P ¹ Silvaticol (86d): R ² = H P ¹ =	Marine-derived fungus <i>Stachyliidium</i> sp.	86a : antiplasmodial activity against <i>Plasmodium berghei</i> 86b : antagonistic activity towards the serotonin receptor 5-HT2B	69 ⁴⁴	 89	<i>Euryops hebecarpus</i>	Not reported
70 ^{45a} ^b				70 ^{45a} ^b	 90a	Endophytic fungus <i>Colletotrichum</i> sp. CRI535-02	Cytotoxic toward the HepG2 cell line and potent antioxidant
71 ^{45c}				71 ^{45c}	 chrysoarticulin C (90b)	Culture broth of <i>leptosphaeria</i> sp.	Antifungal activity
						Culture broth of <i>Chrysosporium articulatum</i>	Active against sortase A, a bacterial transpeptidase.

Scheme 3. Synthesis of 3-Pyrrolidinyl Phthalide

Scheme 4. 3-Alkylidene Phthalides from *o*-Alkynylbenzoic Acids

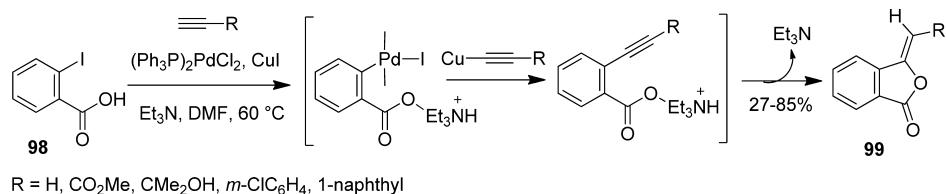
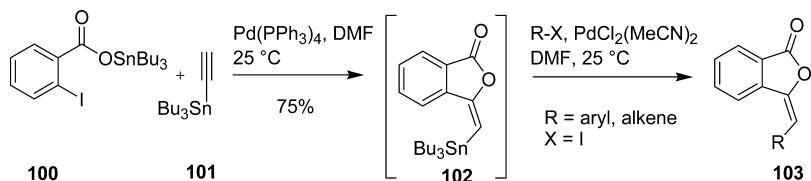
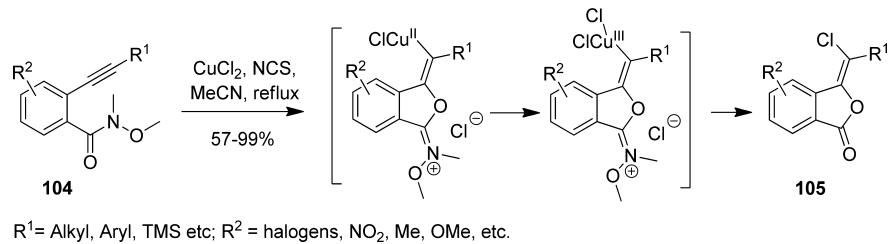
A Cannizzaro-type reaction, involving ruthenium hydride-catalyzed lactonization of dialdehydes (e.g., **109**), constitutes an atom-economic route to 3-unsubstituted phthalides (e.g., **110**) (Scheme 9).^{53a} The intramolecular addition of the initial

alkoxy–ruthenium complex to the carbonyl group is assumed to be the key step in the lactonization. Naphthalene dialdehyde and some keto aldehydes also responded to the reaction.

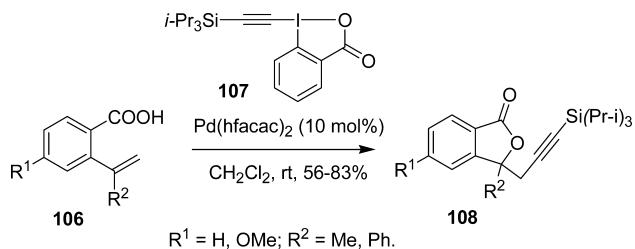
Tischenko reaction^{53b,c} of *o*-dialdehydes (e.g., **109**, Scheme 9) in the presence of $M[N(SiMe_3)_2](THF)_2$ in C_6H_6 at room temperature also provides a general route to phthalides (e.g., **110**). Among different catalysts, amides of heavier alkaline earth metals (Ca, Sr, Ba) are most useful for the reaction.

In 2012, Schmalz's group reported a phthalide formation from *ortho*-formylarylketones **111** through a Cannizarro–Tischenko type reaction (Scheme 10).⁵⁴ Treatment of **111** with a catalytic amount of NaCN in DMSO furnished 3-arylphthalides **114**. Mechanistically, the reaction involves preferential attack of $\text{^}{\text{-}}\text{CN}$ at the aldehyde group of **111** forming intermediate **112**, which then undergoes an intramolecular hydride transfer to form an alkoxide intermediate **113**. Finally, *S*-*exo*-trig attack of the alkoxide at the carbonyl function of **113** allows the lactone ring formation with the release of the catalyst. The generality of the method was established by reaction with a range of *ortho*-acylbenzaldehydes. Application of the methodology in the total synthesis of pestalalactone is described in section 1.3.1.4.

As reported by Willis, *ortho*-formylarylketones **115** can also be converted into enantiomerically enriched phthalides (e.g., **117**) via hydroacylation reaction (Scheme 11) with a Rh-catalyst in the presence of duanphos ligand **116** and a Ag-salt (Scheme 11).⁵⁵ Although overall redox-neutral, these trans-

Scheme 5. Heteroannulation of Aryl Acetylene Leading to 3-Alkylidenephthalides**Scheme 6. Regio- and Stereoselective Synthesis of γ -Alkylidenephthalides via Stille Coupling****Scheme 7. Regioselective Synthesis of 3-(Chloromethylene)phthalides**

$\text{R}^1 = \text{Alkyl, Aryl, TMS etc}; \text{R}^2 = \text{halogens, NO}_2, \text{Me, OMe, etc.}$

Scheme 8. Phthalides via Oxyalkynylation of Styrenes

formations involve both reduction and oxidation of the carbonyl groups giving phthalides in excellent yields with varying ee. The formation of an intermediate complex, for example, 118, with a vacant coordination site was proposed. Enantioselectivity, yield, and reaction rate largely depend upon the counterion (BF_4^- , NO_3^- , MsO^- , TfO^-). Counterions with more coordinating ability result in higher enantioselectivities. The change of R^2 from Me to Et increased the reaction time by 2-fold.

That a sulfone group renders the α -carbon more electrophilic under Lewis acidic conditions has been known from the seminal work^{56a} of Trost and Ghadiri, and the resulting chemistry has been exploited in organic synthesis.^{56b,c} Such a property has been harnessed by Thirumamagal and Narayanasamy for the lactonization of the sulfone acids 119 to the

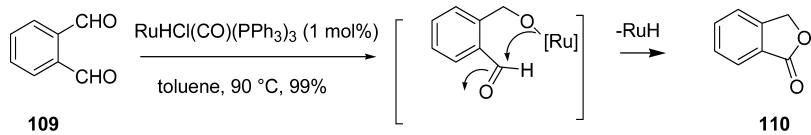
corresponding phthalides 120 by the action of *ortho*-phosphoric acid (Scheme 12).^{56d} However, microwave-assisted transformation of 119 to 120 gave higher yields in shorter reaction time.

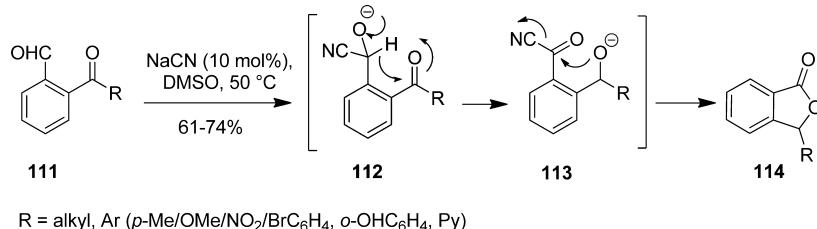
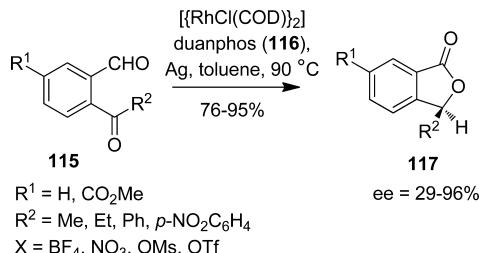
Thermal decomposition of ethyl ω -bromo *o*-toluates is a classical method for the convenient preparation of phthalides.^{57a} Mal and Karmakar recently applied the method in their synthesis of functionalized phthalide 123 (Scheme 13).^{57b} NBS bromination of toluate 121 under refluxing CCl_4 followed by thermolysis of the resulting benzylic bromo compound 122 by heating neat at 160°C furnished lactone 123 via elimination of CH_3Br .

Kraus et al. also adopted the strategy⁵⁸ for the synthesis of 3-functionalized phthalides. Cyanotoluolate 125, prepared by NBS bromination of 124, cyclized to cyanophthalide 126 (Scheme 14) on heating.

1.3.1.2. Oxidative Lactonization. It is one of the most classical and effective ways of forming a phthalide motif. Recent entry to phthalides via oxidative lactonization is found to comprise dihydroxylation and metal-catalyzed C–H activation. Oxidative cyclizations of *ortho*-alkynylbenzaldehydes, 1,2-benzenedimethanol, and *o*-alkyl aromatic carboxylic acid/ester are also well-established strategies.

Dihydroxylation protocol⁵⁹ en route to phthalides is appropriately illustrated by the synthesis of (−)-3-butyl-7-hydroxypthalide (130, Scheme 15) by Ohzeki and Mori. The

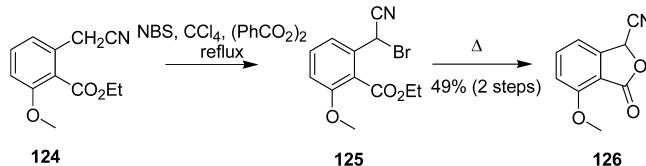
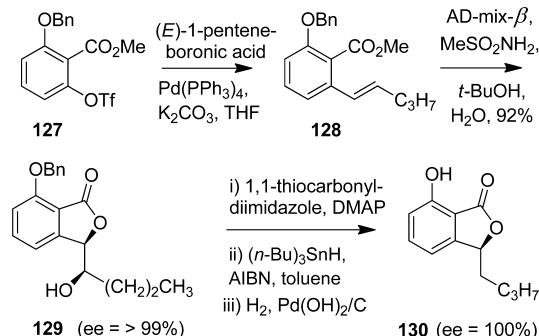
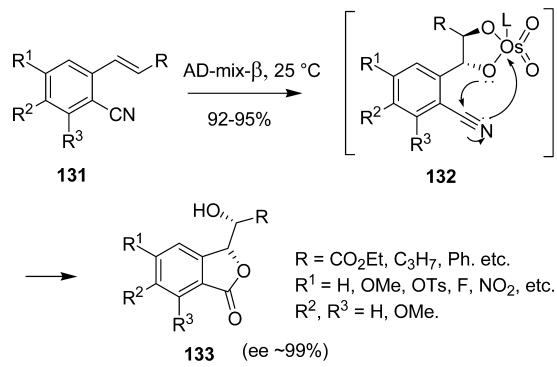
Scheme 9. Intramolecular Lactonization of *o*-Phthalaldehyde

Scheme 10. Schmalz Synthesis of 3-Substituted Phthalides from 2-Formylketones**Scheme 11.** Enantioselective Synthesis of Phthalides via Ketone Hydroacylation**Scheme 12.** Synthesis of 3-Alkylphthalides from Sulfonylethyl Benzoic Acids

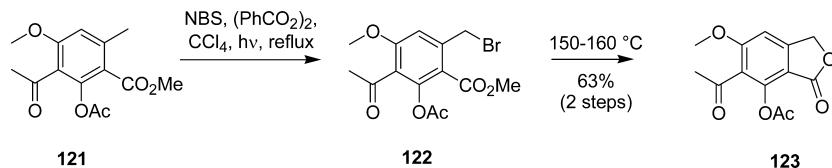
Sharpless asymmetric dihydroxylation of **128**, derived from **127**, using AD-mix- β , MeSO₂NH₂ in *t*-BuOH produced the phthalide **129** via an in situ intramolecular cyclization. Barton deoxygenation followed by Pearlman hydrogenation yielded phthalide **130** with 100% ee.

A similar strategy⁶⁰ when applied to *o*-cyano cinnamates and styrene derivatives **131** resulted in the construction of chiral phthalides **133** via intermediate **132** (Scheme 16). This protocol has subsequently been employed in the asymmetric synthesis of natural products, (+) and (−)-matteuen C (65b,c) (see section 1.3.1.4).

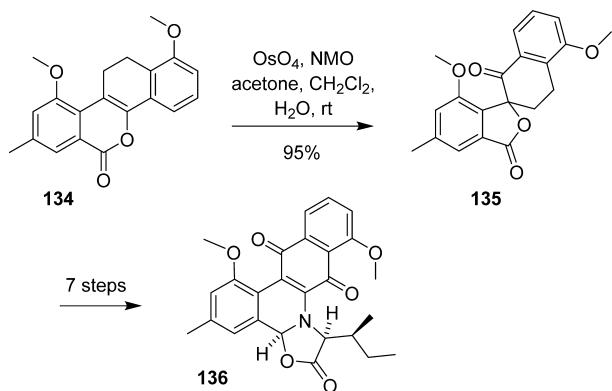
Ishikawa synthesis of dimethyl jadomycin (**136**) required a spirophthalide intermediate, that is, **135**.⁶¹ This was prepared

Scheme 14. Kraus Approach to 3-Cyanophthalide**Scheme 15.** Ohzeki and Mori Synthesis of (−)-3-Butyl-7-hydroxyphthalide**Scheme 16.** Asymmetric Dihydroxylation-Lactonization Route to Phthalides

from **134** by OsO₄-promoted dihydroxylation in the presence of *N*-methylmorpholine *N*-oxide (NMO) followed by in situ lactonization (Scheme 17).

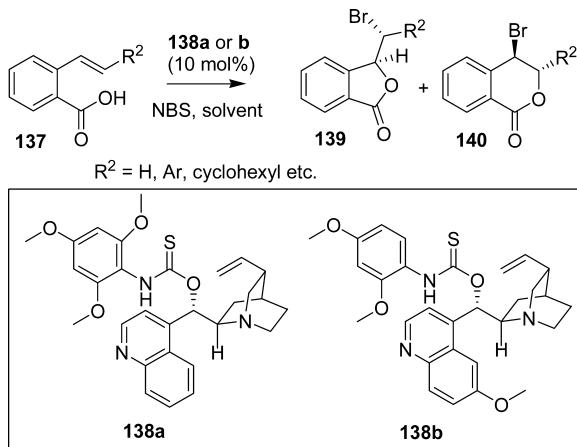
Scheme 13. Synthesis of an Isobenzofuranone via Thermolysis of a Bromomethylbenzoate

Scheme 17. Dihydroxylation-Mediated Synthesis of a Spirophthalide



Bromolactonization^{62a} of *ortho*-alkenylbenzoic acids 137 in the presence of amino-thiocarbamates 138a,b yielded chiral 3-substituted phthalides 139 (Scheme 18) with good yields and

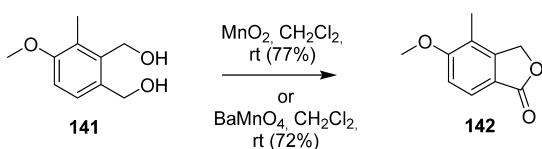
Scheme 18. Bromolactonization Route to Chiral 3-Substituted Phthalides



ee's, along with 3,4-dihydroisocoumarins 140. Although the mechanism is not well understood, it is apparent that the 6-methoxy group of quinine moiety of the catalyst 138b has some influence on the mode of cyclization and ee. The catalyst 138a gives better yield and ee of the product as compared to 138b. Recently, Rueping's group has developed Selectfluor-promoted fluorolactonization of 2-vinylbenzoic acids for the synthesis of fluorine-containing phthalides.^{62b} In the presence of a catalytic amount of (DHQ)₂PHAL, asymmetric induction has been observed. With *m*-CPBA-*p*-TSA at room temperature, *ortho*-alkenylbenzoic acids lead to 3-alkyldinephthalides.^{62c}

Treatment of phthalyl alcohol 141 with activated manganese dioxide or barium manganate gave phthalide 142 (Scheme 19) in good yields, through preferential oxidation of the unhindered

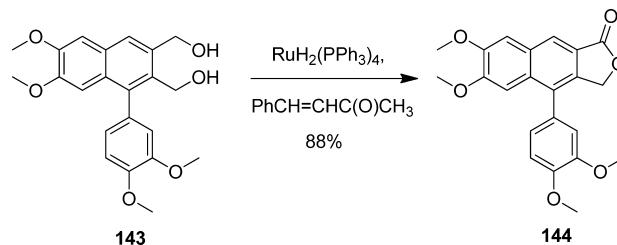
Scheme 19. MnO₂ Oxidation of Phthalyl Alcohols to Phthalides



hydroxymethyl group.⁶³ The methodology is applicable to a variety of substituted phthalyl alcohols. Substrates having substituents (Me or OMe) *ortho* to both of the hydroxymethyl groups give a mixture of phthalides through oxidation at both sites. Such oxidations are also known with Cp*Ir.^{63c}

Similar reactions can also be carried out using Au, Cu, W, or Ru catalyst with good yields and regioselectivity.^{64a–c} For an example, dehydrogenative lactonization^{64d} of biaryl 143, using RuH₂(PPh₃)₄ in the presence of a α,β -unsaturated carbonyl as hydrogen acceptor, provides biaryl phthalide 144, regioselectively (Scheme 20).

Scheme 20. Ru-Catalyzed Dehydrogenative-Lactonization Route to a 3-Unsubstituted Phthalide



N-Heterocyclic carbenes, derived from 148 (Scheme 21), have been shown to induce oxidative lactonization via dual activation of *o*-alkynylbenzaldehydes 145 under aerobic conditions to produce 3-alkyldenephthalides (e.g., 146) in stereo- and regioselective manner (Scheme 21).^{65a} The unactivated alkyne moiety acts as an internal electrophile for the lactonization. The substituents *para* to the alkyne moiety have no prominent effect on reactivity. Yet, the electron-donating groups (R²) *para* to aldehyde retard the reaction. However, the regioselectivity and yields are strongly controlled by the alkyne terminus (R³). In general, 5-*exo*-dig cyclizations leading to phthalides are predominant. Yet, *n*-butyl and TMS-substituted alkynes produce the isocoumarins, for example, 147, as major side products.

The proposed mechanism (Scheme 22) involves initial nucleophilic addition of the *in situ* generated NHC species (derived from deprotonation of the heteroazolium salt) to the aldehyde functionality generating an alkoxyde intermediate, which undergoes an intramolecular nucleophilic attack to the *o*-alkyne moiety activated by DBU-H⁺. Molecular oxygen in air plays an essential role as a source of oxidant for the oxidation of the aldehyde carbon to the corresponding lactonic carbon.

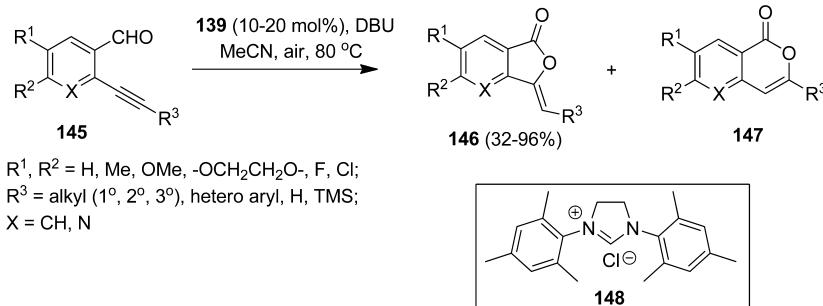
Reaction using NaClO₂-NaH₂PO₄ with similar *o*-alkynylbenzaldehydes also produced 3-alkyldenephthalides regioselectively.^{65b}

There are several reports on the direct synthesis of phthalides via aromatic C–H bond activation. Ackermann's group first introduced Ru(II)-catalyzed formation of 3-alkylphthalides 151 through cross-dehydrogenative alkenylation^{66a} of benzoic acids 149 and alkenes 150 followed by an intramolecular oxa-Michael reaction (Scheme 23). Cu(OAc)₂ acts as the co-oxidant.

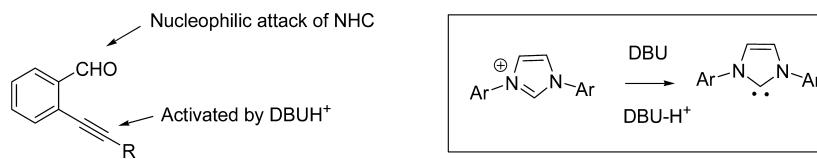
An early report^{66b} by Miura et al. showed that reactions of aromatic carboxylic acids with styrene under palladium catalysis (Pd(OAc)₂, Cu(OAc)₂·H₂O, MS 4 Å, DMF, 100 °C) efficiently produce 3-alkyldenephthalides (14–55%).

In 2009, Yu et al. reported a monoselective alkylation-lactonization reaction of benzoic acids 152 with dibromo-methane for the formation of phthalides 153 (Scheme 24).⁶⁷ Alkylation of C–H bonds takes place *ortho* to COOH in the

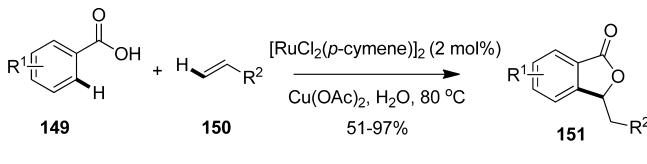
Scheme 21. NHC-Catalyzed Synthesis of 3-Alkylidenephthalides



Scheme 22. Probable Mechanism: NHC-Catalyzed Dual Activation of Two Functionalities

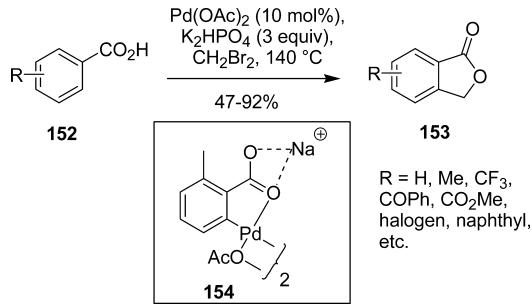


Scheme 23. Rh-Catalyzed Alkenylation Route to 3-Substituted Phthalides



R¹ = alkyl, aryl, halogen; R² = CO₂Et, CN, etc.

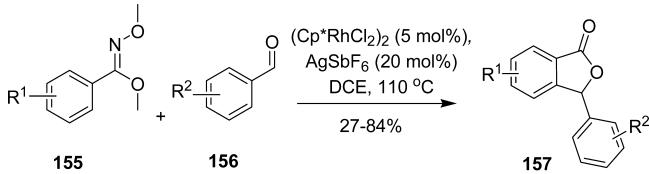
Scheme 24. Yu Lactonization via C–H Bond Alkenylation



presence of Pd(II)-catalyst and K₂HPO₄ as a base. Dibromo-methane as the alkylating agent gave higher yields and also showed greater substrate scope as compared to dichloromethane. Electron-withdrawing halogens, trifluoromethyl, keto, and ester groups are well tolerated. The exclusive mono-selectivity at the less hindered *ortho*-position was explained by the rapid lactone formation of arylpalladium species 154. The reaction produces phthalides with no substituent at C3.

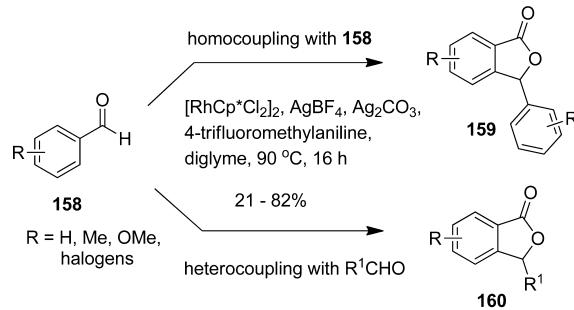
Transition metal-catalyzed C–H activation followed by nucleophilic addition to aldehydes is another potentially useful route to access biologically important phthalides. Bergman et al. showed that Rh(III)-catalyzed C–H bond activation of benzimidates 155 and its subsequent addition to aldehydes 156 furnished 3-arylphthalides 157 in one pot with high yields (Scheme 25).⁶⁸ Herein, the imidate serves as a directing group for the *ortho* C–H bond activation as well as cyclization of the intermediate alcohol. The reaction is also applicable to aliphatic aldehydes. Replacement of N-methoxy group with electron-deficient aryl groups provides higher yields.

Scheme 25. Benzimidates to Phthalides

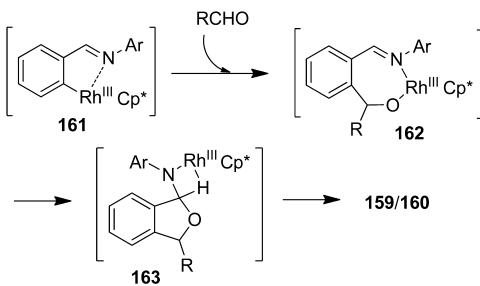


In 2013, a Rh(III)-amine dual catalysis has been reported to produce C3-substituted phthalides, involving a cascade *ortho* C–H activation-insertion-annulation sequence in the presence of [RhCp*Cl₂]₂, AgBF₄, Ag₂CO₃, and 4-trifluoromethylaniline (Scheme 26).⁶⁹ The reaction gave several functionalized aryl and alkyl phthalides (e.g., 159 and 160) in moderate to high

Scheme 26. Rh(III)-Amine-Catalyzed Oxidative Coupling of Aldehydes Leading to Phthalides



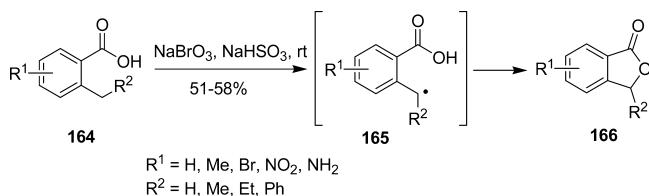
Proposed reaction mechanism



yields through homo- and heterocoupling. The proposed mechanistic cycle involves insertion of Rh(III) species in the *ortho*-position of an in situ generated imine to form intermediate **161**, which attacks a second aldehyde to give **162**. Intramolecular nucleophilic attack of the alkoxy oxygen of **162** on the electrophilic imine carbon gives **163**, which upon β -hydride elimination and hydrolysis provides the phthalide.

Lateral oxidation⁷⁰ of *o*-alkylaromatic carboxylic acids is an important avenue to 3-substituted phthalides. Treatment of benzoic acids **164** with sodium bromate and sodium bisulfite in a two-phase solvent system at room temperature produced phthalides **166** in one-pot operation with moderate to good yields (Scheme 27). The reaction possibly proceeds through

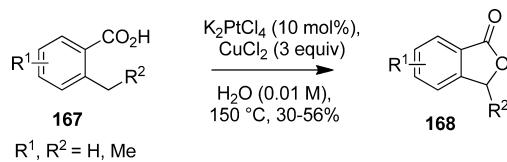
Scheme 27. Oxidative Cyclization of *o*-Alkylbenzenecarboxylic Acids to Phthalides



benzylic bromination of **164** initiated by bromine radical generated in the reaction medium from HOBr, giving **165**. Subsequent ring closure of intermediate **165** produces **166**. The reaction is inefficient with substrates substituted with electron-donating groups.

An entry to phthalides is achieved by Pt-catalyzed oxidative lactonization of *o*-alkyl aromatic carboxylic acids.⁷¹ Reaction of **167** (Scheme 28) with $\text{K}_2\text{PtCl}_4-\text{CuCl}_2$ furnished phthalides

Scheme 28. Phthalides via C–H Activation of *o*-Alkylaromatic Carboxylic Acids

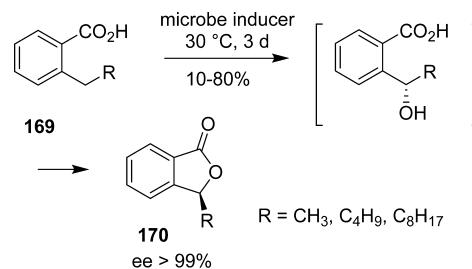


168 in moderate yields. The reaction is assumed to proceed via the chelation of the metal catalyst with the acid functionality and subsequent sp^3 C–H bond activation. Ester, amide, or cyanide derivatives of similar acids also give phthalides in presence of Pd-catalysts.

Oxidative cyclization with $\text{Ag(I)}-\text{Cu(II)}$ reagents^{72a} or hypervalent iodine reagents^{72b–d} is also known for the conversion of *o*-alkylaromatic carboxylic acids to phthalides. Kita's method^{72c} for 3-substituted phthalides using hypervalent iodine reagent such as PhI(OAc)_2 , and KBr , proceeds via benzyl radical intermediates as with CuCl_2 -peroxydisulfate ($\text{Na}_2\text{S}_2\text{O}_8$)^{72e} mediated oxidation (48–85%). Treatment of methyl 3-bromo-2-methylbenzoate with CrO_2Cl_2 in refluxing CCl_4 directly furnished the corresponding phthalide in 75% yield via Etard reaction.^{72g}

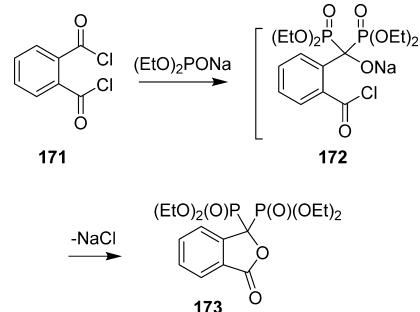
Enzymatic phthalide formation was discovered by Kitayama during the asymmetric hydroxylation⁷³ at benzylic position of 2-alkylbenzoic acids **169** by using *Pseudomonas putida* or *Aspergillus niger* in the presence of an inducer (e.g., *o*-toluic acid) (Scheme 29). Although 3-alkylphthalides **170** were produced in low yields, the enantiomeric excess was >90%.

Scheme 29. Microbial Oxidative Synthesis of 3-Alkylphthalides



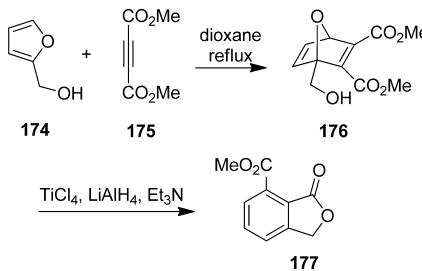
1.3.1.3. Reductive Lactonization. Phthalide-3-phosphonates (e.g., **173**) are of importance due to their bioactivity and usage as important drugs. The synthesis of these types of phthalides has been accomplished via intramolecular reductive cyclization⁷⁴ (Scheme 30). The reaction of phthaloyl dichloride **171** with sodium diethyl phosphite furnished phthalide bisphosphonate **173** via **172**.

Scheme 30. Synthesis of Phthalide 3-Bisphosphonate



Wong's approach^{75a} (Scheme 31) entails a strategy based on the Diels–Alder reaction. The adduct **176** derived from furfuryl

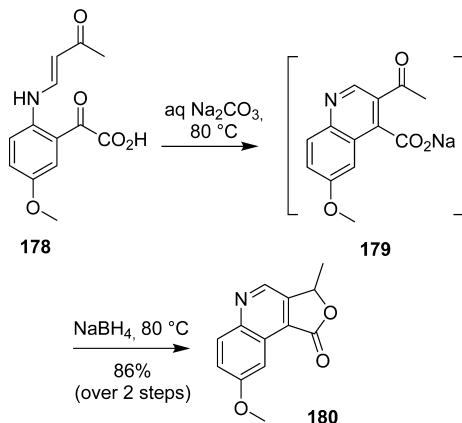
Scheme 31. Wong Diels–Alder Approach to Phthalides



alcohol (**174**) and dimethyl acetylene dicarboxylate (**175**) was deoxygenated with $\text{LiAlH}_4-\text{TiCl}_4$ to produce *o*-hydroxymethylbenzoate, which, in turn, cyclized to the corresponding phthalide **177**. Ring-opening followed by *in situ* aromatization of **176** was also affected by $\text{IrCl}_3-3\text{H}_2\text{O}$.^{75b}

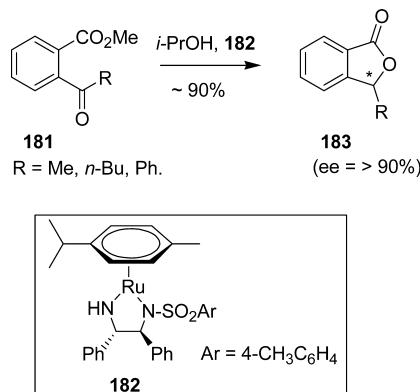
A similar strategy was also applied by Hodge for accessing 3-arylphthalide.^{75c} The use of dihalomaleic anhydrides in Diels–Alder reaction is also known for the synthesis of phthalide of type **177**.^{75d}

The keto carboxylate intermediate **179**, derived from **178** via Friedlander quinoline synthesis, was reduced with NaBH_4 to furnish the angularly fused phthalide **180** in 86% overall yield (Scheme 32).⁷⁶

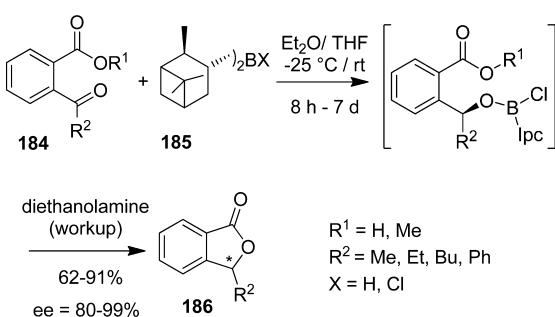
Scheme 32. Nicolaou Synthesis of Quinoline Phthalide

Reductive lactonization of *ortho*-formyl benzamides to phthalides is accomplished by the use of NaBH_3CN as demonstrated in the total synthesis of (\pm)-methyl ether of NG-121 (58).⁷⁷

Enantioselective hydrogenation of prochiral *ortho*-acyl benzoates **181** by chiral ruthenium catalyst **182** permits direct synthesis of optically active 3-substituted phthalides **183** in high yields (Scheme 33).⁷⁸ The driving force for the enantioselectivity of the reaction is the steric bias created by the substituents flanking the keto group in **181**.

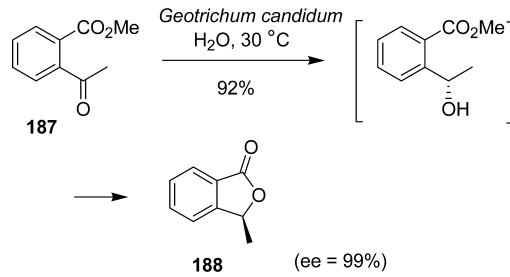
Scheme 33. Asymmetric Transfer Hydrogenation for the Synthesis of 3-Substituted Phthalides

Brown et al. used similar reactions with boron complexes of type Ipc_2BX **185** to produce phthalides in high enantiomeric excess (Scheme 34).^{79a} So, asymmetric reduction of *o*-(1-

Scheme 34. Brown Asymmetric Synthesis of 3-Alkylphthalides

oxoalkyl)methylbenzoates/benzoic acids **184** with diisopinocampheylborans **185** produced a range of 3-substituted phthalides with 80–99% ee. A similar transformation was also observed with chiral oxazolidinone catalyst induced by SmI_2 .^{79b}

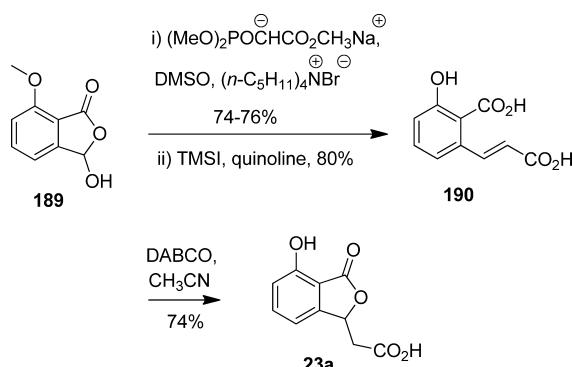
Similarly to microbial hydroxylations (Scheme 29), microbial hydrogenation⁷³ has been found to be effective for the transformation shown in Scheme 35. Asymmetric hydro-

Scheme 35. Kitayama Asymmetric Synthesis of 3-Alkylphthalide

genation of methyl 2-acetylbenzoate (**187**) by *Geotrichum candidum* gave (*S*)-3-methylphthalide (**188**) in 92% yield and 99% ee. Reduction of 2-acetylbenzonitrile by Baker's yeast also gave **188**.⁸⁰

1.3.1.4. Applications in Total Synthesis. The utility of various lactonization protocols in the total synthesis of phthalide natural products is illustrated in this section.

1.3.1.4.1. (\pm)-Isoochracinic Acid (23a). An example of redox-neutral lactonization is found in the synthesis of (\pm)-isoochracinic acid (**23a**, Scheme 36).⁸¹ *o*-Carboxyacrylic

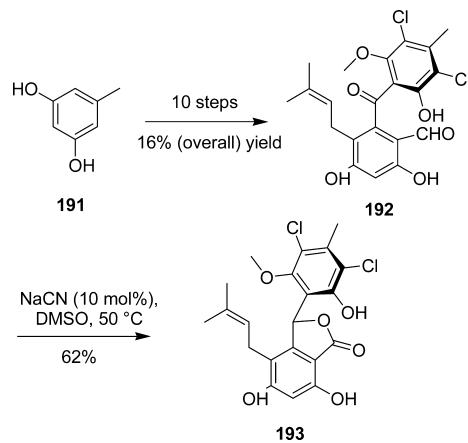
Scheme 36. Synthesis of (\pm)-Isoochracinic Acid

acid **190**, obtained from the corresponding phthalaldehydic acid **189** by Horner–Wardsworth–Emmons reaction followed by *O*-demethylation with TMSI, underwent lactonization in the presence of DABCO at 0 °C to yield phthalide **23a**, the overall yield being 44% from 3-methoxybenzyl alcohol.

1.3.1.4.2. (\pm)-Pestalalactone (193). In Schmalz synthesis, pestalone **191**, obtained from **191**, was treated with NaCN (cat.) in DMSO to furnish *rac*-pestalalactone (**193**) in 62% yield (Scheme 37).⁵⁴

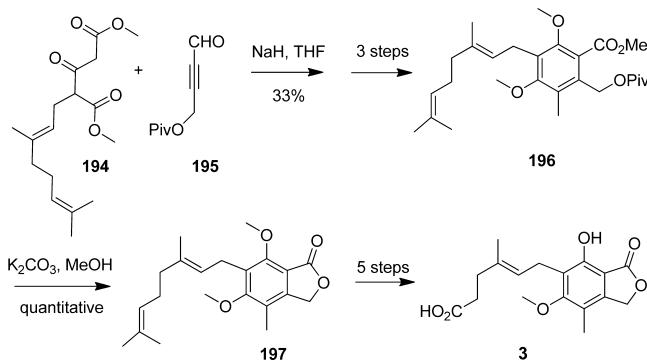
1.3.1.4.3. Mycophenolic Acid (3). Covarrubias-Zuniga's approach⁸² relied on the synthesis of hydroxymethyl benzoate precursors **196** for the regiocontrolled synthesis of mycophenolic acid (3). Michael-induced intramolecular Dieckmann condensation of **194** and **195** was the key step (Scheme 38). Lactonization of **196** by hydrolytic cleavage followed by acid

Scheme 37. Schmalz Synthesis of Pestalactone via Redox-Neutral Lactonization



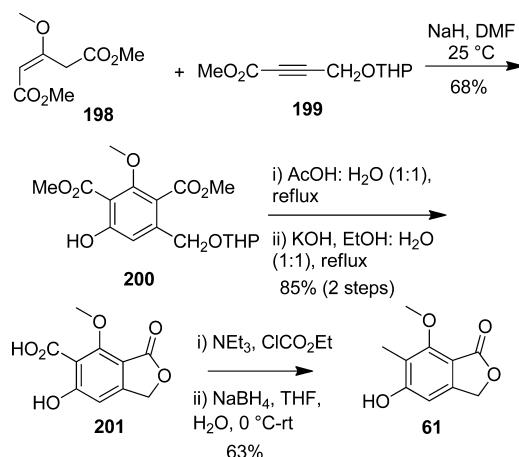
workup gave phthalide **197**, which on further chemical transformations produced mycophenolic acid (**3**).

Scheme 38. Total Synthesis of Mycophenolic Acid



1.3.1.4.4. Nidulol (61). A highly efficient three-step total synthesis⁸³ of the bioactive fungal metabolite nidulol (**61**, Scheme 39) was reported from a trisubstituted resorcinol derivative **200** via **201**. As described earlier in Scheme 38, compound **200** was prepared from aliphatic precursors (**198** and **199**) via a tandem Michael addition–Dieckmann cyclization sequence in one pot. Under hydrolytic conditions,

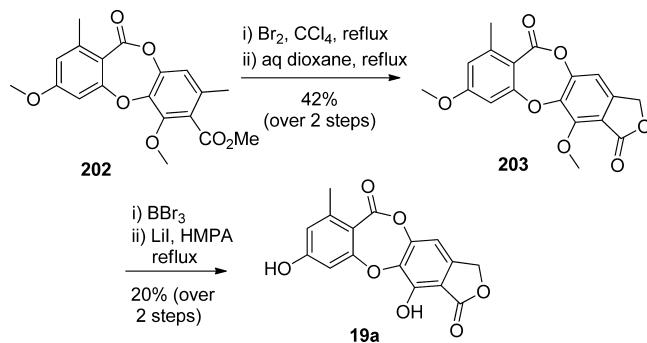
Scheme 39. Total Synthesis of Nidulol through Redox-Neutral Lactonization



compound **200** was converted to **201**. The carboxyl group in **201** was transformed to methyl group in two steps: (i) mixed anhydride formation with ClCO_2Et , Et_3N and (ii) reduction with NaBH_4 .

1.3.1.4.5. Variolaric Acid (19a). The total synthesis of variolaric acid (**19a**) was achieved starting from tricyclic depsidone **202** (Scheme 40). Selective bromination of benzylic

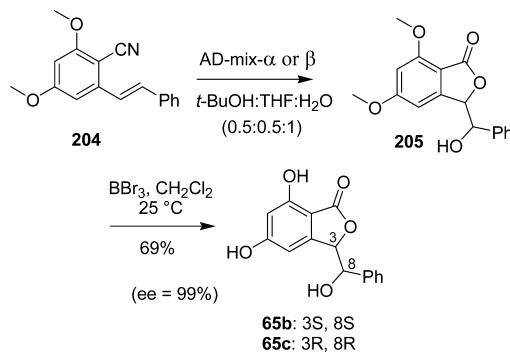
Scheme 40. Total Synthesis of Variolaric Acid (19a) via Redox-Neutral Lactonization



methyl, *ortho* to the ester group, with bromine– CCl_4 followed by hydrolysis in refluxing aqueous dioxane produced phthalide **203**. Demethylations of **203** with BBr_3 and LiI completed the total synthesis.⁸⁴

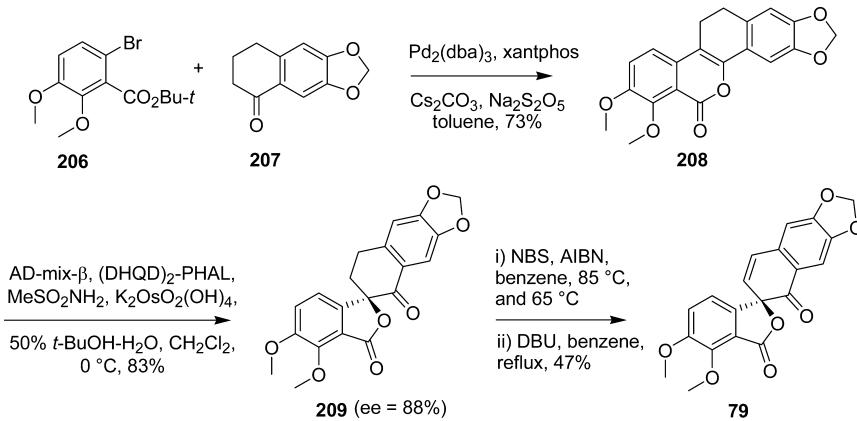
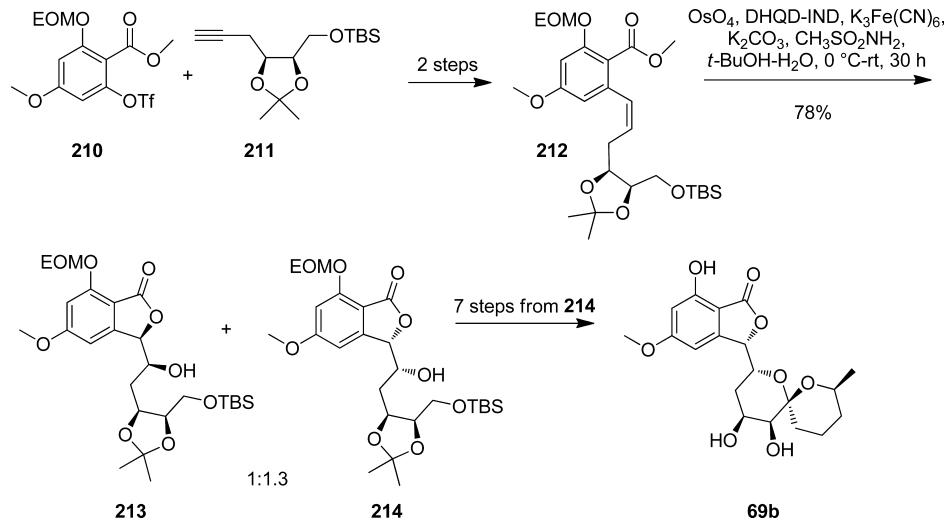
1.3.1.4.6. (+)- and (-)-Matteucen C (65b,c). Application of the dihydroxylation methodology (cf., Scheme 16) afforded (+)- and (-)-matteucen C (**65b,c**) by a two-step sequence starting from **204** in high ee (Scheme 41).⁶⁰ The conditions of the dihydroxylation sufficed the lactonization.

Scheme 41. Total Synthesis of (+)- and (-)-Matteucen C via Oxidative Lactonization



1.3.1.4.7. (-)-Arnottin II (79). Sharpless asymmetric dihydroxylation of dihydroarnottin I (**208**), accessible by the $\text{Pd}_2(\text{dba})_3$ -mediated coupling of *o*-bromobenzoates **206** and α -tetralone **207**, yielded optically active (+)-dihydroarnottin II (**209**) with good enantioselectivity (Scheme 42). Formation of the spiro phthalide-tetralone system in **209** involves oxidative ring contraction of the six-membered enol lactone unit. Successive bromination and dehydrobromination of **209** afforded (-)-arnottin II (**79**).⁸⁵

1.3.1.4.8. 7',8'-Dihydroaigialospirol (69b). Brimble synthesis of **69b** involves a dihydroxylation approach.⁸⁶ *cis*-Alkenylbenzoate **212**, assembled by Sonogashira coupling of **210** and **211**, on Sharpless asymmetric dihydroxylation using OsO_4 in the presence of a chiral ligand (e.g., DHQD-IND)

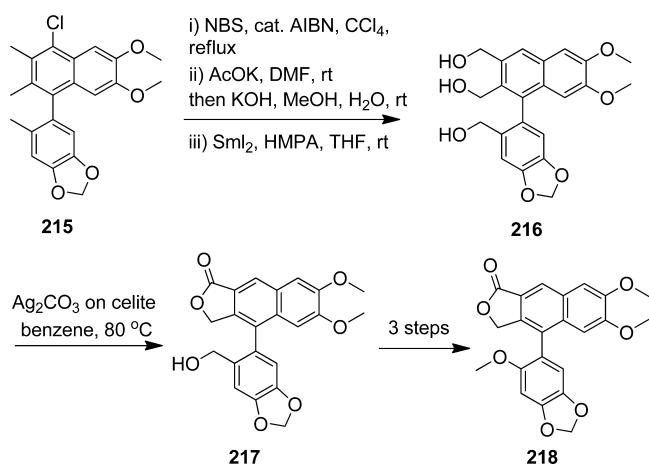
Scheme 42. Total Synthesis of (−)-Arnottin II via Dihydroxylation-Lactonization Process**Scheme 43.** Total Synthesis of 7',8'-Dihydroaigialospirol via Dihydroxylation-Lactonization Strategy

furnished a diastereomeric mixture of phthalides 213 and 214 via an *in situ* lactonization (Scheme 43). Separation of the isomers followed by a series of reactions including a crucial Nozaki–Hiyama–Kishi coupling afforded the natural product 69b.

1.3.1.4.9. (±)-6'-Methoxyretrojusticidine B (218). α -Aryl-naphthalene lignans are of great importance due to their usefulness as anticancer drugs. The first total synthesis⁸⁷ of complex phthalide-containing lignan, (±)-6'-methoxyretrojusticidine B (218) (initially proposed name procumphthalide A), was reported by Nishii et al. (Scheme 44). The precursor 215 was converted to triol 216 through consecutive benzylic bromination, hydrolysis, and nuclear dehalogenation. With Fetizon's reagent (Ag_2CO_3 –Celite), triol 216 was converted into 217, which was elaborated to the natural product 218 in three steps.

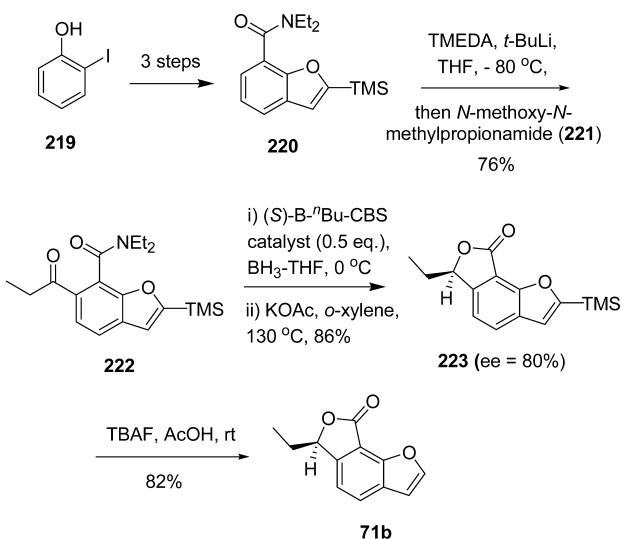
1.3.1.4.10. (+)-(R)-Concentricolide (71b). The first enantioselective total synthesis of (+)-(R)-concentricolide (71b), an anti HIV drug, was accomplished by Chein and co-workers (Scheme 45).⁸⁸ Directed *ortho*-metalation of benzofuran 220, obtained from 219, followed by acylation with Weinreb amide 221 furnished amide 222. Enantioselective reduction of 222 by BH_3 –THF in the presence of CBS-catalyst produced 223, which on desilylation with TBAF yielded 71b.

1.3.2. Reduction of Phthalic Anhydrides and Phthalaldehydic Acids. **1.3.2.1. Methodology.** Reduction of

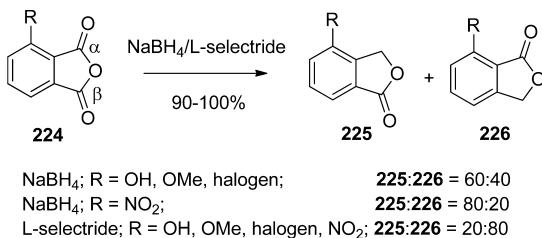
Scheme 44. Total Synthesis of 6'-Methoxyretrojusticidine B via Oxidative Lactonization

phthalic anhydrides to phthalides is a well-studied route in view of easy accessibility of the starting materials. The parent phthalic anhydride is conveniently reduced to phthalide by NaBH_4 in DMF.^{89a} However, the reduction of unsymmetric anhydrides (e.g., 224, Scheme 46) produces isomeric phthalides (e.g., 225 and 226).⁸⁹ Among the various reducing agents examined, metal hydrides are preferably used for such

Scheme 45. Chein Total Synthesis of (+)-(R)-Concentricolide via Reductive Lactonization



Scheme 46. Synthesis of Phthalides via Reduction of Anhydrides



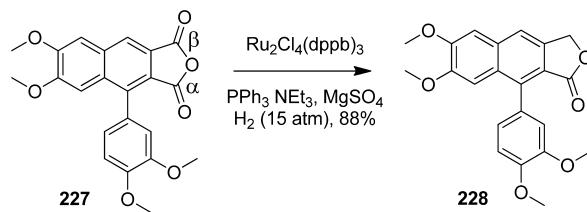
reductions. The regioselectivity of the reduction depends upon the nature of the substituents in the aromatic ring as well as the nature of the reducing agents. Smaller sized hydrides such as NaBH₄, LiBH₄, etc., show almost no selectivity on reduction of the anhydrides having electron-releasing substituent like hydroxyl, methoxy, or halogens at the 3-position. Yet good selectivity is observed with substrates having electron-withdrawing group (e.g., NO₂) at the 3-position giving 225 as major products. With bulky reducing agents such as L-selectrides, β -carbonyl is reduced giving 226 as major product.⁸⁹ The selectivities are explained on the ground of both electronic and steric effects.

A very recent report by Mal et al. showed that the alkyl groups do not significantly influence the selectivity.⁹⁰ The yields of 225 and 226 varied between 25% and 30% in the reduction of the anhydrides 224 (R = Me or Et) by NaBH₄ in THF-MeOH.

In 1986, Ishii et al. described a highly regioselective Ru-catalyzed reduction of anhydride.^{64d} Hydrogenation of 227 in the presence of Ru₂Cl₄(dppb)₃ gave product 228 where β -carbonyl was reduced (Scheme 47) with regioselectivity over 99%. α -Carbonyl reduced product was obtained in almost similar regioselectivity from corresponding diol (obtained by LAH reduction of 227) using Ru-catalyst along with a hydrogen acceptor benzalactone (Scheme 20). In both cases, the regioselectivity is controlled by the steric bulk of the substituents.

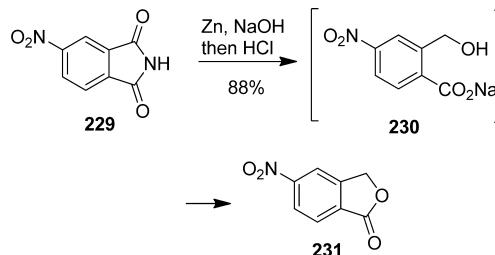
The most convenient laboratory preparation⁹¹ of a phthalide (e.g., 231) is the reduction of phthalimide (e.g., 229) with

Scheme 47. Regioselective Synthesis of Phthalides via Selective Reduction of Anhydrides



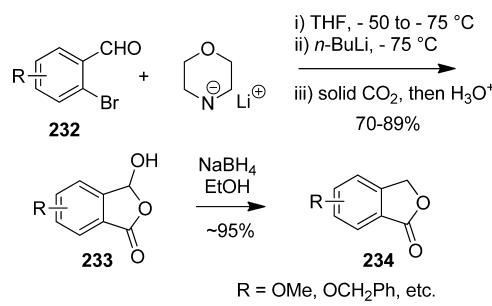
activated zinc in aqueous sodium hydroxide (Scheme 48). The intermediate salt, *o*-hydroxymethyl sodium benzoate 230, on acidification furnishes phthalide 231.

Scheme 48. Synthesis of Phthalides from Phthalimides



The phthalaldehydic acids are useful precursors for the synthesis of phthalides. For example, phthalaldehydic acids 233, obtained in a three-step one-pot operation from *o*-bromobenzaldehyde 232, on reduction with NaBH₄ in EtOH furnished 3-unsubstituted phthalides 234 in almost quantitative yields (Scheme 49).⁹²

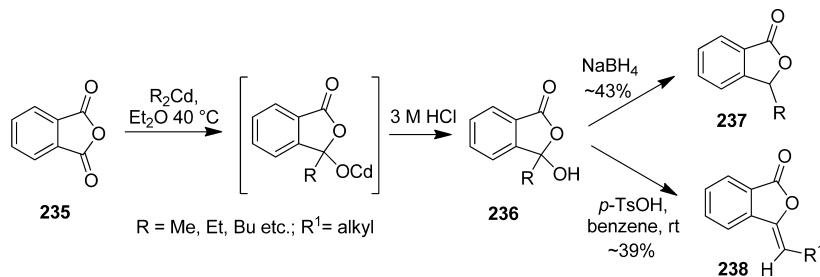
Scheme 49. Synthesis of Phthalides via Deoxygenation of Phthalaldehydic Acids



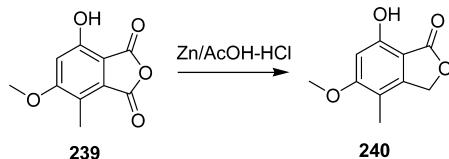
Reaction of dialkylcadmiums, prepared from Grignard reagent and CdCl₂, with phthalic anhydride 235 gave 3-substituted 3-hydroxyphthalides 236 in moderate yields (Scheme 50).⁹³ Further reduction of 236 with NaBH₄ furnished 3-alkylphthalides 237. Dehydration of 236 with *p*-TSA afforded Z-alkylidene phthalides 238.

1.3.2.2. Applications in Total Synthesis. **1.3.2.2.1. Mycophenolic Acid (3).** Selective reduction of phthalic anhydrides to phthalides has been utilized in the total synthesis of mycophenolic acid (3).⁹⁴ Reduction of phthalic anhydride 239 with Zn-AcOH-HCl selectively furnished 240 (Scheme 51). The key phthalide intermediate 240 was then transformed to mycophenolic acid (3) in a six-step sequence consisting of thermal rearrangement, ozonolysis, Wittig reaction, selective hydrogenation, etc.

Scheme 50. Dialkylcadmium Addition Route to 3-Substituted Phthalides



Scheme 51. Total Synthesis of Mycophenolic Acid via Reduction of Phthalic Anhydride



Katoh et al. applied the reduction strategy to diester 242 for the synthesis of antifungal phthalides 244 and 245 (Scheme 52).^{95a} The key phthalide 243 was prepared by Alder–Rickert reaction^{95b} between cyclohexadiene derivative 241 and DMAD followed by regioselective reduction of the resulting diester 242 by sequential treatment with TBAF, NaOH, and Zn–AcOH–HCl.

1.3.2.2.2. Bicuculline (33) and Capnoidine (251). The synthesis of natural products 33 and 251 has been accomplished by the nucleophilic addition of 1-siloxyisobenzofuran 249 to iminium ion 250 as the key step (Scheme 53).⁹⁶ The synthesis started with bromoaldehyde 246. Bromine–lithium exchange followed by quenching with CO₂ afforded phthalaldehydic acid 247. Chemoselective reduction of 247 with NaBH₄ gave phthalide 248, which was converted into the reactive silyloxybenzoisofurans 249 by treatment with s-BuLi–TMSiCl. Diastereoselective addition of 249 to 250 in the presence of CsF, BMI·BF₄, furnished natural products 33 and 251 in 3.5:1 ratio.

1.3.2.2.3. (±)-Hypodermin B (47). A racemic total synthesis⁹⁷ of hypodermin B (47) (Scheme 54), a lead for treatment of asthma and CNS illness, was achieved by selective

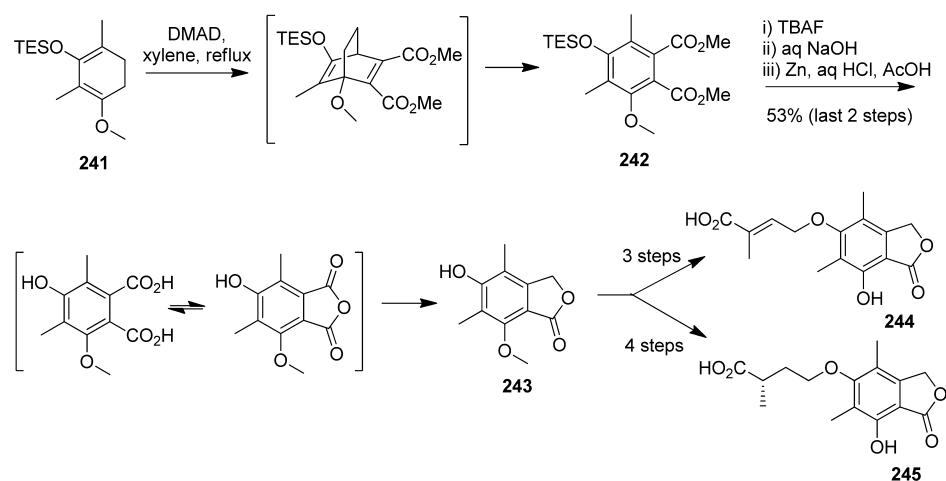
reduction of the anhydride 253 with LiAlH(*t*-BuO)₃ at 0 °C in 99% yield. Compound 253 was prepared from 252 in three steps. The keto carbonyl group in 253 probably renders the conjugated carbonyl group more electrophilic toward the reduction with hydride ion.

1.3.3. Oxidation. *1.3.3.1. Oxidation of Phthalans and Naphthalenes.* The selective and catalytic oxidation of phthalans is frequently used for the synthesis of phthalides. A variety of oxidants, KMnO₄, Oxone-KBr, H₅IO₆, RuO₂, NaClO₂, are reported in the literature. Zhang oxidation⁹⁸ process for the synthesis of phthalide moiety involves an in situ prepared hypervalent iodine reagent. Treatment of 1,3-dihydroisobenzofuran (254) with 2-iodoxybenzenesulfonic acid (IBS, 255) catalyst, generated in situ by oxidation of sodium 2-iodobenzenesulfonate (256) by Oxone in the presence of tetra-*n*-butylammonium hydrogen sulfate, in anhydrous acetonitrile at 60 °C, resulted in the parent phthalide (110) with 80% yield (Scheme 55).

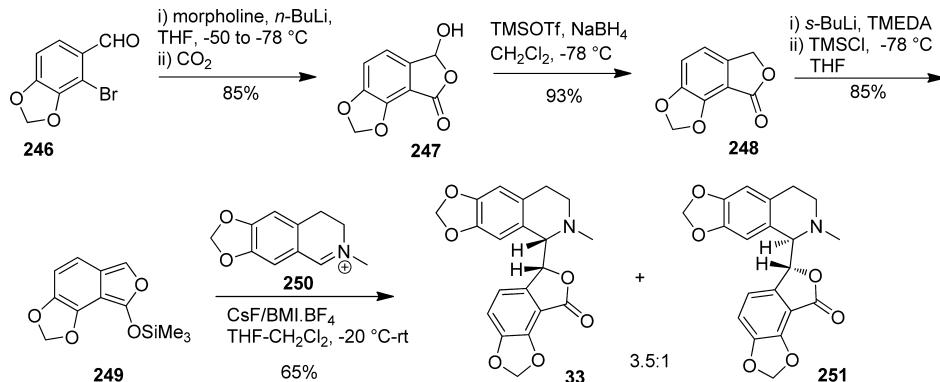
Similar transformations, that is, 254→110 were observed with Co-ZIF-9, a heterogeneous catalyst, in the presence of O₂ and NaOH (Scheme 56).⁹⁹ It also resulted in phthalaldehyde and phthalic acid as byproducts. The presence of NaOH accelerates the oxidation process. The reaction is proposed to proceed via a radical pathway involving peroxyphthalan 256.

KMnO₄ has been found effective for the oxidation of phthalans to phthalides.^{100a} Using a similar methodology, Basak and his group reported the synthesis of 3-unsubstituted benzophthalides by the benzylic oxidation of phthalans, prepared via Garratt–Braverman cyclization (Scheme 57).^{100b,c} KMnO₄–CuSO₄ was used to oxidize phthalan 257, which produced a mixture of products 258 and 259. The yield

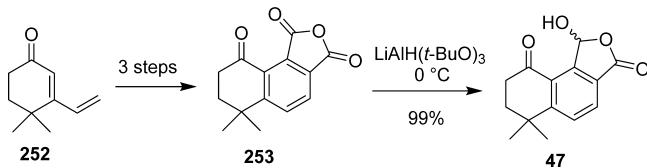
Scheme 52. Synthesis of Naturally Occurring Antifungal Phthalides



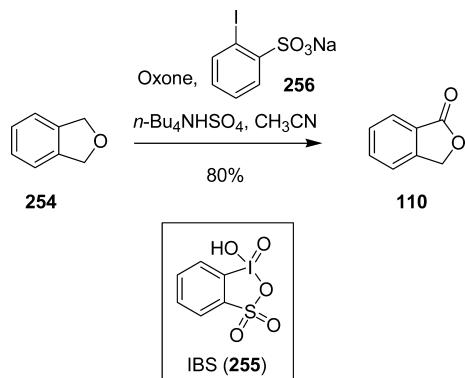
Scheme 53. Total Synthesis of Bicuculline and Capnoidine



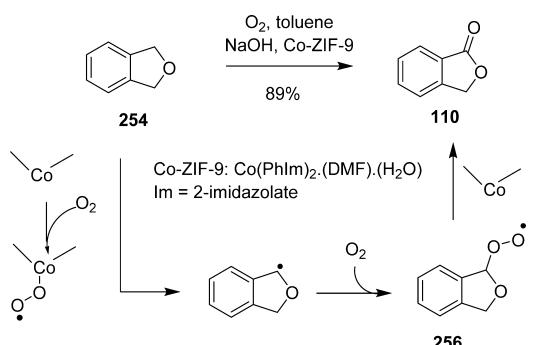
Scheme 54. Total Synthesis of Hypodermine B



Scheme 55. IBS-Catalyzed Oxidation of Phthalan



Scheme 56. Cobalt-Catalyzed Oxidation of Phthalans to Phthalides



of **258** was always substantially higher than that of **259**, and in the case of phthalans having substituents at C-5, only compound **258** was produced. The regioselectivity of the oxidation is attributed to the increase in steric hindrance caused by the C-4' substituents. Garratt-Braverman cyclization-mediated synthesis of phthalan **259** is discussed in phthalan section 2.3.3.2.

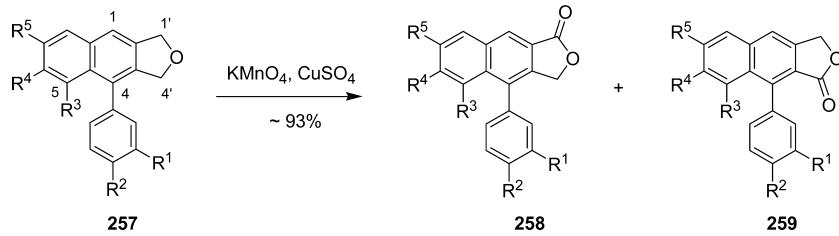
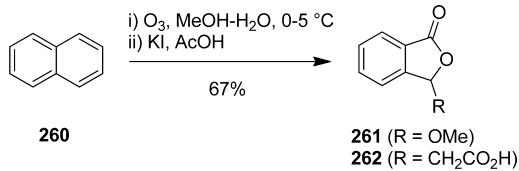
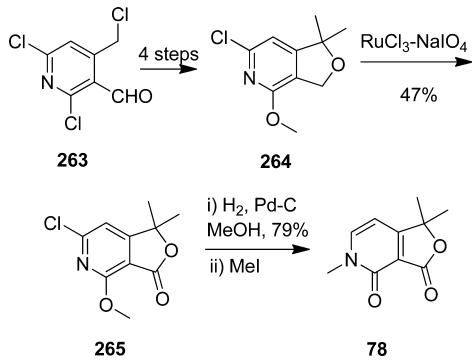
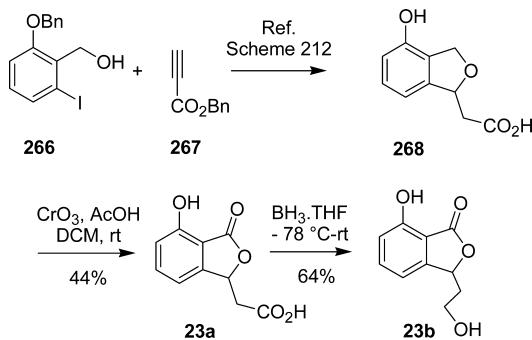
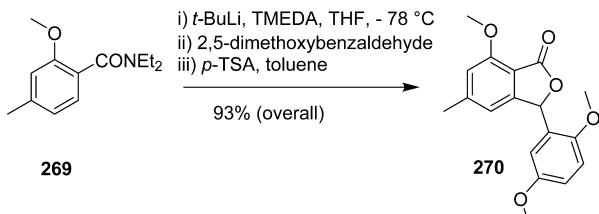
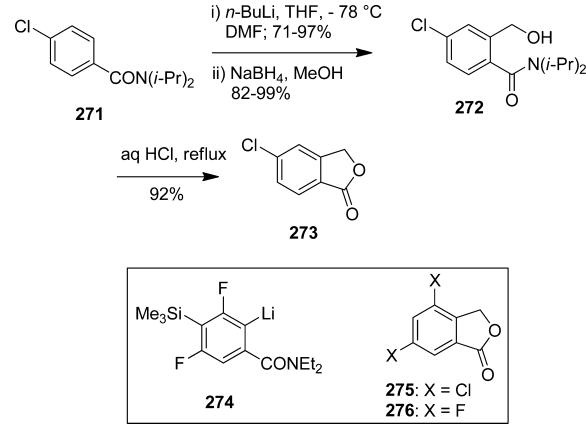
An interesting approach toward the synthesis of 3-methoxyphthalide (**261**) is ozonolysis of naphthalene (**260**).^{101a} Naphthalene underwent selective cleavage of one aromatic ring, when treated with ozone in aqueous methanol. Subsequent reduction of the peroxy intermediate with KI in acetic acid afforded **261** as the major product (Scheme 58). On the other hand, ammonium molybdate-H₂O₂-mediated oxidation of naphthalene (**260**) in the presence of H₂O₂ and AcOH yielded **262**.^{101b}

1.3.3.2. Applications in Total Synthesis. **1.3.3.2.1. Cerpegin (78).** Benzyllic oxidation of phthalans is shown to be a viable route to cerpegin (**78**), a naturally occurring alkaloid.¹⁰² RuCl₃-NaIO₄ oxidation of azaphthalan **264**, derived from chloro aldehyde **263**, provided azaphthalide **265** (Scheme 59). This was then converted into cerpegin (**78**) using a two-step sequence, dechlorination and *N*-methylation.

1.3.3.2.2. (±)-Isoochracinic Acid (23a) and Isoochracinol (23b). Their synthesis was accomplished from 3-deoxyisoochracinic acid **268** (Scheme 60), which, in turn, was prepared from **266** and **267** by using Kwon methodology¹⁰³ described in Scheme 212. Benzyllic oxidation of phthalan **268** with CrO₃ produced **23a**, which on reduction with BH₃-THF furnished isoochracinol (**23b**).

1.3.4. Nucleophilic Addition. **1.3.4.1. Addition of o-Metalated Aromatics to Carbonyls.** The 1,2-addition of organometallic derivatives to aldehydes/ketones followed by acid-catalyzed lactonization is probably the most widely used method for the synthesis of substituted phthalides. To this end, directed *ortho*-metalated aromatics are mostly effective.^{3a,104} For example, Owton et al. used *N,N*-diethyl 2-methoxy-4-methylbenzamide (**269**) for the synthesis of phthalide **270** (Scheme 61),^{104c} which has found its use in the synthesis of anthraquinones related to rhein, a widely used drug for osteoarthritis, vascular diseases, etc.^{104d} The process is merited by the fact that a wide range of products can be prepared by varying the aldehydes. A similar reaction, when applied to furfural, gave 3-furylphthalide.^{104e}

A new industrial scale synthesis of 5-substituted phthalides (e.g., 5-chloro/fluoro/trifluoromethyl),^{105a} reported by Faigl et al., utilized directed *ortho*-metalation of readily available benzamides (Scheme 62). For example, 4-chloro-*N,N*-diisopropylbenzamide (**271**) was *ortho*-lithiated in the presence of *n*-BuLi in THF at -78 °C and subsequently formylated with DMF and then reduced with NaBH₄ to give hydroxymethyl amide **272**. Acid-catalyzed lactonization of **272** gave 5-chlorophthalide **273** in high overall yield. Likewise, the synthesis of 4,6-dichlorophthalide **275** and 4,6-difluorophthalide

Scheme 57. Synthesis of Lignans from Garratt–Braverman Cyclization Product**Scheme 58.** Synthesis of 3-Methoxyphthalide via Ozonolysis of Naphthalene**Scheme 59.** Total Synthesis of Cerpegin via Phthalan Oxidation**Scheme 60.** Synthesis of Isoochracinic Acid and Isoochracinol**Scheme 61.** Directed *ortho*-Lithiation Route to 3-Arylphthalides**Scheme 62.** Directed *ortho*-Lithiation Route to Halogenated Phthalides

276 was reported by the same group.^{105b} The synthesis of 276 involved 4-trimethylsilyl-2-lithiobenzamide intermediate 274. The silyl group in 274 was required to avoid isomerization to the thermodynamically more stable 4-lithio species. 5-Substituted phthalides (e.g., 273) are particularly important because of their use as intermediates in the synthesis of citalopram (764, Figure 6, section 2.1) and their derivatives.⁶

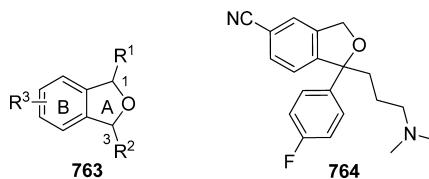
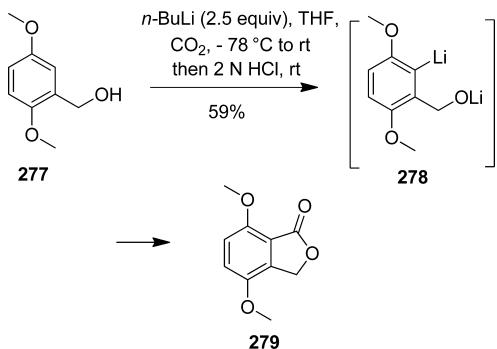


Figure 6. Structures of phthalan and citalopram (764).

On the way to the total synthesis of antibiotics K115B₁s (alnumycins),^{106a} phthalide 279 was prepared in one pot from benzylic alcohol 277. Treatment of the alcohol with *n*-BuLi formed lithiated intermediate 278, which on immediate quenching with CO₂ and acid-catalyzed lactonization produced the phthalide 279 (Scheme 63).^{106b}

For enantioselective synthesis of phthalides, Pedrosa et al. employed perhydro-1,3-benzoxazines as the chiral templates.¹⁰⁷ Thus, lithium–bromine exchange of 280 with *t*-BuLi followed by quenching with benzaldehyde gave a mixture of diastereomers 281 and 282 in a 2.2:1 ratio (Scheme 64). Hydrolytic cleavage of the *N*,*O*-ketal in 281 by reaction with diluted ethanolic HCl gave phthalan 283. Oxidation of the resulting phthalan 283 with *m*-CPBA and BF₃·Et₂O gave enantiopure phthalide 284. The reaction is also useful for the preparation of 3-alkylphthalides.

Scheme 63. Lithiation-Carboxylation of Benzyl Alcohols

In an analogous strategy,¹⁰⁸ a titanium complex is used for the synthesis of 3-arylphthalides. Chiral [2-(1,3-oxazolidin-2-yl)phenyl]-titanium complexes **287**, derived from corresponding lithio derivatives **286**, on reaction with aryl aldehydes gave **288** (Scheme 65). Subsequent, acid-catalyzed hydrolysis followed by PCC oxidation provided phthalide **291**. Transmetalation of **286** to **287** was required for better diastereoselectivity. With the titanium complexes, enantiomeric excesses were in the range of 77–98%, as compared to 5–33% with the corresponding chiral organolithium complexes. The methodology is however limited to only aromatic aldehydes.

The use of the oxazoline moiety as a directing group in the synthesis of aromatic lignan lactones (e.g., **294** and **295**) was pioneered by Meyers et al.¹⁰⁹ The oxazoline directed *ortho*-metalation of **292** with *s*-BuLi followed by reduction with NaBH_4 afforded hydroxymethyl derivative **293**, which on acid hydrolysis produced phthalides of type **294** and **295** (Scheme 66).

Meyers et al. also used chiral oxazolines for the enantioselective synthesis of 3-substituted and 3,3-disubstituted phthalides.¹¹⁰ Thus, *ortho*-lithiated aryl oxazoline **296**, obtained by the treatment of *n*-BuLi with *o*-halo aryloxazoline, was treated with alkyl or aryl esters or anhydrides to get 2-keto aryloxazoline **297** (Scheme 67). Treatment of alkyl or aryl Grignard reagent produced compound **298**, which on acid hydrolysis gave **299** with 50–80% ee. Direct treatment of unsymmetrical ketone with **296** produced 3,3-disubstituted phthalides, but with poor ee.

As reported by Capriati et al., *N*-alkylphenylaziridines **300** could be utilized for the synthesis of 3-aminomethylphthalides **302**, by aziridino group-induced directed *o*-lithiation followed

by trapping of the resulting intermediate **301** with CO_2 (Scheme 68).¹¹¹

Yus' approach was based on generation of *ortho*-lithiated species by reduction of dibenzothiins.¹¹² The reaction of **303** with lithium and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) in THF at -78 °C produced dianion **304**, which on sequential reactions with ketones and CO_2 produced 3-substituted phthalides **306** (Scheme 69). The reaction worked well with both aliphatic and aromatic aldehydes, average yields being 60%.

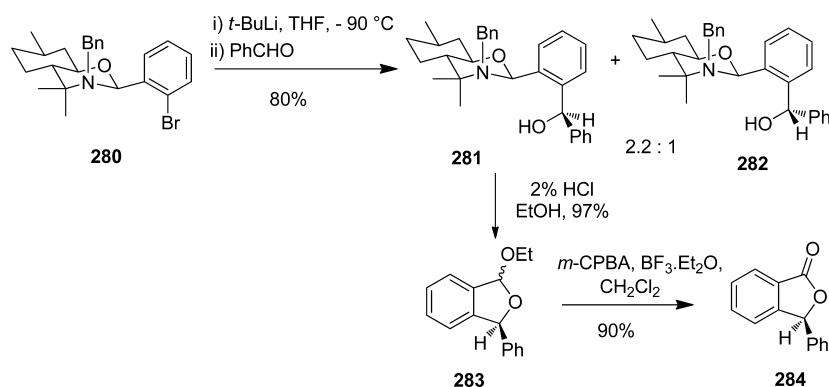
The synthesis of 3,3-disubstituted phthalides from 2-bromostyrenes **307** was developed on the basis of metal-halogen exchange.¹¹³ The lithio-derivatives **308**, derived from **307**, on reaction with carbon dioxide gave the corresponding lithium 2-vinylbenzoates **309**, which on acidolysis afforded phthalides **310** via protolactonization (Scheme 70).

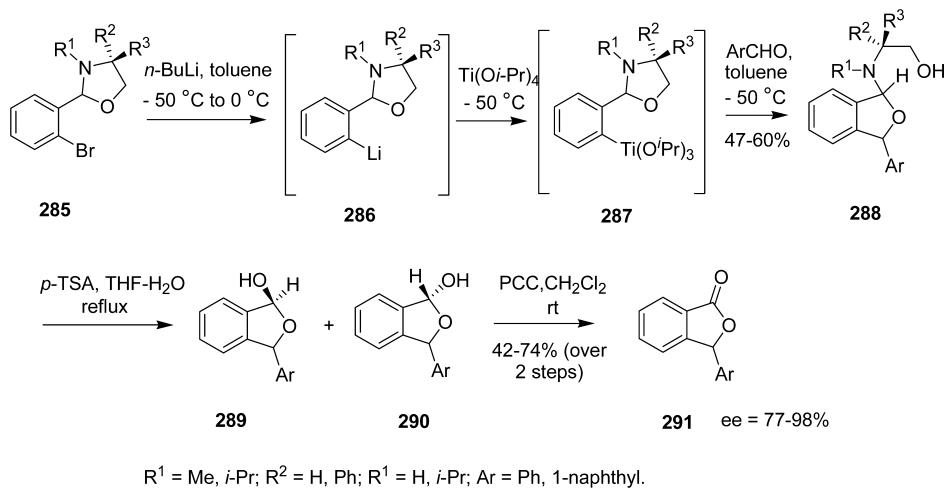
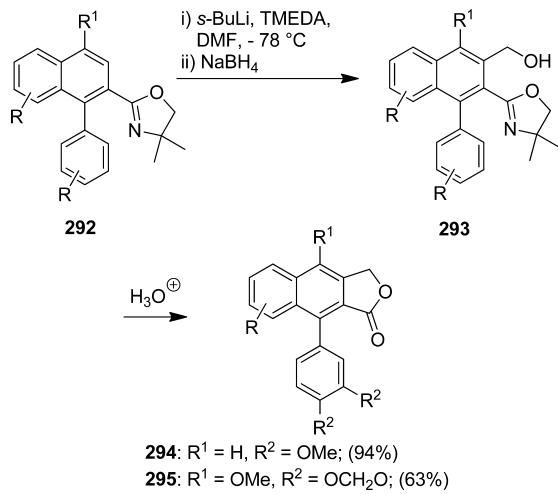
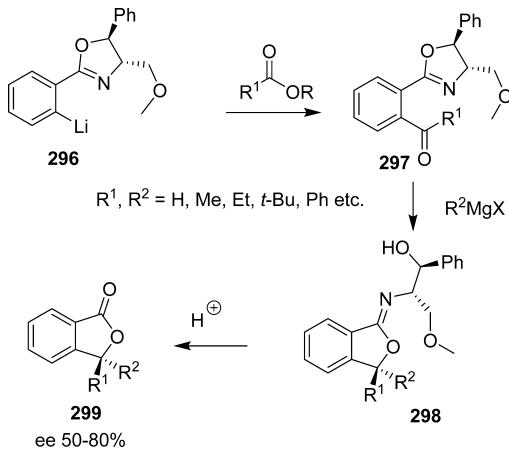
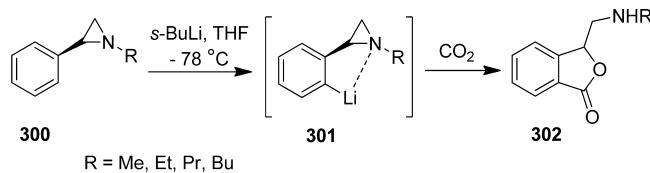
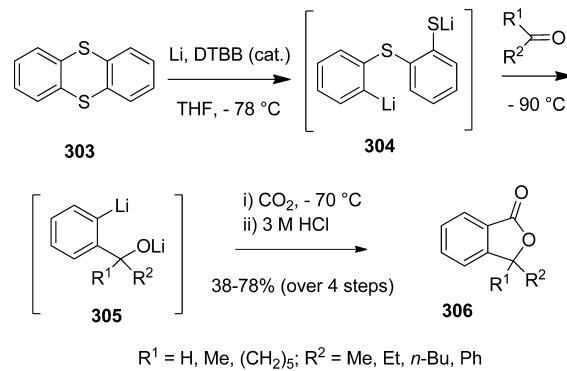
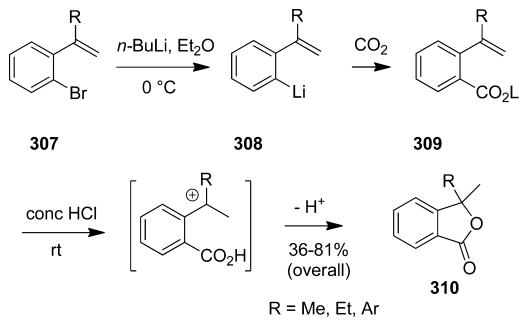
Iodobenzoates such as **311** also serve as the precursors for phthalides under a variety of conditions. Iodine-lithium exchange of **311** with mesityllithium followed by reaction with ketones allowed the synthesis of 3-substituted phthalides **312** (Scheme 71).^{114a} The *tert*-butyl ester group remained unaffected during the initial stage.

Similar transformations, involving nucleophilic addition of arylzinc compounds to aldehydes in tetramethylurea, were accomplished in good yields (63–83%) with stoichiometric amount of CrCl_3 .^{114b}

Knochel and co-workers explored facile halogen-magnesium exchange for the synthesis of highly functionalized phthalides.^{115a} Their protocol with *i*-PrMgCl culminated in the synthesis of 3-arylphthalides and 3,6-fused spirophthalides from similar *o*-iodobenzoates.^{115b} Schmalz's group developed a Mg-I exchange-driven route^{116a} to analogues of cyclo-mumbaistatin **316**, the spiro-lactone form of the natural product mumbaistatin. The arylmagnesium intermediate **314**, obtained from anthracene **313** through Mg-I exchange, underwent anionic homo-Fries rearrangement at elevated temperature to form spirophthalide **315**. Subsequent oxidation produced the mumbaistatin analogue **316** (Scheme 72). A similar homo-Fries rearrangement was also reported leading to an unanticipated formation of phthalide **317** from *o*-bromo benzylic O-carbamate in the presence of excess *s*-BuLi in THF (Scheme 72).^{116b}

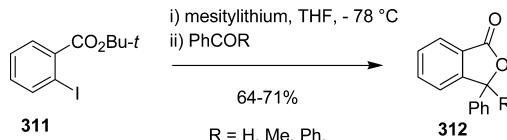
Arylmagnesium/zinc intermediates with chiral auxiliaries provide an enantioselective route to 3-substituted phthalides.¹¹⁷ The arylmagnesium intermediates **319**, derived from **318** by treatment with *i*-PrMgCl, reacted with a range of aldehydes either directly or via zinctated species to afford **320**. Acid-

Scheme 64. Diastereoselective Synthesis of Enantiopure 3-Substituted Phthalides

Scheme 65. Organotitanium Ate Complexes in Asymmetric Synthesis of Phthalides**Scheme 66.** Synthesis of Phthalide Lignans via *ortho*-Metalation**Scheme 67.** Enantioselective Synthesis of Phthalides Using Chiral Oxazoline as Directing Group**Scheme 68.** Reactivity of Aziridines in the Synthesis of 3-Aminomethylphthalides**Scheme 69.** Synthesis of Phthalides from Thianthrenes**Scheme 70.** Synthesis of 3,3-Disubstituted Phthalides via Carboxylation of 2-Lithiostyrenes

catalyzed lactonization of 320 produced phthalides 321 with good yields and ee (Scheme 73). Strong affinity of Mg²⁺ or Zn²⁺ to the imidazole moiety is invoked to explain the asymmetric induction.

Lin et al. developed a Ni-catalyzed tandem addition-cyclization route to synthesize optically active halogen-substituted phthalides from *o*-halobenzaldehydes 322.¹¹⁸ In the presence of chiral bidentate ligand (*S*)-BINAP, two

Scheme 71. Phthalides from Iodobenzoates

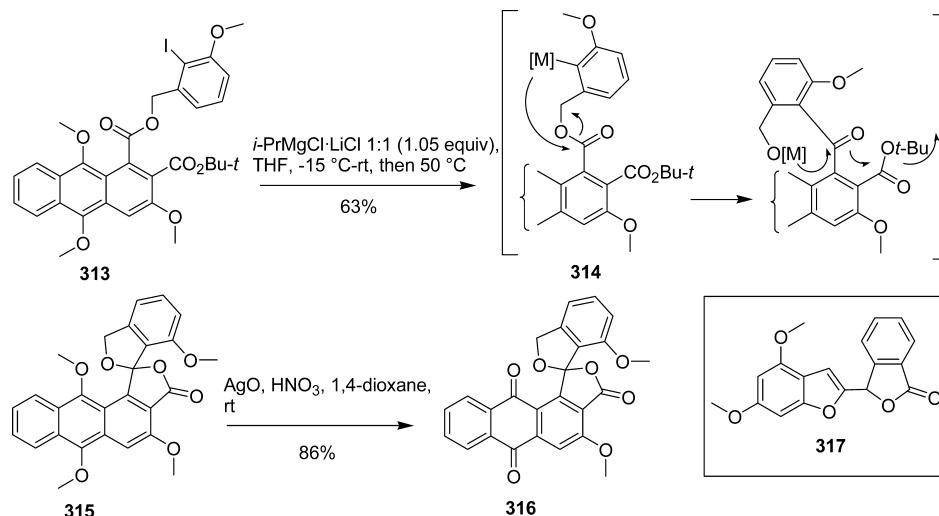
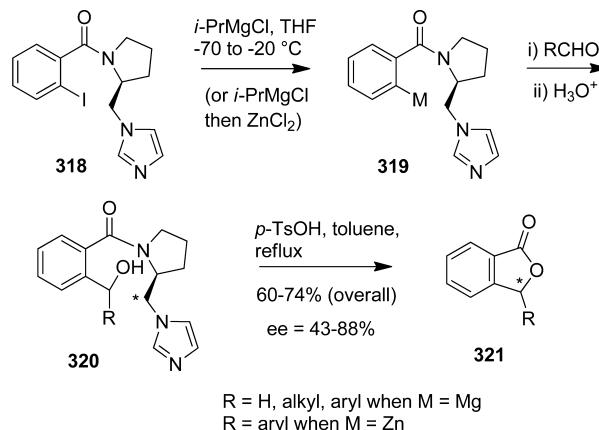
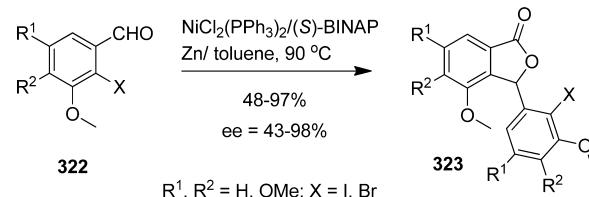
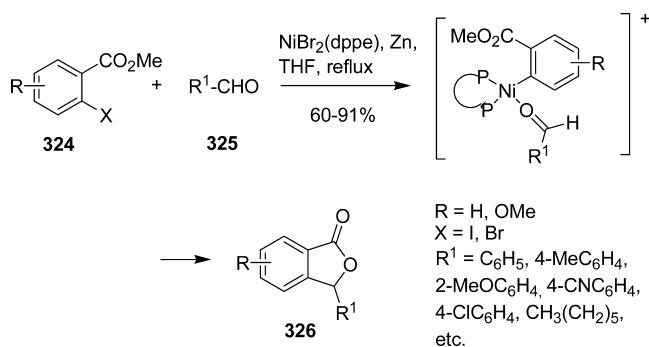
molecules of 322 underwent asymmetric cyclocondensation to phthalides 323 with moderate to excellent ee (Scheme 74).¹¹⁹

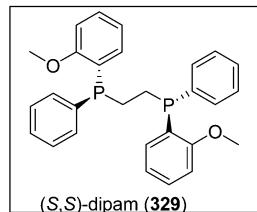
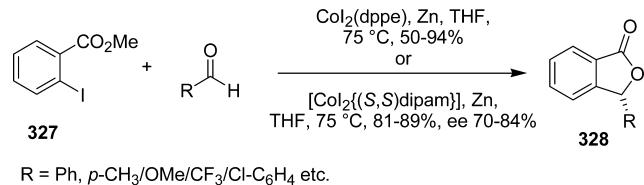
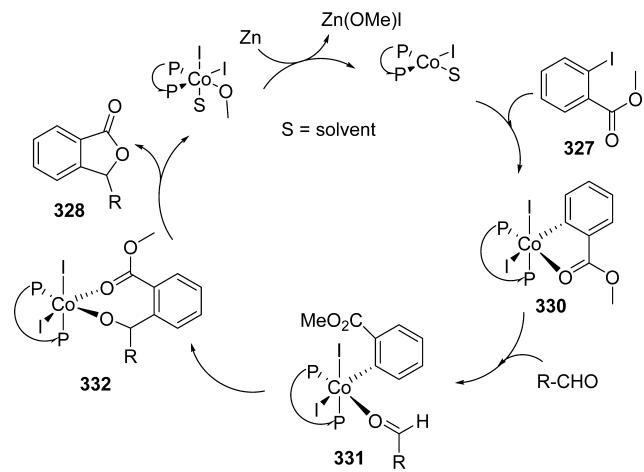
The Rayabarapu approach involves a similar Ni-complex-catalyzed zincation of *o*-halobenzoic esters 324 and their reaction with aldehydes 325 en route to 3-substituted phthalides 326 (Scheme 75).¹¹⁹ The methodology works well for both 3-alkyl and 3-aryl phthalides. The reaction works better with bromobenzoates than iodobenzoates. The reactivity of the aldehydes is sensitive to the nature of substituents. While the average yield was 80%, that with *p*-tolualdehyde was 48%, and *p*-anisaldehyde was inert to the reaction.

Cheng et al. realized the cobalt version¹²⁰ of the above reaction. Reaction of methyl 2-iodobenzoate (327) with aromatic aldehydes in the presence of [CoI₂(dppe)] and Zn powder in dry THF at 75 °C gave good to excellent yields of phthalide derivatives 328 (Scheme 76). High enantioselectivity of the products is achieved by employing a suitable bidentate chiral ligand of type 329.

Mechanistically, *ortho* cobaled benzoate 330 undergoes coordination with an aldehyde to give 331, which undergoes rearrangement to cobalt–alkoxide intermediate 332. The coordinated alkoxy group in 332 then undergoes intramolecular nucleophilic addition to the ester group to produce phthalide 328 (Scheme 77).

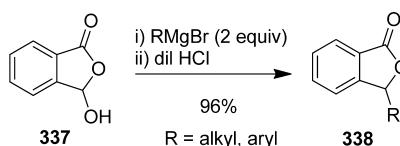
Besides organometallics of Li, Mg, Ti, and Zn metals, organosilanes^{121a,b} have found applications in the synthesis of phthalides. Treatment of *o*-silylbenzamides 333 with benzaldehyde in the presence of CsF–HMPT followed by TsOH gave phthalide 335 in good yields (Scheme 78).^{121c} Similar transformation was also observed in the presence of *t*-BuP4 (a phosphazene base) and AcOH–toluene,^{121d} giving phthalides 335 in 78% yield (Scheme 78). In this case, the reactive species is phosphazinium 336, which reacts with benzaldehyde to give *O*-silylated intermediate 334, with the release of *t*-BuP4.

Scheme 72. Schmalz Approach to cyclo-Mumbaistatin Analogue**Scheme 73. Enantioselective Synthesis of 3-Substituted Phthalides****Scheme 74. Ni-Catalyzed Tandem Addition-Cyclization Route to Phthalides****Scheme 75. Ni-Catalyzed Cyclization Strategy to Phthalides**

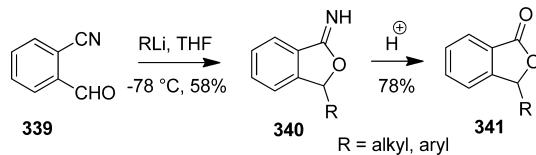
Scheme 76. Organocobalt Route to Chiral Phthalides**Scheme 77. Proposed Mechanism for the Co-Catalyzed Cyclization**

1.3.4.2. Addition of Alkyl/Aryl Metals to Phthalaldehydic Acids and Derivatives. The reaction of Grignard reagents (alkyl or aryl) with phthalaldehydic acid (337) or its derivatives followed by acid-catalyzed lactonization is a well-established route for the synthesis of 3-substituted phthalides (e.g., 338, Scheme 79).^{122a} Racemic 3-*n*-butylphthalide (**2a**) was prepared using butylmagnesium bromide.^{122b} Very recently, this protocol has been used in synthesis of a series of *n*-butylphthalide derivatives in conjunction with their biological activities.

A more efficient and general synthesis of 3-substituted phthalides was developed by Kobayashi et al.¹²³ Nucleophilic

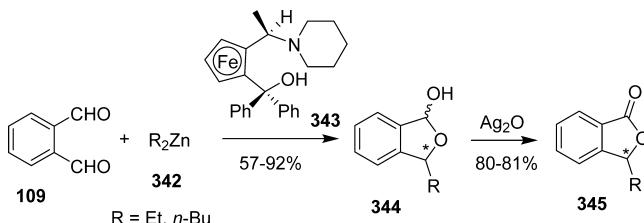
Scheme 79. Nucleophilic Addition of Grignard Reagents to Phthalaldehydic Acid

addition of RLi to the carbonyl carbon of 2-cyanobenzaldehyde (339) followed by intramolecular cyclization furnished 340, which, on hydrolysis, gave corresponding phthalides 341 (Scheme 80). Although the reaction was successful with

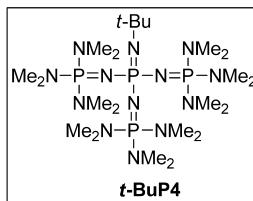
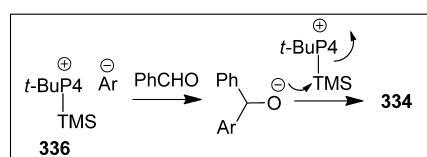
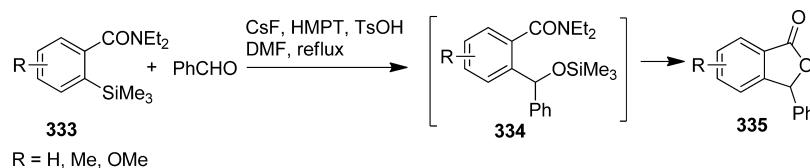
Scheme 80. Phthalides from 2-Cyanobenzaldehyde via 3*H*-Isobenzofuran-1-ylidenamines

different types of organolithiums (both alkyl and aryl including lithium enolates), the reaction was not efficient with Grignard reagents (EtMgBr or PhMgBr).

Phthalaldehyde (**109**), on reaction with dialkylzincs **342** in the presence of 1,2-disubstituted ferrocenyl amino alcohols (e.g., **343**) as chiral catalysts, led to chiral lactols **344**, which on oxidation with Ag₂O gave enantioenriched 3-alkylphthalide **345** (Scheme 81) with 80–90% ee.¹²⁴

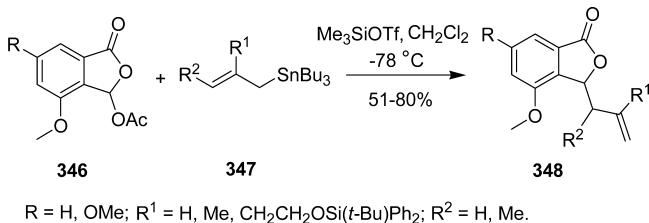
Scheme 81. Watanabe Asymmetric Approach to 3-Substituted Phthalides

Typically, three general approaches are used for the synthesis of 3-allylic phthalides (e.g., **348**). They are based on organotin, organoindium, and organosilicon reagents. Brimble developed the coupling reaction of the acetates of 3-hydroxyphthalides

Scheme 78. Carbodesilylative Addition Leading to 3-Arylphthalides

(e.g., 346) with allylstannane (e.g., 347) in the presence of TMSOTf (Scheme 82).¹²⁵ Substituents at C2 (R^1) of the allyl

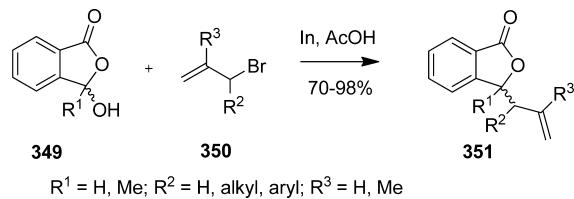
Scheme 82. Brimble Synthesis of 3-Allylphthalides



motif do not affect the outcome of reaction, but C3 (R^2) substituents decrease the yield. The strategy has been employed in the synthesis of spiroketal phthalans related to papulacandin natural products.

Treatment of phthalaldehydic acids 349 and allylindium bromide, generated in situ by the action of indium with allyl bromides 350, in the presence of 1 equiv of AcOH produced 3-allylphthalides 351 (Scheme 83).^{126a} Addition of acetic acid as an additive increased the yields and diastereoselectivity as well as accelerated the reaction rate.

Scheme 83. Lee Approach to 3-Allylphthalides



Asymmetric version of this method leading to enantioselective formation of 3-allylphthalides 351 was developed by Dudding et al. Chiral amino alcohols were shown to induce enantioselectivity in such reactions.^{126b}

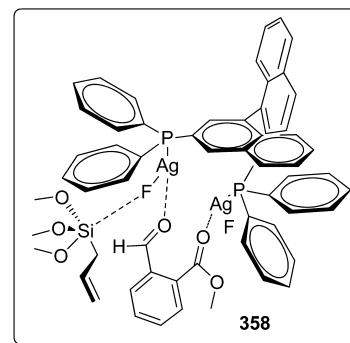
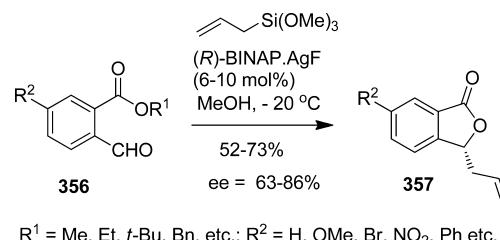
A solid-phase synthesis^{127a} of phthalides via reaction of resin-bound 2-formylbenzoic acid 352 with different organometallic reagents was developed by Knepper et al. (Scheme 84). Treatment of Grignard reagents to 352 at low temperature (-70°C) gave phthalides 353, but at higher temperature addition to ester took place producing *tert*-alcohols. On the other hand, organozinc reagents produced 353 only at higher temperature. In the presence of an amino alcohol (e.g., 354), organozinc reagents gave phthalides in moderate yields, without

the formation of reduction or addition products. Allylsilanes also underwent Sakurai-type addition reaction with 352 in the presence of TiCl_4 to give 3-allylphthalides 355 in good yields (Scheme 84). However, the reaction fails with lithium reagents, MeLi , EtLi , BuLi , etc., providing inseparable mixtures of various alcohols even at low temperatures.

Nucleophilic addition of octylmagnesium bromide to phthalic anhydride (235, Scheme 50) resulted in 3,3-diethylphthalide as the major compound (73%). However, the reaction with anhydride 224 ($\text{R} = \text{OH}$, Scheme 46) gave a mixture of phthalides, among which 4- and 7-hydroxy 3-octyl phthalide showed significant PPAR- γ binding activity.^{127b}

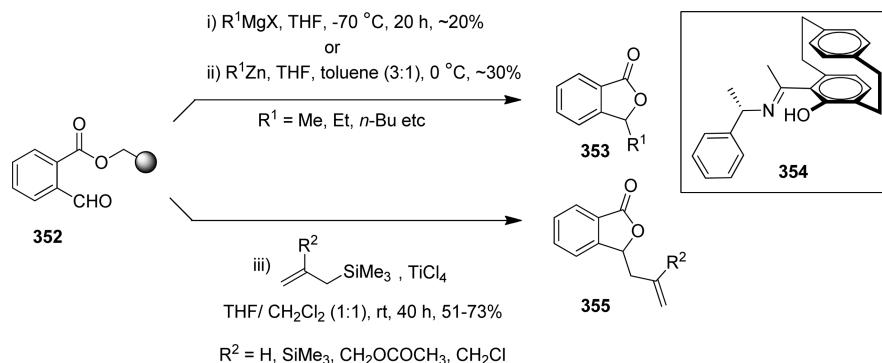
Application of $\text{Ag}(\text{F})$ -catalyzed Hosomi–Sakurai reaction to 2-formylbenzoates 356 in the presence BINAP led to chiral 3-allylphthalides 357 (Scheme 85).¹²⁸ The reaction was proposed to proceed via the complex 358, which underwent enantioselective allylation and intramolecular transesterification to produce the desired product.

Scheme 85. Hoshomi–Sakurai Reaction of 2-Formylbenzoates



1.3.4.3. Addition of MCN , RSR , RSO_2H , etc., to Phthalaldehydic Acids and Derivatives ($M = \text{Metal}$). Phthalaldehydic acids and their *ortho*-formylbenzamide derivatives, obtainable via *ortho*-metalation methodologies,^{3a,104a,b}

Scheme 84. Solid-Phase Synthesis of Phthalides

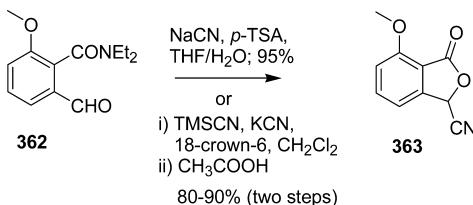


have proven to be versatile intermediates for the preparation of 3-cyanophthalides (e.g., 361, Scheme 86), 3-phenylsulfanylphthalides (e.g., 367, Scheme 88), and 3-phenylsulfonylphthalides (e.g., 368, Scheme 88), the established first generation Hauser donors. Syntheses of these phthalides were initially reported by Kraus,⁵⁸ Hauser,^{129a} Mal,^{129b} and Meyers.^{129c} Later, a few modified and advanced methods have also been reported.

For the preparation of 3-cyanophthalides 361, Swenton^{130a} and Russell^{130b} protocols are most frequently used. Nucleophilic addition of KCN to phthalaldehydic acids 359 under acidic conditions at 0 °C furnishes cyanohydrins 360. In the presence of Vilsmeier salt, the cyanohydrins 360 undergo cyclization to give 361 (Scheme 86). Yields are sensitive to the substituents, especially to methoxy groups. DCC was used for the cyclization of 360 by Russell et al., which was found to be superior for the preparation of fluoro-substituted 3-cyanophthalides.^{130b}

An interesting conversion of the readily accessible *o*-formylbenzamides to 3-cyanophthalides was reported by Snieckus.^{131a} Synthesis of 3-cyano-7-methoxyphthalide (363) was achieved in excellent yield from *N,N*-diethyl-2-formyl-6-methoxybenzamide (362) by the treatment with sodium cyanide and an equivalent amount of *p*-TSA in aqueous THF (Scheme 87). However, the reaction gave variable yields of

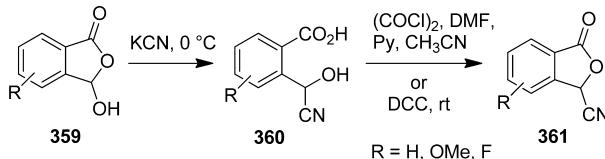
Scheme 87. Snieckus and Okazaki Synthesis of 3-Cyanophthalides



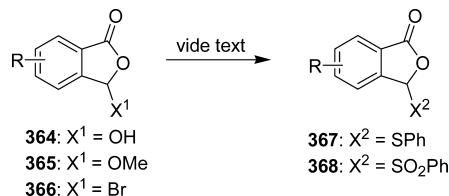
products when applied to other functionalized amides. The Okazaki protocol,^{131b} that is, a mixture of TMSCN, KCN, and 18-crown-6 in acetic acid (Scheme 87), appeared to be more general for such transformations.

The work of Hauser^{129b} on the synthesis of 3-phenylsulfonylphthalides 368 from phthalaldehydic acid derivatives 364–366 was utilized by many groups such as Mal,^{132a,b} Swenton,^{132c} Meyers,^{129c} etc. In most cases, the reagents used were (i) PhSH, *p*-TSA followed by *m*-CPBA or H₂O₂–AcOH; (ii) PhSO₂Na, AcOH; (iii) PhSO₂H, BF₃·Et₂O, etc. Mal et al. reported the synthesis of phthalide sulfone 368^{132b} from methoxy phthalide 365 (Scheme 88). Tatsuta's synthesis of 368 involved treatment of formylbenzamides (e.g., 362, Scheme 87) with sodium benzenesulfinate in acetic acid.^{132d} 3-Bromophthalide (366) can also be converted to the corresponding 3-phenylsulfanylphthalide 367 in the presence of PhSH, NEt₃.

Scheme 86. Swenton and Russell Approach to 3-Cyanophthalides

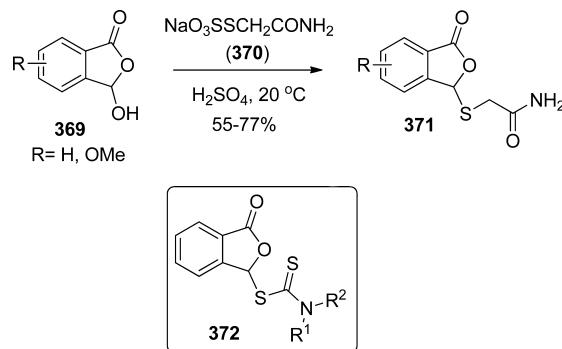


Scheme 88. Synthesis of 3-Phenylsulfonyl Phthalides



Borodkin's method for the synthesis of functionalized phthalides bearing a 3-alkylthio group (e.g., 371) uses Bunte salt (370) (Scheme 89).^{133a} The methodology is based on the reaction of the Bunte salt (nucleophile) with phthalaldehydic acids 369 in the presence of H₂SO₄.

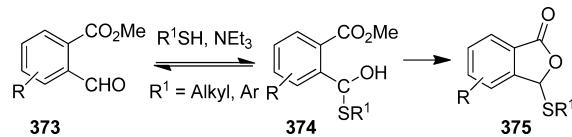
Scheme 89. Bunte Salt-Mediated Preparation of 3-Sulfanylphthalides



Reaction of 3-halophthalides (e.g., 366) with dithiocarbamates R²R¹N—C(=S)SH (R¹ = R² = alkyl) has been shown to be an environmentally benign preparation of 3-(dithiocarbamyl) phthalides 372.^{133b}

The base-catalyzed reversible nucleophilic addition of thiols to *ortho*-formylbenzoate 373, followed by the spontaneous intramolecular lactonization of the intermediates 374, readily furnished 3-thiophthalides 375 in a single operation (Scheme 90).¹³⁴ Bulkier aliphatic thiols and aromatic thiols with

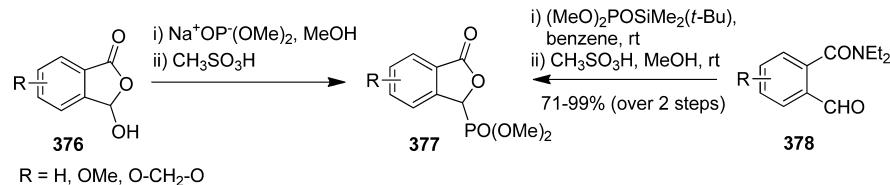
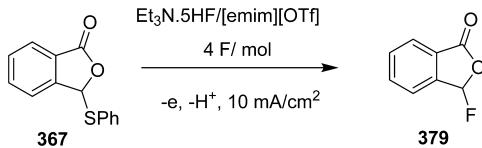
Scheme 90. Thiol-Mediated Synthesis of 3-Thiophthalides



electron-donating groups undergo faster reaction. Following this protocol, synthesis of 3-cyanophthalide was achieved in high yields using acetone cyanohydrin [Me₂C(CN)(OH)], which generates CN[−] under the reaction condition.

Phthalide-3-phosphonates 377 are usually prepared by reaction of phthalaldehydic acids 376 with sodium dimethyl phosphite in methanol.^{135a} Alternatively, *o*-formylbenzamides 378 can be reacted with *tert*-butyldimethylsilyl dimethyl phosphite followed by desilylation and cyclization using methanesulfonic acid at room temperature to provide phthalides 377 in very high yield (Scheme 91).^{135b}

The simplest 3-fluorophthalide 379 was synthesized by anodic fluorodesulfurization strategy (Scheme 92).^{136a} Anodic fluorination of 3-phenylsulfanylphthalide (367) or phthalide (110, Scheme S6) in an ionic liquid produced 379. These

Scheme 91. Synthesis of Phthalide-3-phosphonates**Scheme 92.** Synthesis of 3-Fluorophthalide

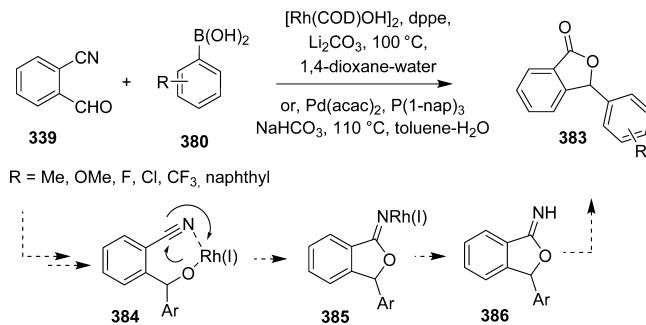
methods have been studied with limited substrates with moderate success. Phthalide **379** was alternatively prepared by the reaction of 2-carboxybenzaldehyde with (diamino)sulfur trifluoride.^{136b}

1.3.4.4. Transition Metal-Catalyzed Nucleophilic Addition of Organoboronic Acids to Substituted Aldehydes. Palladium-catalyzed reactions of arylboronic acids with aldehydes leading to carbinols have been found useful in the synthesis of 3-arylphthalides. Such reactions of arylboronic acids with *o*-formylbenzaldehydes or *o*-formylbenzonitriles or *o*-formylbenzoates in the presence of transition metals provide 3-arylphthalides.

The method of Cheng et al. involves a one-pot Pd(II)-catalyzed addition of arylboronic acids **380** to phthalaldehyde (**109**) and subsequent intramolecular lactonization strategy for accessing 3-arylphthalides **383** using PdCl₂, P(1-nap)₃, and K₂CO₃ (Scheme 93).^{137a} 3-Alkenylphthalides were also prepared by this protocol. The intermediates **382**, derived from **381**, have been proposed to undergo β -H elimination to furnish phthalides **383**.

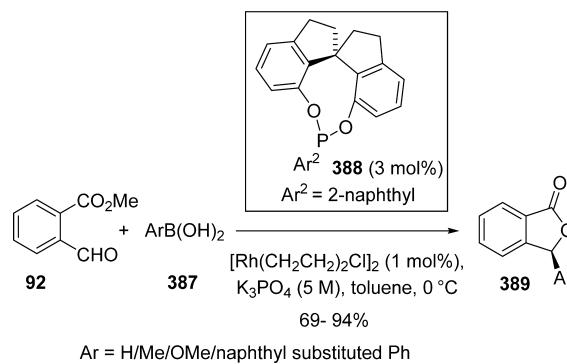
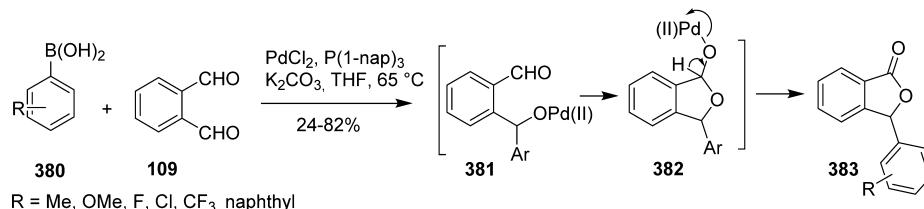
Likewise, Rh- and Co-catalyzed additions also afforded 3-arylphthalides in moderate to high yields.^{137b,c} The optimized reaction conditions for Rh-catalyzed reaction are [Rh(COD)-Cl]₂ (5 mol%), dppb (5 mol%), and K₂CO₃ (2 equiv) in dry DCE at 65 °C, and for Co-catalyzed reactions are CoI₂, dppe, and K₂CO₃ in THF at 80 °C. Co-catalyzed reactions seem to be insensitive to the electronic nature and bulkiness of the aryl part of the boronic acids, whereas Rh-catalyzed reactions are sensitive to the electronic effects.

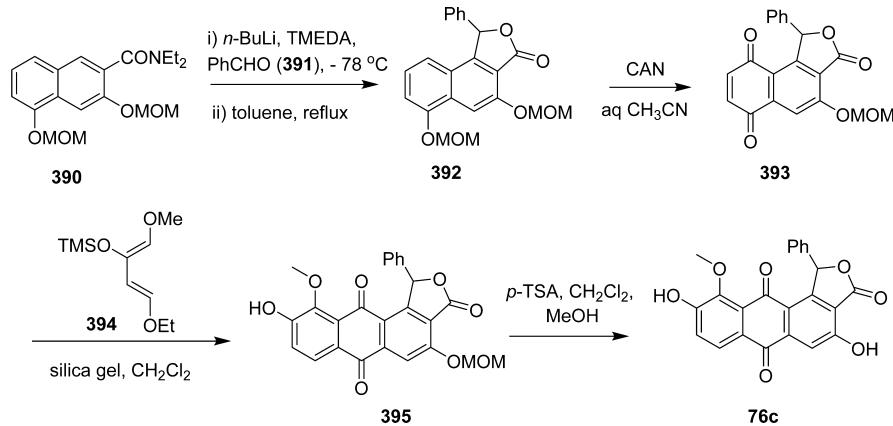
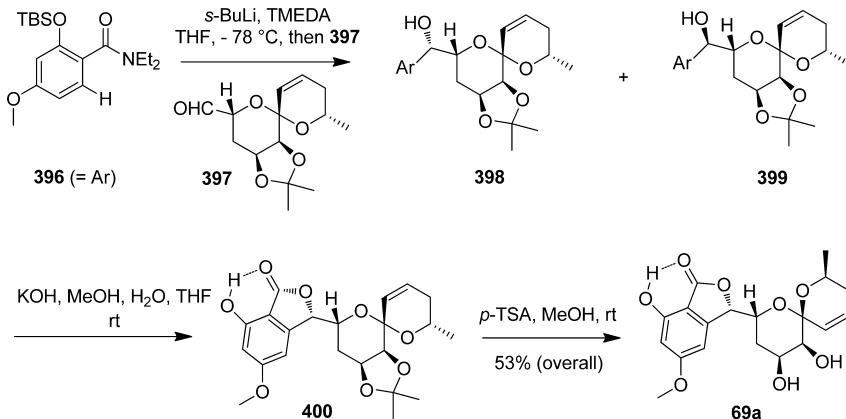
In 2011, Cheng et al. extended their earlier work^{137a} to formylbenzonitrile **339**. Reaction of **339** with arylboronic acids **380** in the presence of Rh catalysts afforded 3-arylphthalides **383** (Scheme 94).¹³⁸ The yields with the *p*-substituted arylboronic acids are usually higher than that with the corresponding *o*-substituted acids, indicating influence of the steric bulk of the phenyl ring of arylboronic acids. Such

Scheme 94. Rh-Catalyzed Reaction of Arylboronic Acids with Phthalaldehydonitrile

reactions are proposed to take place via the intermediates **384**, **385**, and **386**.

Akin to the work of Kuriyama^{139a} on palladium-catalyzed ([Pd(allyl)Cl]₂) thioether-imidazolinium carbene ligand and CsF-mediated arylation of aldehydes with organoboronic acids, Rh-catalyzed ([Rh(CH₂CH₂)Cl]₂) addition of aryl boronic acids **387** to methyl 2-formylbenzoate (**92**) was reported.^{139b} The reaction is general for a large number of arylboronic acids. Under similar conditions, an asymmetric version was also developed. The reactions with SPINOL-based phosphate ligand **388** gave chiral 3-substituted phthalides **389** with 63–83% ee and in high yields (Scheme 95).

Scheme 95. Rh-Catalyzed Addition of Arylboronic Acids to *o*-Formylbenzoate**Scheme 93.** Pd-Catalyzed Reaction of Arylboronic Acids with Phthalaldehyde to 3-Arylphthalides

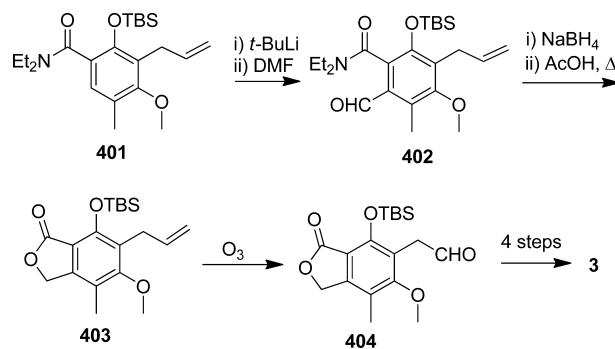
Scheme 96. Total Synthesis of (\pm)-Basidifferquinone C via *ortho*-Lithiation ApproachScheme 97. Total Synthesis of (+)-Aigialospirol Using *ortho*-Lithiation Strategy

1.3.4.5. Applications in Total Synthesis. **1.3.4.5.1. (\pm)-Basidifferquinone C (76c).** Takikawa synthesis¹⁴⁰ of 76c involved a crucial *ortho*-lithiation of naphthalene carboxamide 390 with *n*-BuLi followed by quenching with benzaldehyde (391) and subsequent thermal lactonization to provide phthalide 392 (Scheme 96). Oxidation of 392 with CAN furnished quinone 393 quantitatively. The Diels–Alder reaction of 393 with Danishefsky diene 394 followed by selective *O*-deprotection led to the completion of the synthesis of basidifferquinone C (76c).

1.3.4.5.2. (+)-Aigialospirol (69a). The synthesis of this complex natural product was also achieved via amide directed *ortho*-lithiation. Chiral aldehyde 397, obtained in 12 steps from (S)-glycidol via a RCM, was reacted with *ortho*-lithiated 396 to give diastereomeric alcohols 398 and 399 in a 1:1.4 ratio. Interestingly, the alkaline hydrolysis of 398 provided 400 directly, and under the conditions 399 epimerized to 398. As a result, both of the isomeric alcohols ended up with a single phthalide, that is, 400 upon alkaline hydrolysis. Finally, (+)-aigialospirol¹⁴¹ (69a) was obtained by deketalization of the phthalide 400 with methanol in the presence of *p*-toluenesulfonic acid (Scheme 97).

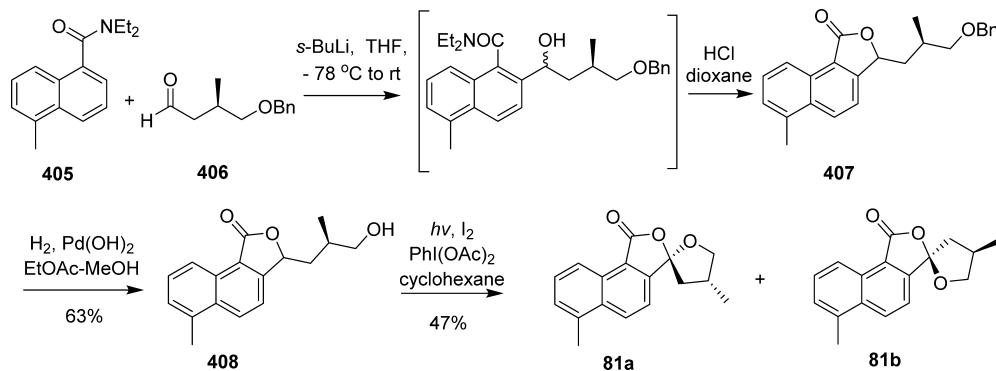
1.3.4.5.3. Mycophenolic Acid (3). Synthesis of densely substituted benzene rings is one of the major challenges in organic synthesis. Patterson synthesis¹⁴² of mycophenolic acid (3) used a hexasubstituted benzene derivative 402, obtained via directed *ortho*-lithiation of 401. NaBH₄-mediated reduction of 402 followed by acid-catalyzed lactonization furnished phthalide 403, which, after a series of transformations, afforded

mycophenolic acid (3) via 404 (Scheme 98). The overall yield of this 14-step synthesis of the natural product was 38%.

Scheme 98. Total Synthesis of Mycophenolic Acid via *ortho*-Lithiation Approach

1.3.4.5.4. Danshenspiroketalactone (81a) and epi-Danshenspiroketalactone (81b). Recently, Brimble's group reported the synthesis of danshenspiroketalactone (81a) and *epi*-danshenspiroketalactone (81b), two components of Danshen, a traditional Chinese medicine.¹⁴³ The phthalide spiroketal moieties of the natural products were assembled via a directed *ortho*-lithiation and oxidative radical cyclization as the key steps. The *ortho*-lithiation of amide 405 followed by treatment with aldehyde 406, resulted in naphthofuranone 407 in moderate yield (Scheme 99). Debenzylation of 407 to 408

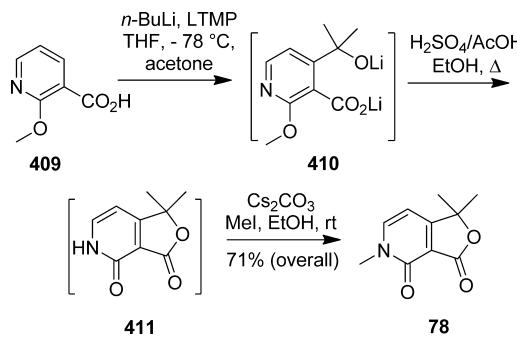
Scheme 99. Total Synthesis of Danshenspiroketalactones



followed by radical cyclization with I₂, PhI(OAc)₂, and light gave the natural products 81a,b.

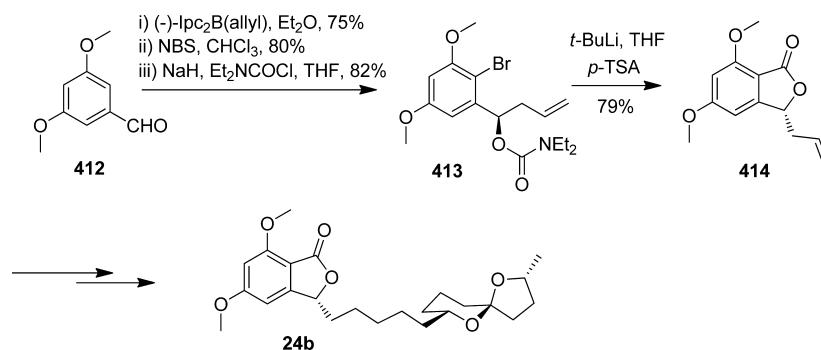
1.3.4.5.5. Cerpegin (78). It is an attractive target and has been synthesized^{144a} by several groups. Marsais' synthesis was based on lithiation of commercially available 2-methoxynicotinic acid (409).^{144b} The reaction of lithio-intermediate of 409 with acetone followed by acid-catalyzed cyclization of resulting dilithio species 410, and *N*-alkylation of 411 using methyl iodide and Cs₂CO₃, gave the natural product 78 (Scheme 100).

Scheme 100. Marsais Synthesis of Cerpegin



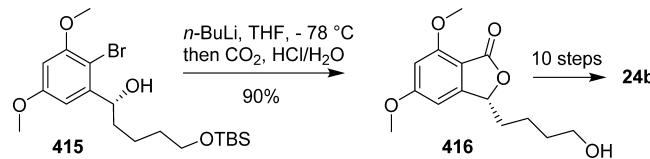
1.3.4.5.6. (+)-Spirolaxine Methyl Ether (24b). Intramolecular carbamoylation via lithiation of optically active 413 by bromine–lithium exchange with *t*-BuLi furnished enantiopure 3-allylphthalide 414 (Scheme 101).¹⁴⁵ A three-step reaction sequence comprising enantioselective allylation, ring bromination, and carbamoylation allowed the formation of 413 from 412. Phthalide 414 was elaborated to (+)-spirolaxine methyl ether (24b) in a few steps.

Scheme 101. Total Synthesis of (+)-Spirolaxine Methyl Ether



The Trost synthesis of 24b relied upon carboxylation of lithio intermediate derived from bromine–lithium exchange of optically active unprotected alcohol 415 as the key step.^{146a} The resulting phthalide 416 was then elaborated to 24b through Wittig reaction followed by chain elongation and [PdCl₂(PhCN)₂]-promoted spiroketalization (Scheme 102). The synthesis of (±)-cordrastine, an isoquinonylphthalide, was synthesized via the formation of an aryllithium as the key step and its carboxylation.^{146b}

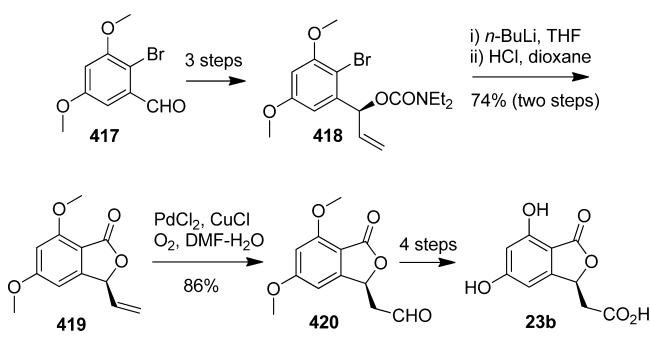
Scheme 102. Trost Synthesis of (+)-Spirolaxine Methyl Ether



1.3.4.5.7. Herbaric Acid (23b). Intramolecular carbamoylation of 418 led to the synthesis of chiral 3-vinylphthalide 419 en route to the first synthesis of herbaric acid 23b (Scheme 103).¹⁴⁷ Carbamate 418, prepared in three steps from 417 using microwave-assisted chemoenzymatic kinetic resolution as a crucial step, was lithiated with *n*-BuLi, intramolecularly carboxylated, and lactonized to produce chiral vinylphthalide 419. Regioselective Wacker oxidation of 419 to aldehyde 420 followed by second oxidation and *O*-deprotection provided herbaric acid (23b).

1.3.4.5.8. (+)-Pestaphthalide A (66a) and (−)-Pestaphthalide B (66b). Koert synthesis of these epimeric natural products is based on an intramolecular carboxylation of a carbonate.¹⁴⁸ Nuclear bromination of 421 and subsequent

Scheme 103. Brimble Synthesis of Herbaric Acid via Intramolecular Carbamoylation



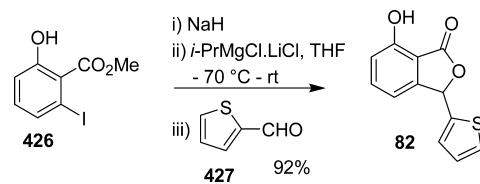
bromine–lithium exchange of the resulting bromo derivative **422** with *tert*-butyllithium at $-78\text{ }^{\circ}\text{C}$ afforded aryllithium intermediate **423**, which immediately rearranged to phthalide **424** (Scheme 104). Interestingly, formation of dihydroisocoumarin was not observed. Finally, BBr_3 -mediated demethylation of **424** completed the synthesis of **66a**. Similarly, $(-)$ -pestaphthalide B (**66b**) was synthesized starting from **425**.

1.3.4.5.9. (\pm) -Chrycolide (82). The first synthetic route to **82** involves treatment of **426** with sodium hydride followed by *i*-PrMgCl·LiCl in THF at $-70\text{ }^{\circ}\text{C}$ and trapping of the resulting intermediate with thiophene carboxaldehyde **427** (Scheme 105).^{115b} The reaction did not necessitate protection of the OH group of phenol **426**.

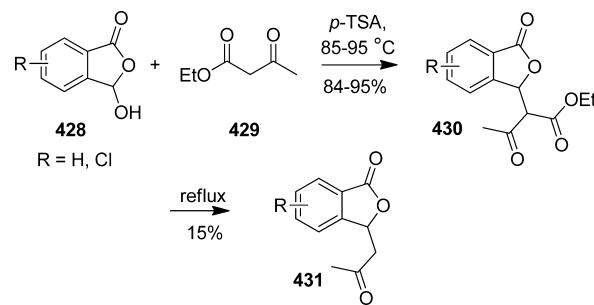
1.3.5. Condensation. **1.3.5.1. Aldol-Type Condensation of Phthalides and Its Derivatives.** Aldol reaction, one of the most versatile carbon–carbon bond-forming reactions, has been found useful in the synthesis of 3-substituted phthalides. Donati et al. reported that *p*-TSA-catalyzed condensation of phthalaldehydic acids **428** and ethyl acetoacetate (**429**) gave 3-substituted phthalides **430** as an inseparable mixture of two diastereomers (Scheme 106).^{149a} Prolonged reaction led to the formation of ketones **431** via deethoxycarbonylation. A similar type of reactions was reported to take place also with K_2CO_3 ^{149b,c} and montmorillonite K-10^{149d} assisted by microwave irradiation.

A base-catalyzed condensation is reported to take place with 3-ethoxyphthalide (**432**).¹⁵⁰ In the presence of NaOEt, diethyl malonate underwent condensation with **432** to give **434** (Scheme 107). This was further transformed to 3-carboxymethylphthalide **435** in two simple steps. The formation of **434** has been explained by isomerization of **432** to **433**, which,

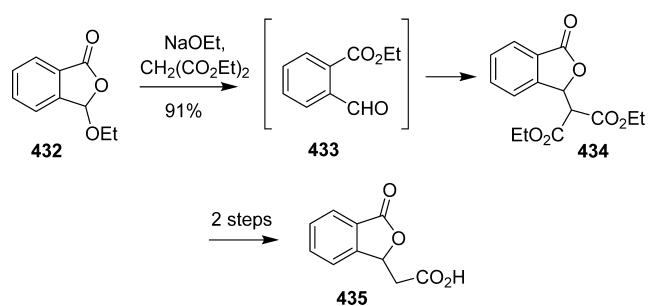
Scheme 105. Synthesis of (\pm) -Chrycolide via *ortho*-Magnesiation



Scheme 106. Tandem-Aldol-Lactonization of Phthalaldehydic Acid and EAA



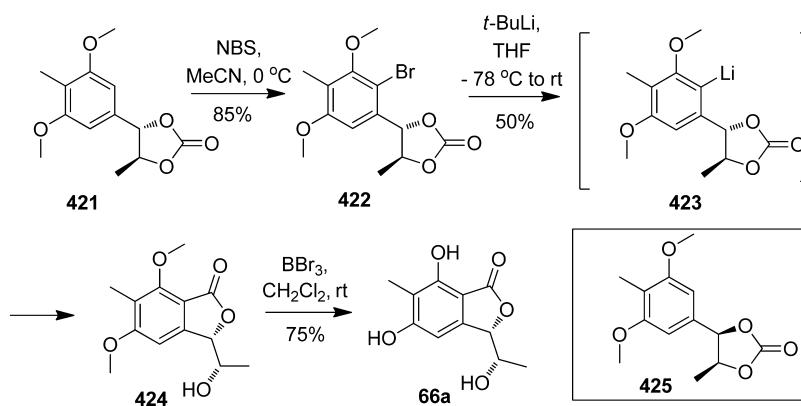
Scheme 107. Base-Catalyzed Reaction of 3-Alkoxyphthalide

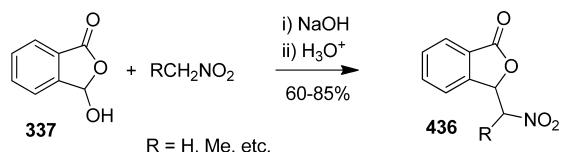


in turn, undergoes aldol-type condensation to the respective product. The reaction is extendable to ethyl cyanoacetate but not to ethyl acetoacetate.

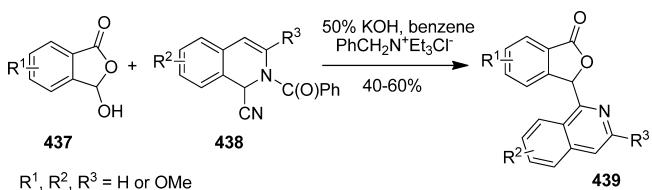
In the presence of NaOH, phthalaldehydic acid **337** undergoes Henry-type condensation with a variety of nitroalkanes to give 3-(nitroalkyl)isobenzofuranones **436** in 60–85% yields (Scheme 108).^{151a,b} Improved yield of the products was obtained when the reaction was carried out with Et_3N in DMSO.^{151c}

Scheme 104. Total Synthesis of $(+)$ -Pestaphthalide A and $(-)$ -Pestaphthalide B

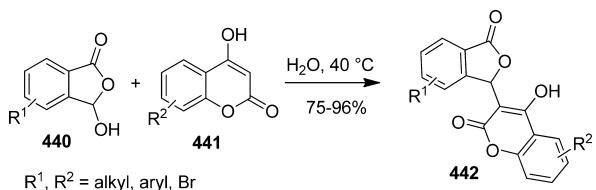


Scheme 108. Synthesis of Phthalidylnitromethanes

In the similar vein, Reissert compounds 438 react with phthalaldehydic acids 437 in the presence of KOH and benzyl triethylammonium chloride to give isoquinolylphthalide 439 (Scheme 109).¹⁵² Such reactions are not applicable to 3-ethoxy or 3-bromophthalides.

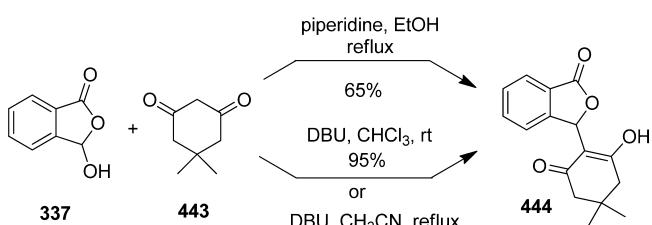
Scheme 109. Synthesis of Isoquinolyl Phthalides

Aldol-type condensation has recently been developed as a highly efficient method for the synthesis of coumarin-containing phthalides,¹⁵³ anticipating such phthalides may provide unusual bioactivity due to the individual activity of phthalides and coumarins. Reactions of 4-hydroxycoumarins 441 with phthalaldehydic acids 440 furnished 3-(4-hydroxy)-coumarinylphthalides 442 with 75–96% yields (Scheme 110).

Scheme 110. Synthesis of 3-(4-Hydroxy)coumarinylphthalides

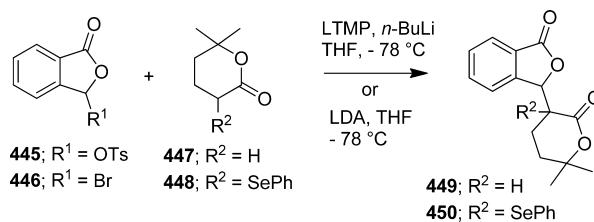
The reaction is tolerant with various functionalities (Me, OMe, Br, etc.) at both of the aromatic nuclei. In the place of coumarins, 4-hydroxy-2-quinolones can also be used to yield 3-(4-hydroxy)quinolinylphthalides.

Likewise, dimedone (443) reacts with phthalaldehydic acid (337) in refluxing ethanol containing piperidine to give phthalide 444.^{154a} Mal et al. modified the method by replacing piperidine with DBU, and developed a more efficient regiospecific synthetic route to 3-(2,6-dihydroxyphenyl)-isobenzofuranones like 444 (Scheme 111).^{154b} The reaction

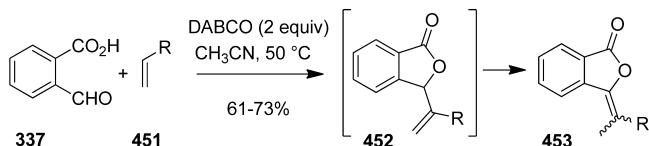
Scheme 111. Condensation of Phthalaldehydic Acid with Dimedone

is faster and high yielding. It was generalized with a variety of cyclic and acyclic 1,3-dicarbonyl compounds. This strategy was applied to the total synthesis of isopestacin (63) and cryphonectric acid (64) in completely regiospecific manner (discussed in section 1.3.5.3.4).

Lane and Pinder showed that δ,δ -dimethyl- δ -valerolactones 447 and 448 can be reacted with 3-[*(p*-toluenesulfonyloxy)-phthalide (445) to afford 3-substituted phthalides 449 and 450, respectively, in good yields (Scheme 112).^{155a,b} The yield of the reaction between 446 and 447 was low.

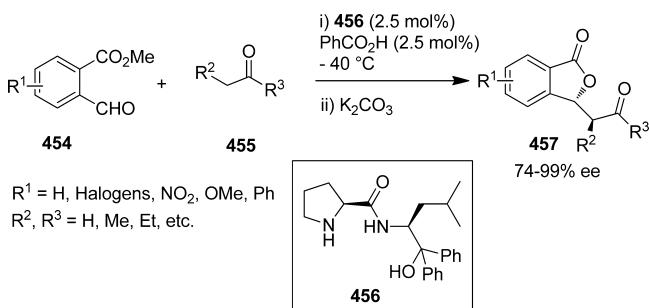
Scheme 112. Condensation of 3-Functionalized Phthalides with δ -Valerolactones

Incipient carbanions, generated under Baylis–Hillman conditions, also react with 2-carboxybenzaldehyde (337). Thus, DABCO-catalyzed reaction of 337 with alkenes 451 gave alkylidene phthalides 453 via 452.¹⁵⁶ In case of acrylonitrile or acrylic acid esters, only *E*-isomers of 453 were produced (Scheme 113).

Scheme 113. Baylis–Hillman Route to 3-Alkylidene Phthalides

R = CO₂R', CN, C(O)R"; R' = Me, Et, *t*-Bu; R" = Me, Et

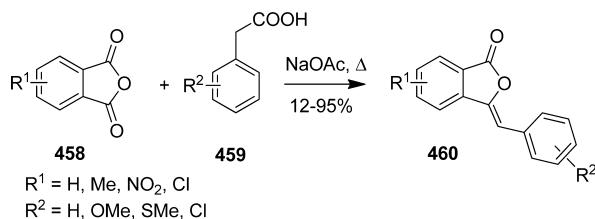
Wang et al. disclosed a novel synthesis of chiral 3-substituted phthalides 457 based on organocatalytic asymmetric aldol-lactonization reaction of 2-formylbenzoic esters 454 with ketones/aldehydes 455 catalyzed by chiral L-prolinamide alcohol 456 (Scheme 114).¹⁵⁷ Because of the amphiphilic nature, 454 act as aldol acceptors as well as electrophiles for the consequent lactonization. Natural product (*S*)-(−)-3-butylph-

Scheme 114. Chiral 3-Substituted Phthalides via Organocatalytic Aldol-Lactonization Protocol

thalide (**2b**) was synthesized utilizing the methodology as discussed in section 1.3.5.3.1.

Sodium acetate-promoted condensation^{158a} of phthalic anhydride **458** with aryl acetic acids **459** directly gives 3-alkyldenephthalides **460** in moderate to good yields (Scheme 115). Wittig reaction of phthalic anhydrides also produces

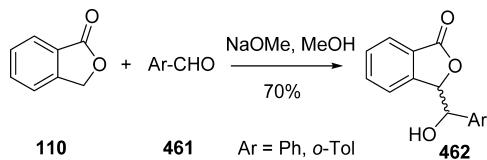
Scheme 115. Condensation of Phthalic Anhydride with Arylacetic Acids



similar phthalides as elaborated in section 1.3.5. In a different report, similar transformations were also observed under microwave irradiation in the presence of acetic anhydride as catalyst.^{158b}

3-Alkylidene phthalides are alternatively obtained by the use of phthalide anions as nucleophiles. Zimmer and Barry showed that in the presence of strong bases like NaOMe, 3-unsubstituted phthalides (e.g., **110**) underwent aldol-type condensation with aryl aldehydes **461** to give corresponding diastereoisomeric 3-(α -hydroxybenzyl)phthalides **462** in good yields (Scheme 116).^{159a} Likewise, LDA was found to work for such reactions in the total synthesis of (\pm)-narlumicine (**38**).^{159b}

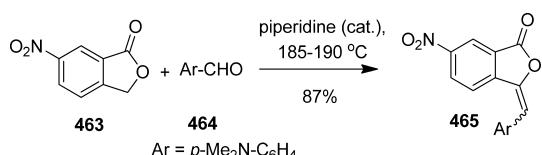
Scheme 116. Synthesis of 3-Hydroxybenzylphthalides by Anionic Reaction of Phthalide



The methylene group of the parent phthalide is not sufficiently reactive to condense with aldehydes in the presence of amine bases. Yet, a nitro group in the 6-position as in 6-nitrophthalide **463** makes the methylene sufficiently acidic to promote reaction with aromatic aldehyde **464** in the presence of piperidine to give 3-arylidene phthalide **465** (Scheme 117).¹⁶⁰

Dallavalle et al. utilized Horner–Wadsworth–Emmons (HWE) reaction of diethyl phthalide-3-phosphonate **466** with keto aldehyde **467** for the synthesis of 3-alkyldene phthalide **468**, which on subsequent hydrogenation gave methyl ether of sporotricale **469** (Scheme 118).^{161a} Later, the same strategy

Scheme 117. Condensation of Phthalides with Aldehydes: Synthesis of 3-Arylidene Phthalides



was employed to synthesize (+)-spirolaxine methyl ether (**24b**) from **466** and [6,5]-spiroketal aldehyde **470**.^{161b}

1.3.5.2. Aldol-Induced Benzannulation. In this section, the construction of both rings of phthalides by intramolecular aldol reaction is described. Ricca et al. depicted an uncommon synthetic pathway^{162a} for the synthesis of **474**, an intermediate for the natural product, mycophenolic acid (**3**) (Scheme 119). The open-chain substrate **472**, obtained from isoxazole **470**, on treatment with sodium methoxide transformed to butyrolactone **473** in an unspecified yield through an intramolecular aldol condensation. Dieckmann-type condensation of **473** with *n*-BuLi produced 5,7-dihydroxy-4-methylphthalide (**474**), a natural product isolated from *Aspergillus flavus*.^{162b}

Jiménez's version of Scheme 119 for the synthesis of 5,6,7-trisubstituted phthalide metabolite **479** is presented below (Scheme 120).¹⁶³ Unlike Scheme 119, butyrolactone **478** was formed by NaH-mediated intramolecular Michael addition of **477**, prepared by condensation **475** and **476**. Dieckmann-type condensation of the lactone **478** furnished phthalide **479**, when treated with *t*-BuOK.

Another example of intramolecular condensation mode of accessing phthalide is that of a duly functionalized β -polyketide chain.¹⁶⁴ Hydrogenation of masked β -polyketonic system **482**, prepared by condensation of isoxazoles **480** and **481**, afforded open-chain enaminoketone **483**, which on treatment with dry HCl in anhydrous nonpolar solvents produced phthalide **484** after aqueous workup (Scheme 121).

Villemin benzannulation route¹⁶⁵ consists of the reaction of α -hydroxyketones **485** with 2 equiv of *tert*-butyl 3-oxobutanoate (**486**) in the presence of a heterogeneous catalyst KF–Al₂O₃ under microwave irradiation to produce highly functionalized phthalides **488** in moderate to good yields (Scheme 122). Mechanistically, a double Knoevenagel condensation of **485** with **486** furnished the intermediate **487**, which after Claisen–Dieckmann reaction and subsequent aromatization yielded **488**.

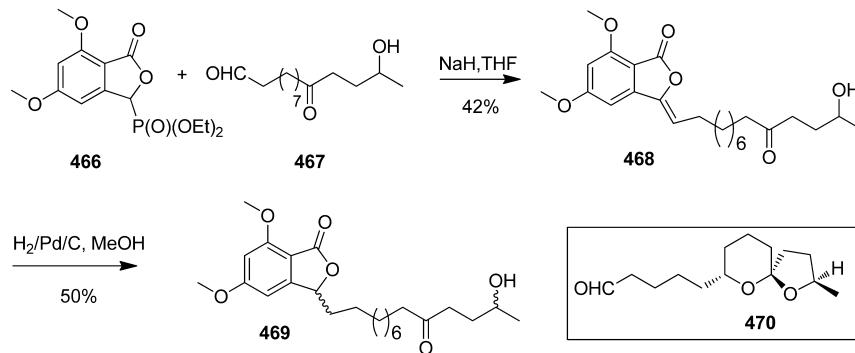
1.3.5.3. Applications in Total Synthesis. **1.3.5.3.1. (S)-(–)-3-Butylphthalide (2b).** There have been reported several syntheses of NBP (**2a**).^{2c} The Wang asymmetric synthesis of the natural product (*S*)-(–)-3-butylphthalide (**2b**) was accomplished in three steps.¹⁵⁷ Condensation of methyl 2-formylbenzoate (**92**) with 2-butanone in the presence of PhCO₂H and catalyst **489** furnished phthalide **490**, which was deoxygenated to **2b** via dithiane **491** (Scheme 123). The presence of an acid additive, for example, PhCO₂H, enhanced the efficiency of the condensation.

1.3.5.3.2. (±)-Isoochracinic Acid (23a). It was synthesized in two steps from formylbenzamide **492**. Nucleophilic addition of acetic acid dianion to **492** followed by *p*-TSA-catalyzed cyclization afforded phthalide **493**, which was demethylated with BBr₃ to afford isoochracinic acid (**23a**) in 40% overall yield (Scheme 124).¹⁶⁶

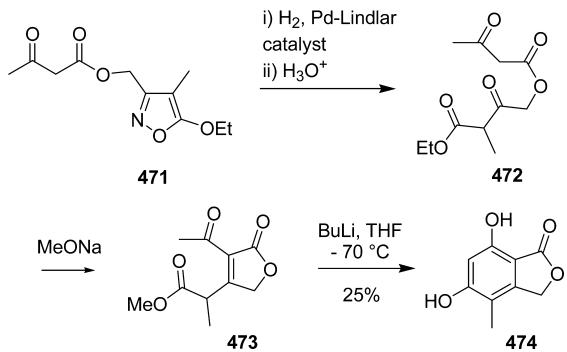
Alternatively, Wittig reaction of 4-methoxyphthalic anhydride (**494**) with benzyloxycarbonylmethylene triphenylphosphorane **495** produced a mixture of 3-alkyldene phthalides (**496**–**498**) (Scheme 125).¹⁶⁷ Compounds **496** and **497** on Pd–C-catalyzed hydrogenation afforded **493**, the key intermediate of isoochracinic acid (**23a**).

1.3.5.3.3. Catalpalactone (27). The naturally occurring phthalide catalpalactone (**27**) was synthesized by application of Pinder's work described in Scheme 112. The key phthalide **449** was converted to **27** via **450** in a two-step sequence:

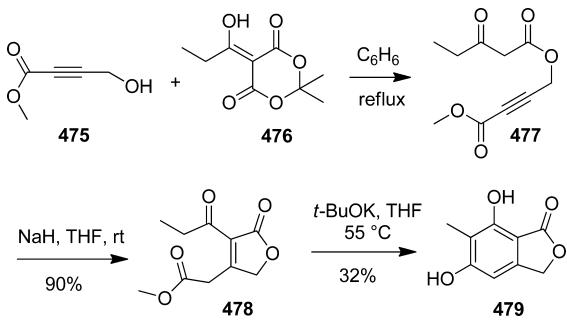
Scheme 118. HWE Reaction in the Synthesis of Sporotricale Methyl Ether



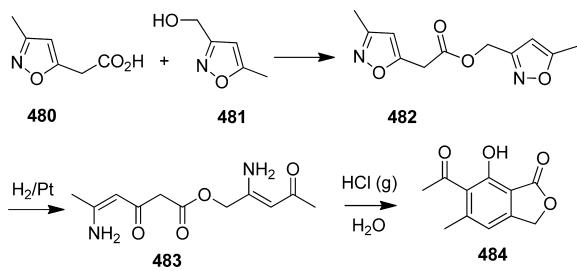
Scheme 119. Anionic Benzannulation Route to 5,7-Dihydroxy-4-methylphthalide



Scheme 120. Michael–Dieckmann-Induced Benzannulation Route to Phthalides



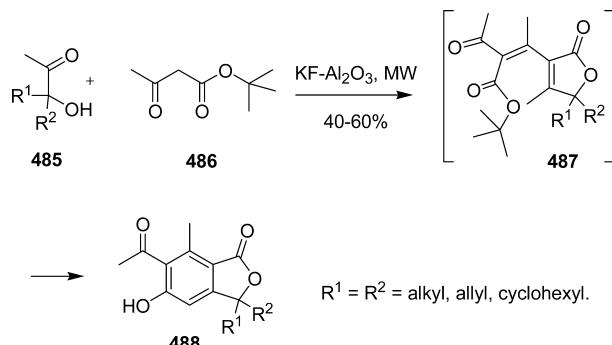
Scheme 121. Acid-Catalyzed Benzannulation: Synthesis of Hydroxyphthalides



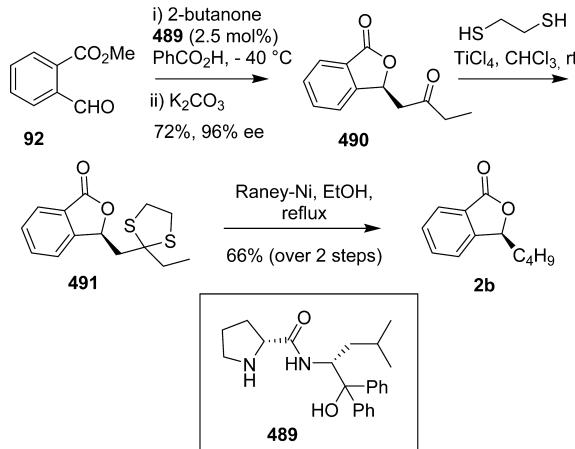
phenylselenylation with LTMP–(PhSe)₂ and oxidative phenyl deselenylation with H₂O₂–AcOH (Scheme 126).¹⁵⁵

1.3.5.3.4. Isopestacin (63) and Cryophonectric Acid (64). The regiospecific route to 3-(2,6-dihydroxyphenyl)phthalides involving DBU-catalyzed condensation of phthalaldehydic acids and 1,3-diketones, as described in Scheme 111, was developed

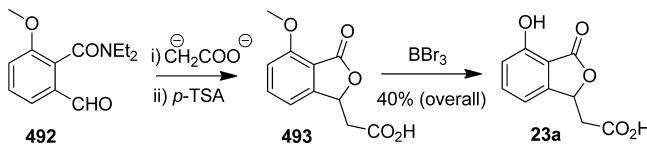
Scheme 122. Knoevenagel-Initiated Benzannulation Route to Hydroxyphthalides



Scheme 123. Total Synthesis of (S)-(−)-3-Butylphthalide

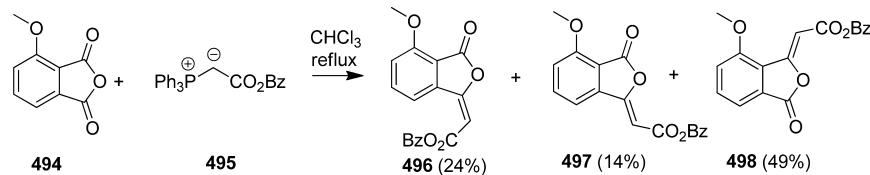


Scheme 124. Synthesis of Isoochracinic Acid

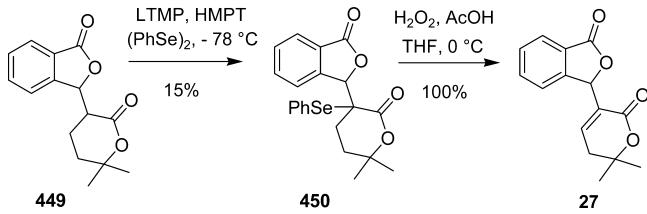


by Mal et al. and applied to the total synthesis of isopestacin (63) and cryophonectric acid (64) (Schemes 127 and 128).^{154b} Condensation of phthalaldehydic acid 501, prepared from 2,5-dimethylanisole (499) via benzamide 500 involving a four-step reaction sequence, with 1,3-cyclohexanedione gave phthalide 502 in 60% yield. Aromatization of 502 with Hg(OAc)₂–NaOAc and subsequent demethylation of resorcinolylphthalide

Scheme 125. Synthesis of Isoochracinic Acid via Wittig Reaction



Scheme 126. Synthesis of Catalpalactone

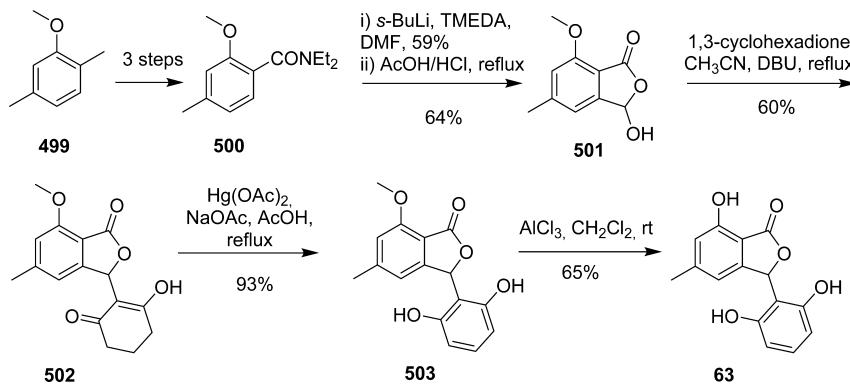


503 with anhydrous AlCl_3 in dichloromethane provided isopestacin (**63**) in 65% yield (Scheme 127).

An analogous reaction sequence was applied to phthalaldehydic acid **505** for the synthesis of cryphonectric acid (**64**, Scheme 128).^{154b} The sequence required DBU-mediated condensation of **505** with **506**, $\text{Hg}(\text{OAc})_2$ -promoted aromatization of **507**, and functional group interconversion of the resulting resorcinoyl phthalide **508**. The preparation of acid **505** involved a four-step reaction sequence from **504** consisting of NBS-bromination, acid hydrolysis, OH-protection, and basic hydrolysis.

1.3.5.3.5. Cerpegin (78). Adopting their benzannulation strategy (Scheme 122), Villemin et al. described two flexible routes¹⁶⁸ to cerpegin (**78**) and their analogues. Route 1 (Scheme 129) described a one-pot three-step synthesis of cerpegin (**78**) and its analogues from hydroxyketones **509**. The three steps include: (i) condensation of **509** with diethyl malonate (DEM) (**510**), (ii) condensation of the resulting lactone **511** with 1,3,5-triazine (**512**), and (iii) *N*-alkylation of **513** using different *N*-alkyl halides to give derivatives of **78** in 71–98% yields. On the other hand, route 2 involves the addition of methylamine to enaminone **515** under solvent-free conditions to afford cerpegin (**78**) derivatives in excellent yields. Herein, enaminolactones **515** served as electrophilic reagent, which were prepared by the condensation of the 2(*S*H)-furanone **511** with DMFDEA (**514**) under solvent-free conditions.

Scheme 127. Synthesis of Isopestacin



1.3.6. Electrophilic and Nucleophilic Aromatic Substitution.

1.3.6.1. Methodology. The reactivity of arene nuclei toward both electrophilic and nucleophilic reagents has been utilized in the synthesis of various phthalides. The Friedel–Crafts alkylation of 3-hydroxy-4-methylbenzyl alcohol (**516**) with formaldehyde in the presence of tin(IV) chloride (cat.) and NEt_3 allowed regioselective one-pot synthesis of phthalide **519** (Scheme 130).¹⁶⁹ The proposed mechanism involved formylation to **517**, formation of hemiacetal **518**, and Tischenko-type reaction to **519**.

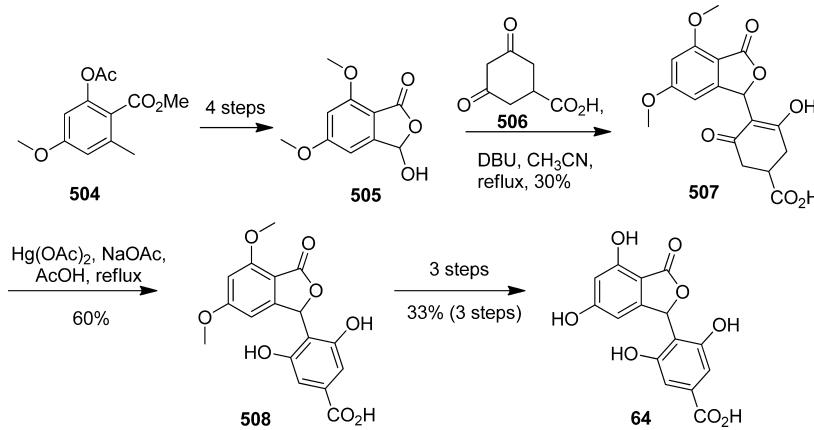
The preparation of 3-arylphthalides from phthalaldehydic acids **337** by aromatic substitution with phenols was discovered in 1894 by Bistrzycki and Oehlert.^{170a} Sulfuric acid-catalyzed substitution^{170b–d} of substituted benzenes **520** with **337** produced corresponding 3-arylphthalides **521** and **522** (Scheme 131) in or without the presence of water. The reactions are simple and high yielding, but suffer from the lack of regioselectivity. Formation of the mixtures of regioisomeric products is intrinsic to the reactions.

Similar to the reactions of benzene derivatives **520** (Scheme 131), 2-alkylfurans **524** react with phthalaldehydic acids **523** in aqueous dioxane in the presence of HClO_4 , to give 3-(2-furyl)phthalides **525** along with 2-carboxyaryldifurylmethanes (Scheme 132).¹⁷¹

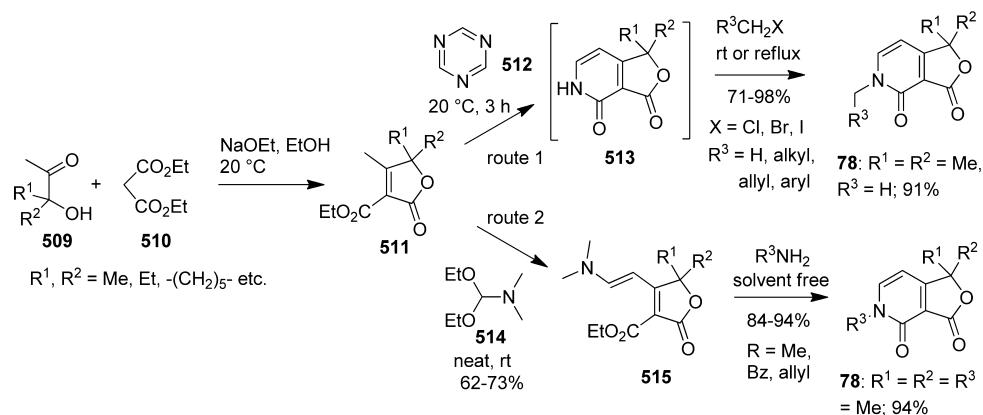
The individual biological activities of phthalides and indoles have prompted the discovery of hybrid heterocyclic compounds. Indoles, which resemble enamines in reactivities, are sufficiently reactive toward phthalaldehydic acids. A variety of indoles **527** react with the phthalaldehydic acids **526** in water without the use of any catalyst to give 3-indolylphthalides **528** via Friedel–Crafts reaction (Scheme 133).^{172a} In contrast, methyl ester of **526** does not react with indole under similar conditions. Identical reactions catalyzed by acidic cation exchange resin amberlyst-15 or $\text{TsOH}\cdot\text{H}_2\text{O}$ are also reported.^{172b}

Nucleophilic displacement of iodine by cyano group of **530**, obtained from **529**, was carried out by copper(I) cyanide. Basic hydrolysis of the resulting nitrile with subsequent cyclization

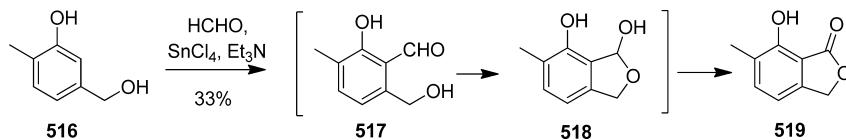
Scheme 128. Synthesis of Cryphonectric Acid



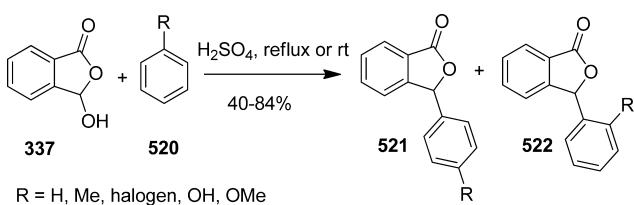
Scheme 129. Total Synthesis of Cerpegin and Their Analogues



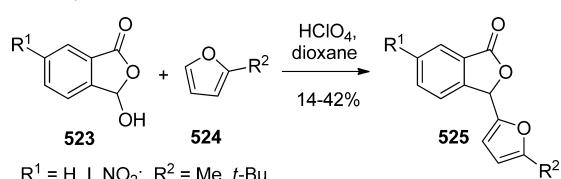
Scheme 130. Friedel–Crafts Alkylation Strategy for Synthesis of Phthalides



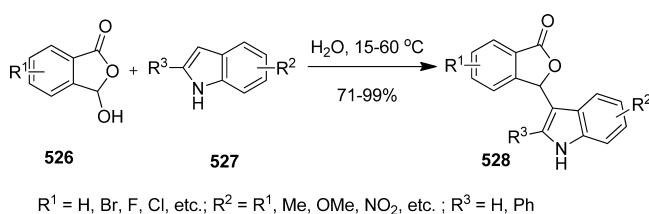
Scheme 131. Substitution Reaction of Arenes with Phthalide to 3-Arylphthalides



Scheme 132. Electrophilic Substitution of Furans with Phthaldehyde Acids



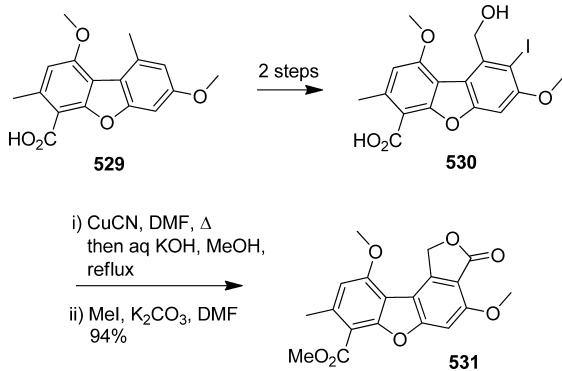
Scheme 133. Synthesis of 3-Indolyl-Substituted Phthalides



and methylation led to the formation of methyl di-O-methylporphyrilate (**531**), a derivative of natural dibenzofuran porphyrilic acid (**59**) (Scheme 134).¹⁷³

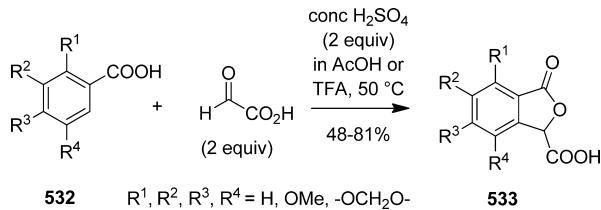
1.3.6.2. Application in Total Synthesis. **1.3.6.2.1. (±)-*α*-Noscapine (36b).** Noscapine is a well-known cough suppressant used for decades. Recently, it has been found to exhibit antitumor activity.^{174a} While the route of Santos^{174b} involved addition of a 1-silyoxyisobenzofuran to an isoquinolinium salt prepared through Bischler–Napieralski reaction, Xu reported the Bischler–Napieralski reaction of a phthalide-containing amide.^{174c} The required intermediate phthalide-3-carboxylic acid **533** was synthesized by electrophilic sub-

Scheme 134. Synthesis of Methyl Di-O-methylporphyrilate via Nucleophilic Aromatic Substitution



stitution of substituted benzoic acids 532, with glyoxalic acid in the presence of an acid such as AcOH or TFA (Scheme 135).

Scheme 135. Synthesis of Phthalide-3-carboxylic Acids via Electrophilic Aromatic Substitution

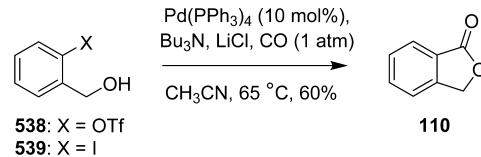


Phthalide 534, prepared following Scheme 135, on sequential treatment with thionyl chloride and amine hydrochloride 535, furnished compound 536. Bischler–Napieralski reaction of 536 in the presence of POCl₃, and subsequent diastereoselective reduction with NaBH₄ generated tetrahydroisoquinoline phthalide 537 (Scheme 136). N-Methylation and debromination allowed the formation of (\pm)- α -noscapine (36b).^{174c}

1.3.7. Cyclocarbonylation. *1.3.7.1. Methodology.* Pd-catalyzed cyclocarbonylation is another popular route for the synthesis of phthalides. The reaction generally involves aryl halides/triflates, CO gas, and a palladium catalyst, which retains its activity in the presence of a base. The catalytic cycle involves the oxidative addition of Pd, insertion of carbon monoxide into the palladium–carbon bond, and reductive elimination of Pd induced by the attached alcohol function. As an example, carbonylation of *o*-hydroxymethylphenyltriflate 538 gave

phthalide 110 in 60% yield (Scheme 137).^{175a} Triflates are preferred over halides on the consideration that triflates can

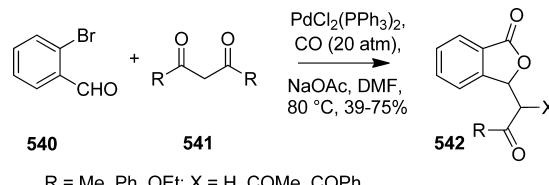
Scheme 137. Pd-Catalyzed Cyclocarbonylation of *o*-Hydroxymethyl Aryltriflates



undergo faster reaction. In a recent study, Pd-catalyzed cyclocarbonylation of *o*-iodobenzyl alcohol 539 is shown to be facilitated by supercritical CO₂, an alternative to conventional solvents.^{175b}

Reaction of *o*-bromobenzaldehyde (540) with 1,3-dicarbonyl compounds 541 in the presence of CO and PdCl₂(PPh₃)₂ leads to 3-substituted phthalides 542 via carbonylative cyclization (Scheme 138).¹⁷⁶ The reaction is sensitive toward temperature, pressure, and the nature of base. With ethyl acetoacetate and DEM, deethoxycarbonylated products were obtained in low yields.

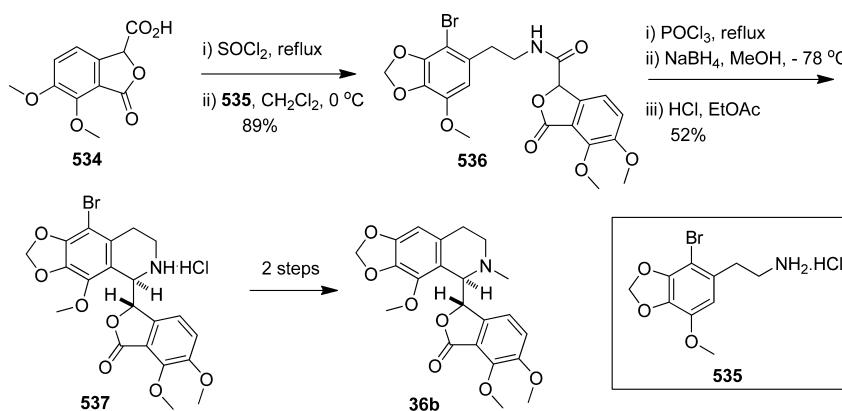
Scheme 138. Pd-Catalyzed Cyclocarbonylation Route to 3-Substituted Phthalides



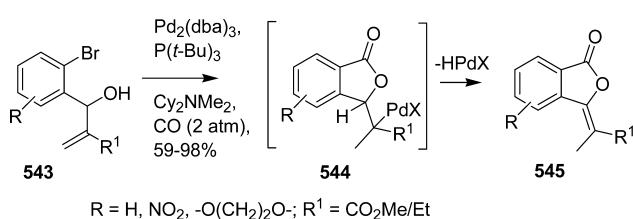
Baylis–Hillman adducts 543 of *o*-bromobenzaldehyde and activated alkenes can be engaged into palladium-catalyzed cyclocarbonylation reaction to give 3-alkylideneephthalide 545 with good yields and selectivity.¹⁷⁷ The reaction takes place in CO atmosphere in the presence of Pd₂(dba)₃ catalyst and proceeds via a proposed palladium–hydride intermediate 544 (Scheme 139).

An application of the Pd(II)-catalyzed cyclocarbonylation of *o*-bromobenzyl alcohol 546 is found in the synthesis of phthalide isoquinolines 547 (Scheme 140),¹⁷⁸ which exhibit a variety of physiological activities, including inhibitory neuro-

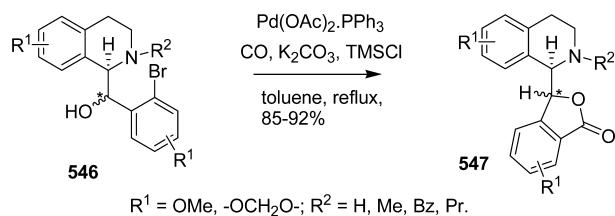
Scheme 136. Total Synthesis of (\pm)- α -Noscapine



Scheme 139. Pd-Catalyzed Cyclocarbonylation of Baylis–Hillman Adducts



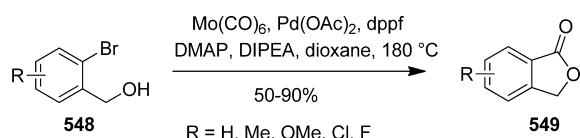
Scheme 140. Phthalideisoquinoline Synthesis via Carbonylation Approach



transmitter, γ -aminobutyric acid (GABA) antagonism. The *threo*- and *erythro* phthalide isoquinolines were synthesized from corresponding *threo*- and *erythro* amino alcohols of 546, respectively.

Alterman et al. utilized solid Mo(CO)₆ as the source of CO instead of gaseous CO for the synthesis of phthalides.¹⁷⁹ Thus, cyclocarbonylation of *o*-bromobenzylalcohols 548 with Mo(CO)₆ in the presence of Pd(OAc)₂, dppf, DMAP, and DIEA yielded corresponding phthalides 549 under microwave heating (Scheme 141). Bromobenzyl alcohols with both electron-rich and electron-deficient groups were used as substrates.

Scheme 141. Mo(CO)₆-Mediated Cyclocarbonylation of *o*-Bromobenzyl Alcohols to Phthalides



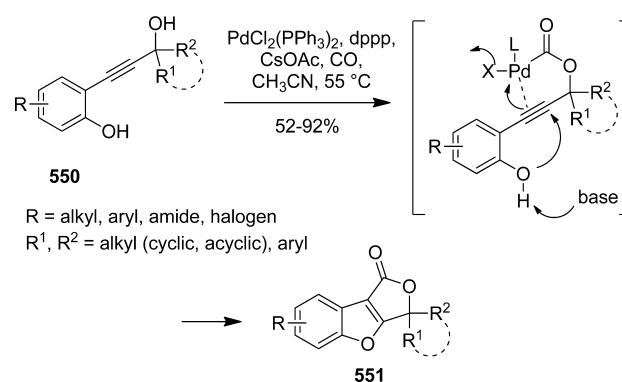
Construction of benzofuran analogues 551 was achieved via intramolecular carbonylative cyclization of *o*-alkynylphenols 550 using PdCl₂(PPh₃)₂ and dppp in the presence of CsOAc at 55 °C in acetonitrile under a balloon pressure of CO (Scheme 142).¹⁸⁰ Substrates with varying R groups resulted in the corresponding phthalides with good to excellent yields. Increase in yields of the phthalides was observed with tertiary alcohols.

1.3.7.2. Application in Total Synthesis. The utility of the cyclocarbonylations is evident from numerous applications in total synthesis. Select examples are presented below.

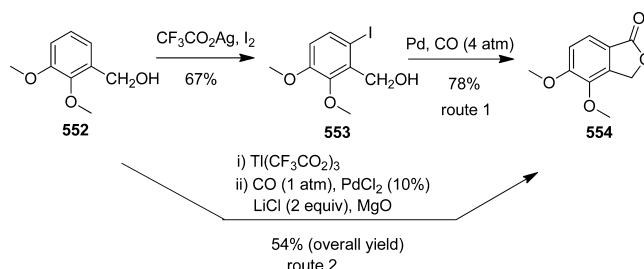
1.3.7.2.1. Pseudomeconin (554). In 1980, Cowell and Stille reported Pd(0)-catalyzed cyclocarbonylation of *o*-iodobenzyl alcohols as a route to pseudomeconin (554).^{181a} Starting from 2,3-dimethoxybenzyl alcohol (552), compound 554 was achieved in two steps via 553 (route 1, Scheme 143). An almost similar synthesis (route 2) involving *o*-thallation of benzyl alcohol 552 and subsequent palladium-catalyzed cyclocarbonylation of the thallated intermediate in CO atmosphere was described by Larock.^{181b}

1.3.7.2.2. Mycophenolic Acid (3). The key intermediate phthalide 556 of the 11-step Lee synthesis of mycophenolic

Scheme 142. Synthesis of Benzo[*b*]furo[3,4-*d*]furan-1-ones via Carbonylative Annulation

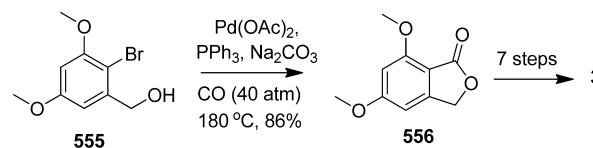


Scheme 143. Synthesis of Pseudomeconin via Cyclocarbonylation



acid (3) was accessible by palladium-catalyzed cyclocarbonylation of bromobenzyl alcohol 555 (Scheme 144).¹⁸²

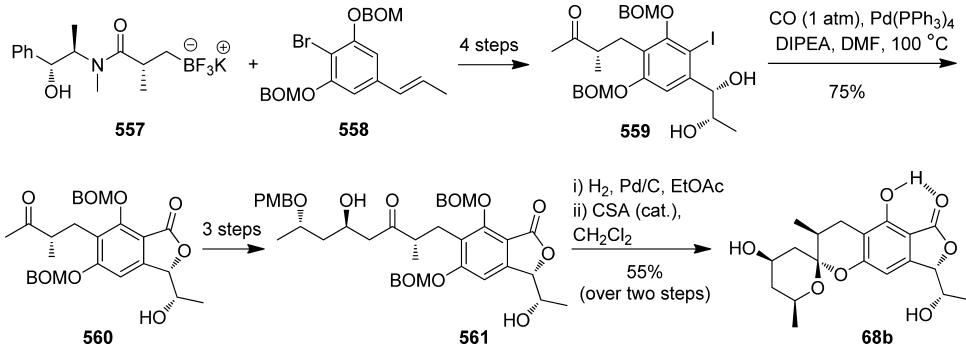
Scheme 144. Synthesis of a Phthalide via Cyclocarbonylation Approach



1.3.7.2.3. Virgatolide B (68b). The first synthesis of spiroketal-fused phthalide virgatolide B (68b) was reported by Brimble et al. in 2013, involving a regioselective intramolecular cyclocarbonylation process as the key step.¹⁸³ Palladium-catalyzed Suzuki coupling of enantiomerically enriched potassium β -trifluoroboratoamide 557 with aryl bromide 558 followed by some functional group conversion allowed the construction of α -chiral β -arylated ketone 559 (Scheme 145). The Pd-catalyzed cyclocarbonylation of 559 afforded the chiral phthalide 560 in 75% yield. Elaboration of side chain using aldol reaction furnished ketone 561 with excellent diastereoselectivity. Finally, hydrogenolysis followed by spiroketalization under catalytic CSA yielded virgatolide B (68b). The hydrogen bonding shown in 68b explains the regioselectivity of the spiroketalization.

1.3.8. Benzannulation/Cycloaddition. Although the construction of the furan moiety on a benzene nucleus is considered as the preferred mode, recently benzannulation, that is, construction of a benzene ring or simultaneous formation of both rings, is being intensively explored. The transition metal-catalyzed [2+2+2] cycloaddition reactions of alkynes producing phthalides have drawn the attention of many research groups

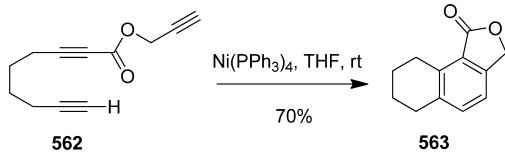
Scheme 145. Total Synthesis of Virgatolide B via Cyclocarbonylation Approach



such as Tanaka and Shibata.^{184a,b} Notwithstanding, the Diels–Alder reactions have also been adopted in many instances.

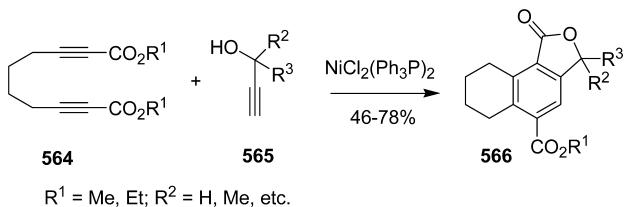
1.3.8.1. Transition Metal-Catalyzed [2+2+2] Cycloaddition. The [2+2+2] cycloadditions are usually promoted by transition metal catalysts such as Ni, Pd, Rh, Ru, etc. For example, angular phthalide **563** was synthesized by Ni(0)-catalyzed intramolecular cyclotrimerization of 2-ynyl ester of nona-2,8-diynoic acid **562** (Scheme 146).¹⁸⁵

Scheme 146. Ni(0)-Catalyzed [2+2+2] Cyclotrimerization to Angular Phthalide



The Ni(0) catalyst was also used in the intermolecular [2+2+2] cycloadditions. Thus, the tetralin lactones **566** were prepared in good yields from octa-1,7-diyne **564** and propargylic alcohols **565** (Scheme 147).¹⁸⁵

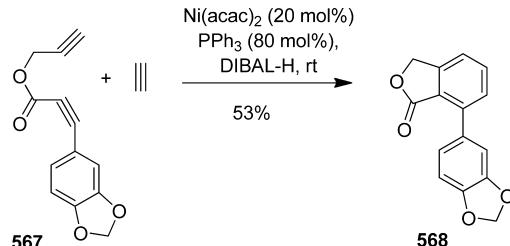
Scheme 147. Ni(0)-Catalyzed Intermolecular Cyclotrimerization



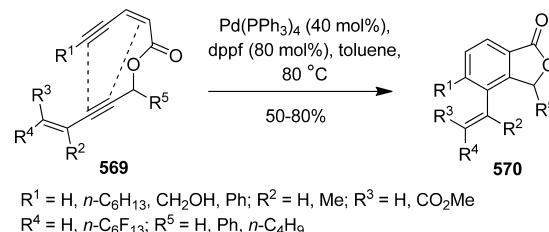
1,6-Diyne of type **567** are reported to undergo Ni(0)-catalyzed [2+2+2] cyclization with unsubstituted or disubstituted acetylenes to yield phthalide **568** (Scheme 148).¹⁸⁶ The methodology has been utilized for the synthesis of natural product, taiwanin C (**18a**).

Palladium(0)-catalysts have been found to promote intramolecular cycloaddition of bis-ynene systems to produce 4-vinylphthalides in moderate to good yields as shown in the transformation of **569** to **570** (Scheme 149).¹⁸⁷ The enyne moieties connected via an ester function act as a 4-carbon unit in the [4+2] benzannulation reaction. The process is completely regioselective and applicable for both 3-unsubstituted and substituted phthalides. The method was applied to the synthesis of pharmacologically important *n*-butylphthalide (**2a**) (discussed in section 1.3.8.3).

Scheme 148. Ni(0)-Catalyzed Crossed Alkyne Cyclotrimerization

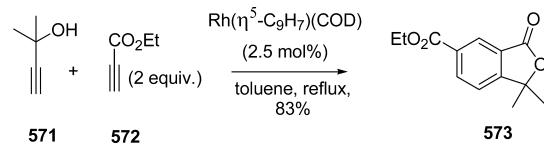


Scheme 149. Palladium-Catalyzed Intramolecular Benzannulation of Bis-enynes



Rhodium complexes are interestingly finding usefulness in the [2+2+2] cycloadditions. In 1985, Booth and co-workers reported that in the presence of a (η^5 -indenyl)rhodium(I) complex, 2-methylbut-3-yn-2-ol (**571**) and two molecules of acetylenecarboxylate **572** form phthalide **573** through sequential [2+2+2] cycloaddition and lactonization (Scheme 150).¹⁸⁸

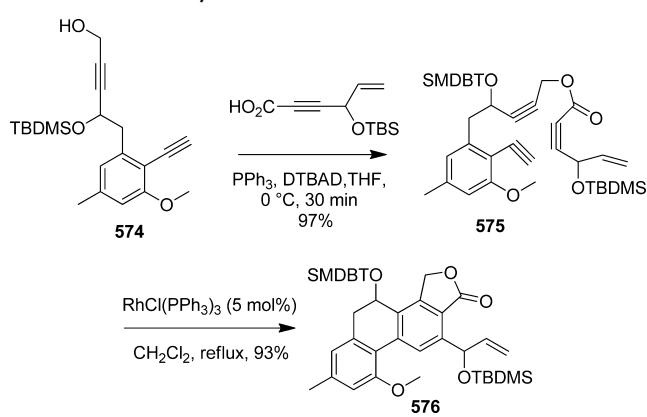
Scheme 150. Rh(I)-Catalyzed [2+2+2] Cycloaddition



An intramolecular version of Scheme 150 led to the key tetracyclic skeleton of complex landomycinone **576**. Rh(I)-catalyzed [2+2+2] cycloaddition of triyne **575** (Scheme 151), prepared from **574**, resulted in the simultaneous formation of B and C rings of the landomycinone skeleton.¹⁸⁹

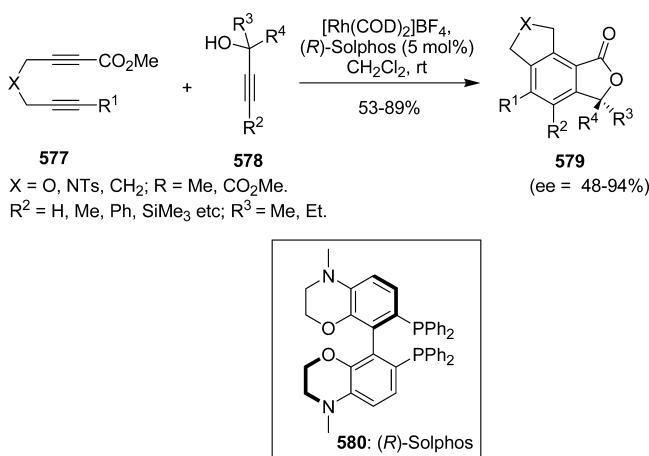
Tanaka et al.¹⁹⁰ described a regio- and enantioselective intermolecular 1,6-diene-alkyne cycloaddition for the synthesis of optically active phthalides **579**. Thus, the Rh(I)-catalyzed reaction involving 1,6-dienes with an alkoxycarbonyl group at

Scheme 151. Rh(I)-Catalyzed [2+2+2] Cycloaddition En Route to Landomycinone Intermediate



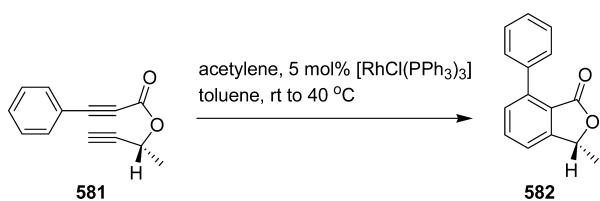
the alkyne terminus 577 and tertiary propargylic alcohols 578 gave phthalides 579 in the presence of chiral phosphine ligand 580 (Scheme 152).

Scheme 152. Enantioselective Rh(I)-Catalyzed Benzannulation Route to Phthalides



The Wilkinson's catalyst is also found to catalyze the intermolecular 1,6-diyne-acetylene cycloaddition.¹⁹¹ Use of chiral 1,6-diyne 581 resulted in the corresponding chiral 3-substituted phthalide 582 (Scheme 153). Racemization of the chiral center was not observed.

Scheme 153. Chiral 3-Substituted Phthalides by Rh(I)-Catalyzed Crossed Alkyne Cyclotrimerization



A less common route to polysubstituted phthalide derivatives is Rh(I)-catalyzed [2 + 2 + 2] cycloadditions of 1,6-dynes with potassium (Z)-(2-bromovinyl) trifluoroborates 584. Dienes 583 reacted with 584 to give phthalides 585 and 586 (Scheme 154).^{192a} Fluoroborates 584 plays a decisive task for this transformation, due to its nucleophilic vinyl borate and

electrophilic vinylbromine moieties (vide mechanism).^{192b} The regioselectivity of the reaction was poor.

Likewise, unsymmetrically bromo-substituted diynes and ethynyltrimethylsilane undergo cyclotrimerization in the presence of precatalysts such as Cp^{*}RuCl(COD) and [Rh(COD)₂]BF₄/BINAP.^{192c}

Synthesis of phthalides 591 required Rh-catalyzed cyclotrimerization of alkynes 587, 588, and 589 followed by Pd(II)-catalyzed cyclocarbonylation of regiospecifically assembled phenylboronates 590 (Scheme 155).¹⁹³ Cp^{*}RuCl(COD) served as the tether to bring the components in closer proximity.

Three-component coupling reaction of phenylacetylene 592, carbon dioxide, and 3-bromo-1-phenyl-1-propyne (593) was catalyzed by AgI, K₂CO₃, and DMAC to furnish arylphthalene lactones 595 and 596 (Scheme 156).¹⁹⁴ The in situ generated 1,6-diyne intermediate 594 underwent formal [2+2+2] cycloaddition to form two regioisomeric phthalides. The ratio of the products was governed by polar effects of the substituents of the aromatic rings. In most cases, phthalides 595 are the major isomers.

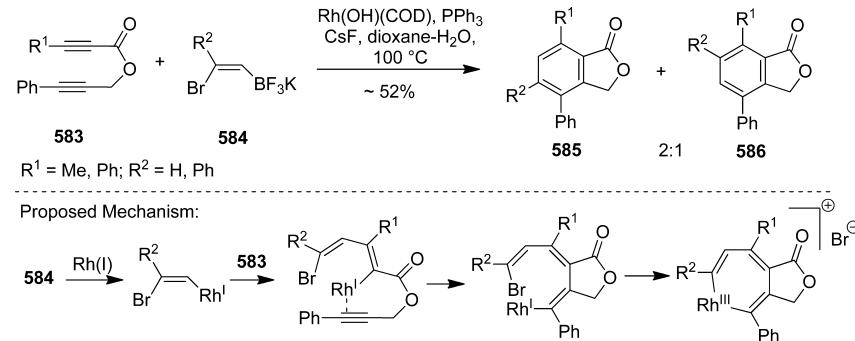
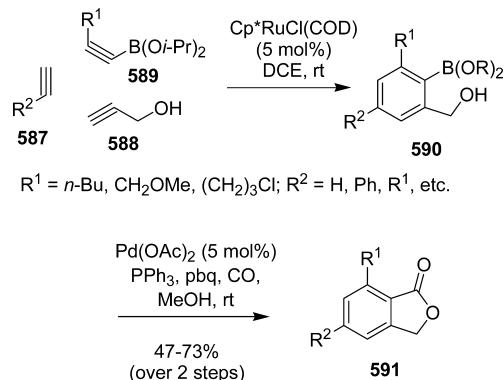
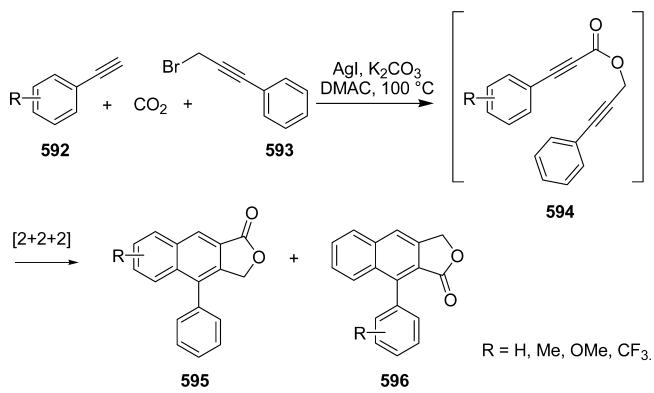
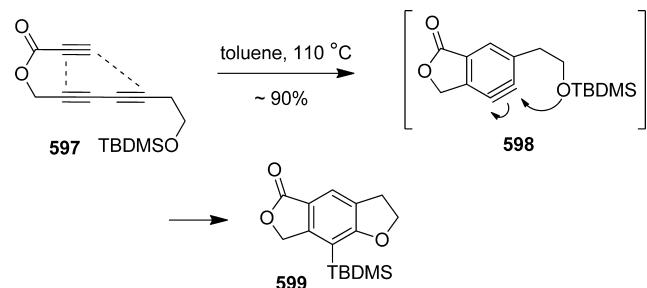
Interestingly, noncatalytic intramolecular cyclization of triyne 597 in refluxing toluene produced tricyclic phthalide derivative 599. The benzyne intermediate 598 is thought to be formed (Scheme 157).¹⁹⁵ No metal catalyst was required for this reaction.

1.3.8.2. Diels–Alder reaction. The Diels–Alder (D–A) reaction is one of most versatile avenues for the construction of carbocycles and heterocycles. It has been exploited in various forms. Watanabe et al. reported intermolecular D–A of 2(5H)-furanones 601 for regioselective assembly of phthalide skeletons.¹⁹⁶ The reaction between 3-(phenylsulfanyl)-2(5H)-furanone 601 and silyloxydienes 600, followed by thermal elimination of phenylsulfenic acid from adducts 602, resulted in mixtures of phthalides 603 and 604 with moderate to good yields, 7-hydroxyphthalides 603 being the major product in each case (Scheme 158).

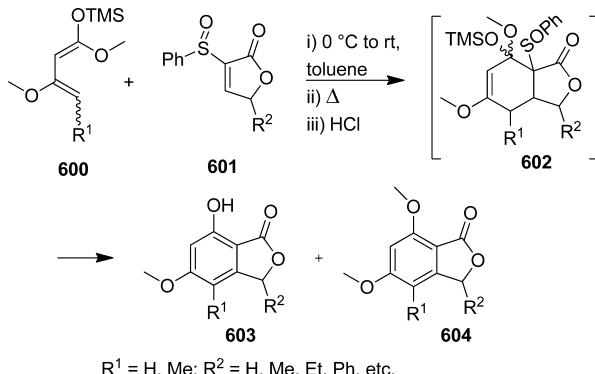
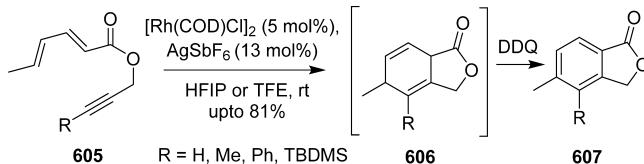
Intramolecular Diels–Alder reactions have also been studied in detail for the synthesis of phthalides. Ester tethered diene 605 has been shown to undergo intramolecular cycloaddition in the presence of cationic Rh(I) species derived from [Rh(COD)Cl]₂ and AgSbF₆ in hexafluoroisopropanol or trifluoroethanol to give phthalide precursor 606, which upon aromatization with DDQ provides phthalides 607 (Scheme 159).¹⁹⁷

Such strategies are also exploited for the construction of both natural and synthetic carbazoles. The double bond at C2 of an indole derivative has been shown to take part in intramolecular D–A reactions. Indole-3-carboxaldehyde (608) underwent domino Wittig–Diels–Alder reaction with Wittig reagent 609 in refluxing diphenyl ether to furnish tetrahydrocarbazoles 610, which on DDQ oxidation yielded carbazolones 611 in good yields (Scheme 160).¹⁹⁸ Both the cis and trans fused diastereomers of 610 were formed in 1:1 ratio as shown. The sequence is also applicable to indole-2-carboxaldehyde for the carbazoles 612.

Lovely's synthesis of benzimidazole phthalide 617^{199a} followed the similar precept for the total synthesis of 7'-desmethylkealiquinone in three steps from imidazole 613 (Scheme 161).^{199b} A DCC-mediated coupling of 613 with arylpropionic acid 614 gave enyne 615, which on heating produced dihydronbenzimidazole 616 in 84% yield. Oxidation of

Scheme 154. Synthesis of Phthalides from Alkenylfluoroborates via [2+2+2] Cycloaddition**Scheme 155.** Sequential [2+2+2] Cyclotrimerization and Cyclocarboxylation Route to Phthalides**Scheme 156.** Arylnaphthalene Lactones Formation via Ag(I)-Catalyzed [2+2+2] Cycloaddition**Scheme 157.** Noncatalytic [2+2+2] Cycloaddition Route to Phthalides

the cycloadduct with MnO₂ furnished benzimidazole phthalide 617 in 89% yield.

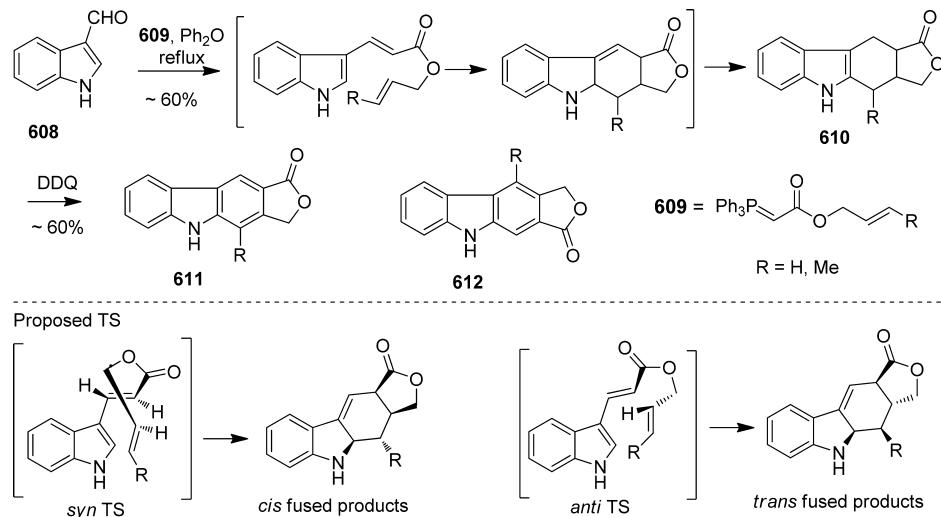
Scheme 158. Synthesis of Phthalides via D–A Reaction of Furanones and Silyloxydienes**Scheme 159.** Rh(I)-Catalyzed Intramolecular [4+2] Cycloaddition of Dienoates

1.3.8.3. Application in Total Synthesis. **1.3.8.3.1. Daurinol (18b) and Retrochinensis (60a).** Their syntheses were accomplished starting from isovanillin involving [2+2+2] cycloaddition of 1,6-diyne 618 as the key step. Arylpropargyl arylpropiolate 618, upon heating in xylene, yielded the corresponding arylnaphthalene lactones 619 and 620 in excellent yields (Scheme 162). The lactones were converted to daurinol (18b) and retrochinensis (60a) through debenzylation and debenzylation followed by methylation, respectively.²⁰⁰

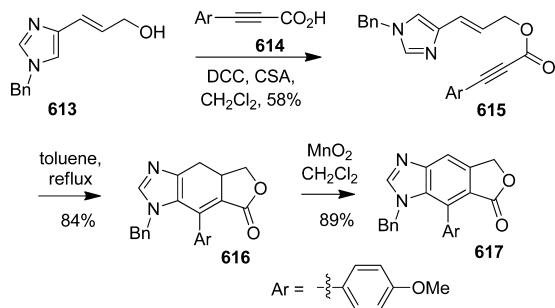
1.3.8.3.2. Alcyopterosin E (22a). Witulski synthesis of 22a entailed cycloaddition of chiral triyne 621 in the presence of RhCl(PPh₃)₄ to give phthalide 622 (Scheme 163).²⁰¹ The final step, formation of O-nitrate, was accomplished by using Bu₄NNO₃, NaNO₃. Following a similar sequence, alcyopterosin L (22b) and M (22c) were also synthesized from 623.

1.3.8.3.3. n-Butylphthalide (2a). The methodology depicted in Scheme 149 was applied to the total synthesis of butylphthalide (2a).¹⁸⁷ Phthalide 625 was obtained from bis-alkyne 624 by means of a palladium-catalyzed intramolecular [2+2+2] benzannulation. It was then converted into 2a in two steps consisting of ozonolysis and Rh(I)-catalyzed decarbonylation (Scheme 164).

Scheme 160. Synthesis of Carbazolones via Tandem Wittig–Diels–Alder Reaction



Scheme 161. Lovely's Diels–Alder Approach to Benzimidazole Phthalide



1.3.8.3.4. Cryptoacetalide (630). The first total synthesis of the tetracyclic terpene natural product **630** was completed in 12 steps via intramolecular [2+2+2] cyclotrimerization coupled with a radical cyclization.²⁰² The triyne **627** was subjected to Cp^{*}RuCl(COD)-catalyzed [2+2+2] cyclotrimerization in toluene under microwave irradiation (300 W). The resulting cycloadduct **628**, on *O*-deprotection with DDQ, gave the tricyclic phthalide **629** in 90% yield, which on irradiation (200 W Xe/Hg lamp) in the presence of iodine and iodobenzene resulted in the formation of an inseparable 2:1 mixture of cryptoacetalide (**630**) and *epi*-cryptoacetalide (**631**) (Scheme 165).

1.3.8.3.5. (R)-(+)Tetrahydro-4,5-seco-furanoeremophilane-5,1-carbolactone 88. Kanematsu et al. developed a synthetic route to tricyclic phthalide **88** via an intramolecular Diels–Alder reaction.²⁰³ In the presence of *t*-BuOK, the

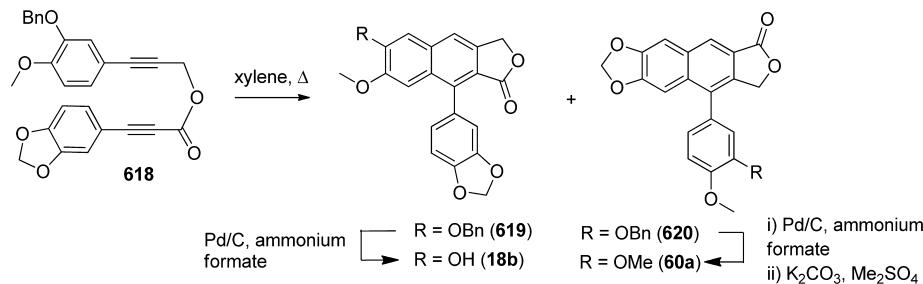
propargyl ether **632** underwent intramolecular Diels–Alder reaction to form **633**, which on subsequent hydration followed by oxidation with Fetizon reagent produced **634**. Two-step dehydrogenation followed by aromatization afforded tricyclic phthalide **635** in good yield. Wacker oxidation of **635** at the terminal double bond furnished natural product **88** in 94% yield (Scheme 166).

1.3.8.3.6. (+)-Spirolaxine Methyl Ether (24b). The total synthesis of potent helicobactericidal compound spiroloxine methyl ether (**24b**) required phthalide **639** as the intermediate. It was synthesized from **638**, the Alder–Rickert product of **636** and **637** (Scheme 167).²⁰⁴ Under the influence of TBAF, both desilylation and lactonization of **638** took place.

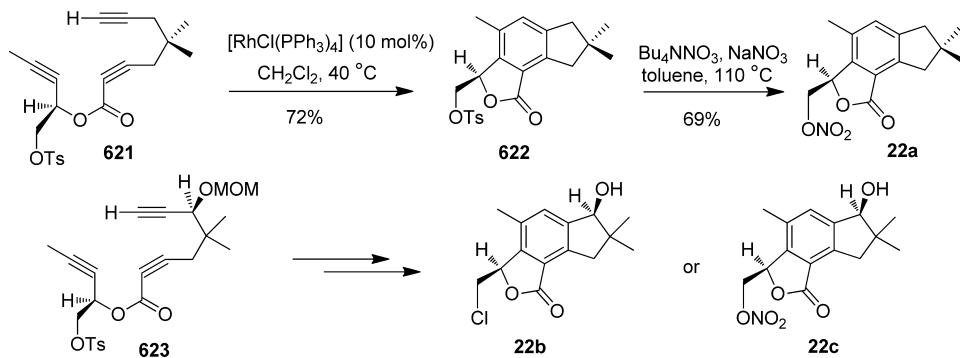
1.3.8.3.7. (±)-Concentricolide (71a). The first racemic synthesis of concentricolide (**71a**),²⁰⁵ a novel compound with anti-HIV-1 activity, was accomplished via a Diels–Alder strategy. Reaction of alkene sulfoxide **641**, obtained from dihydrofuranone **640**, with 3-vinylfuran **642** in refluxing toluene afforded the tricyclic intermediate **643**, which on treatment with CaCO₃ and subsequent aerial oxidation furnished concentricolide (**71a**) (Scheme 168). The yield was very low possibly because of the polymerization of vinylfuran moiety.

1.3.8.3.8. Mycophenolic Acid (3). Following the D–A protocol of Watanabe (Scheme 158), Cruz et al. accomplished a total synthesis of mycophenolic acid (**3**).^{206a} Intermolecular Diels–Alder reaction between TMS protected diene **644** and alkene sulfoxide **645** gave tricyclic phthalide **646** (Scheme 169). In two steps, it was converted to **647**, which was eventually

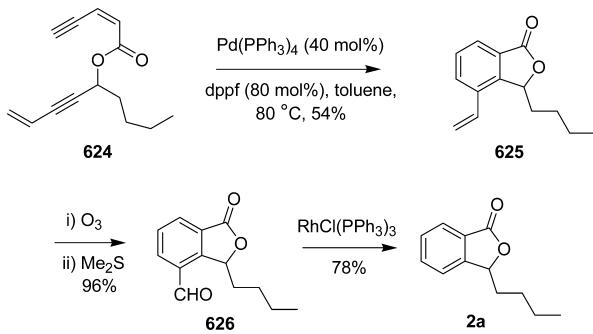
Scheme 162. Synthesis of Daurinol and Retrochinensis



Scheme 163. Total Synthesis of Alcyopterosin E, L, and M



Scheme 164. Total Synthesis of 3-Butylphthalide



converted to mycophenolic acid (3) using the protocol of Patterson and Huang.^{206b}

1.3.9. Rearrangement. *1.3.9.1. Photochemical Rearrangement.* Kobayashi et al. synthesized 3-alkylphthalides **650** by the β -scission of alkoxyl radicals generated by the photolysis of the hypoiodites **649**, which, in turn, was produced by the irradiation of catacondensed benzocyclobuten-1-ol **648** in benzene containing mercuric oxide (HgO) and iodine at room temperature (Scheme 170).²⁰⁷ The yield of the reaction depends upon the size of the nonaromatic ring and substitutions in the benzene ring. Increase in the ring size of nonaromatic ring, that is, cyclohexane to cycloheptane, decreases the yields. Similarly, electron-donating substituents at aromatic ring decrease the yields of the reactions. The process has been applied to the synthesis of unsubstituted, monosubstituted, and disubstituted phthalides. Reduction of **650** with Bu_3SnH gave iodine free 3-substituted phthalides.

Irradiation of 2-(alkoxymethyl)-5-methylphenacyl chloride/benzoate **651** in non-nucleophilic solvent in the presence of a

trace amount of water produced 3-methylphthalide **655** as the major photo product (Scheme 171).²⁰⁸ The conversion resulted from two consecutive photochemical isomerizations. The photoenol **652**, produced from **651** via a 1,5-H shift, underwent addition with water to form 2-acetyl-4-methylbenzaldehyde **653**, which was transformed to **655** via photoenol **654**.

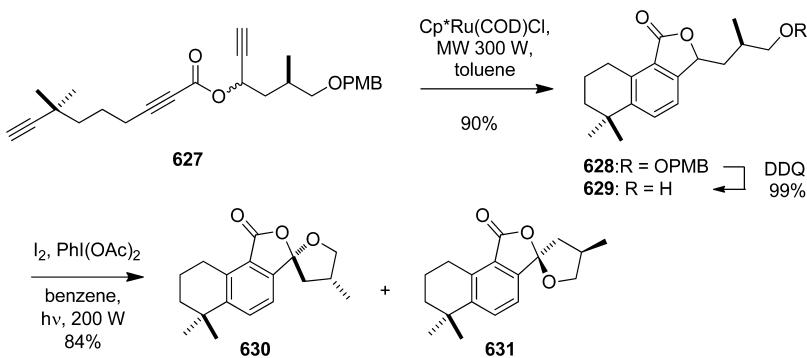
The solid-state photoreaction of 2-arylothio ester **656** or *N,N*-disubstituted-2-benzoylbenzamides **657** produced optically active phthalides **659** and **662** with good yields and ee, respectively (Scheme 172).^{209a,b} The chirality in the products was introduced when compounds crystallized by spontaneous resolution underwent reactions in the crystalline lattices. The reaction path A involving **656** proceeds through an unprecedented intramolecular cyclization followed by a 1,4-phenyl migration as in **658**. The reaction path B involving **657** is proposed to proceed through radical pair intermediates **660** and **661**.

Photoisomerization of 2-aryl-2-methyl/benzylindane-1,3-diones **663** has been shown to yield a mixture of *Z*- and *E*-3-alkylidenephthalides **665** and **666** (Scheme 173) in 86–91% yield.^{210a} The reaction occurred through α -cleavage (Norrish type I) to generate biradical intermediate **664**, which reorganized and cyclized to form two different products.

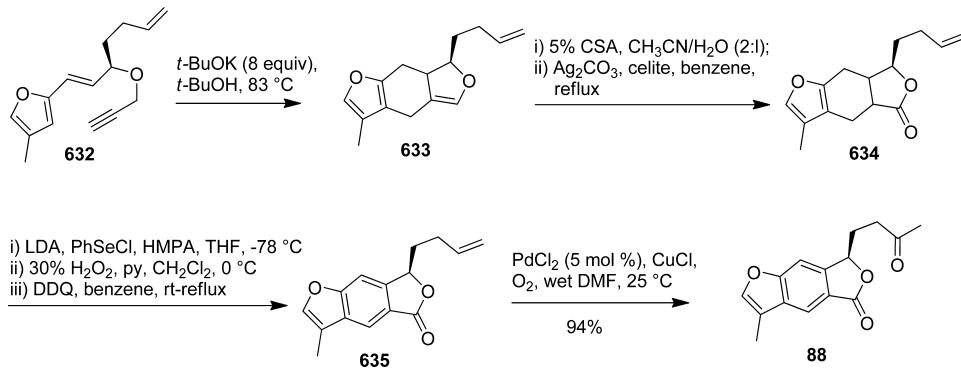
Similar photochemical transformation was observed with 2-ethyl/propyl-1,3-indanodiones under irradiation with a Nd:YAG laser at 294 nm.^{210b}

Schmalz synthesis of 3-substituted phthalides **670** relied on a light-induced isomerization of *ortho*-formylarylketones **667**.⁵⁴ As compared to their nucleophile-induced synthesis (Scheme 10), the photochemical route (Scheme 174) gave slightly higher yields of the phthalide products. Mechanistic consideration suggests a Norrish type II reaction of **667** in the first

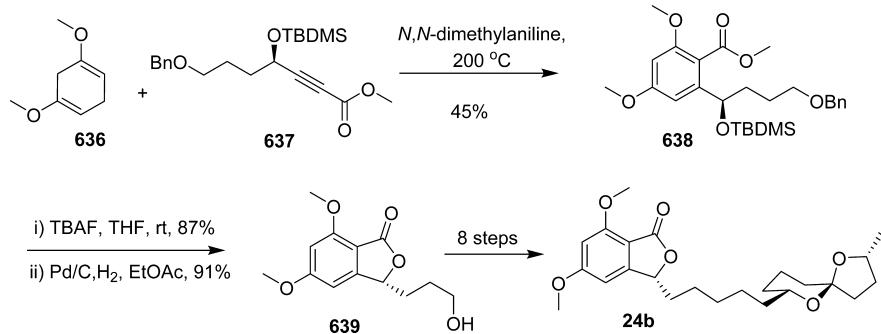
Scheme 165. Total Synthesis of Cryptoacetalide



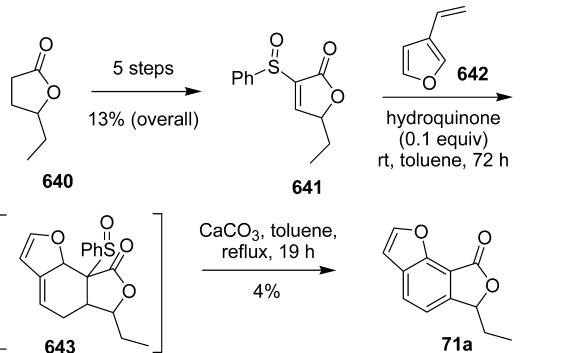
Scheme 166. Kanematsu Diels–Alder Approach to Tricyclic Phthalide



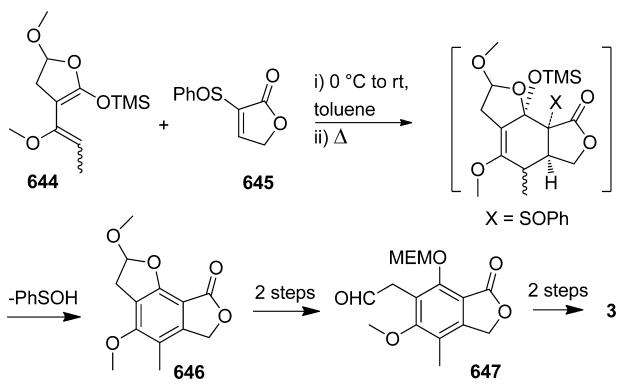
Scheme 167. Yadav Synthesis of (+)-Spirolaxine Methyl Ether



Scheme 168. Diels–Alder Approach to (±)-Concentricolide



Scheme 169. Diels–Alder Approach to Mycophenolic Acid



step, forming an enol-ketene 668, which on cyclization followed by tautomerization produces 670 via 1-hydroxyisobenzofurans 669.

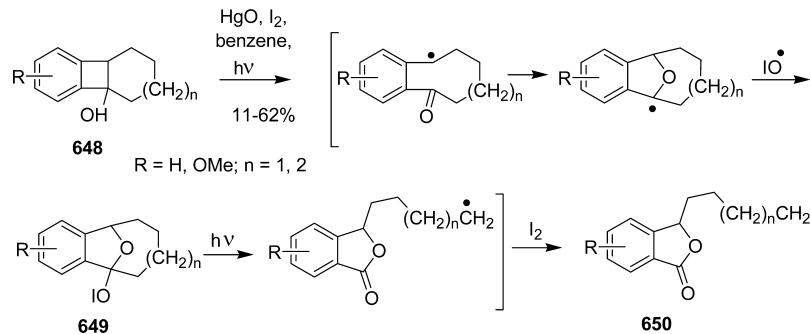
Norrish type II-initiated photooxidation at the benzylic position of the angularly condensed benzo[*a*]anthraquinone systems was pioneered by Krohn et al.²¹¹ For benzylanthraquinone 671, the reaction was carried out under sunlight in dichloromethane solution and ambient conditions to give phthalide 672 (Scheme 175) instead of the corresponding benzylic-carbonyl product. The proposed mechanism suggests a biradical pathway. Initial biradical 673, arising out of Norrish type II reaction of anthraquinone 671, undergoes cyclization with the vicinal lactone carbonyl to form an anthra[2,1-*c*]furan intermediate 674, which on reaction with molecular oxygen yields the stable anthra[2,1-*c*]furan lactone 672 via peroxy intermediate 675.

1.3.9.2. Thermal Rearrangement. Recently, Li et al. have reported the construction of 3,3-disubstituted phthalides by ring contraction of tropones.²¹² The multisubstituted tropone 676, when refluxed with aliphatic alcohols, afforded substituted phthalides 679 (Scheme 176). The yields of the products decreased with increase in the bulk of the alcohol used, MeOH being the most suitable solvent. The proposed mechanistic pathway involves acetal 677, which forms oxetane intermediates 678 via oxygen attack at the carbonyl group followed by 6*π* electrocyclic reaction. Liberation of HCl with concomitant ring-opening produced the phthalide 679.

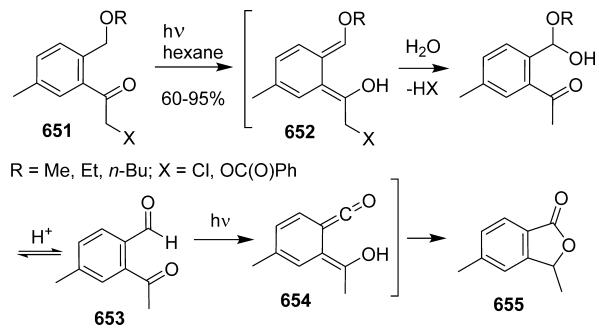
Lead tetracetate-mediated ring expansion of 1,2-dihydrobenzocyclobuteno 680 has been known for the synthesis of phthalide 681 (Scheme 177).²¹³ The formation of the phthalide is explained by β-scission of intermediate 682 to give 683 which cyclizes to 684. Formation of phthalan radical 685 followed by one more β-scission accounts for the formation of 681.

Nair synthesis of phthalides was based on reaction of homophthalic anhydride (686) with various benzils 687. Heating the mixture of 686 and 687 at 145 °C yielded 688 as the major diastereomer along with 689.²¹⁴ The rearrange-

Scheme 170. Kobayashi Rearrangement to 3-Alkylphthalides



Scheme 171. Photochemistry of 2-Alkoxyethyl-5-methylphenacyl Chloride/Benzoate



ment involves the following steps: condensation, decarboxylation, and subsequent ring closure as depicted in the mechanism (Scheme 178). The reaction is general, but the yields vary with the substituents in benzil.

1.3.9.3. Application in Total Synthesis. **1.3.9.3.1. Mycophenolic Acid (3).** Photolysis of N-chlorobenzamides (e.g., 691) provides a new route to phthalides (e.g., 692).²¹⁵ Amide 690 on treatment with *t*-butyl hypochlorite in DCM produced N-chloroamide 691. This, on photolysis, produced iminolactone intermediate, which was immediately hydrolyzed to phthalide 692 (Scheme 179). Chain elongation of the phthalide 692 at C6 led to completion of the total synthesis of mycophenolic acid (3) in four steps.

1.3.9.3.2. Pestalalactone (193). Extending the scope of the methodology illustrated in Scheme 174, Schmalz et al. described an efficient and short synthesis of the natural product, pestalalactone (193), via a facile photolytic transformation of pestalone (192).^{54,216} When pestalone (192),

obtained from orcinol (191), was irradiated with UV light (350 nm) in *d*₆-DMSO, pestalalactone (193) was formed in 80% yield (Scheme 180).

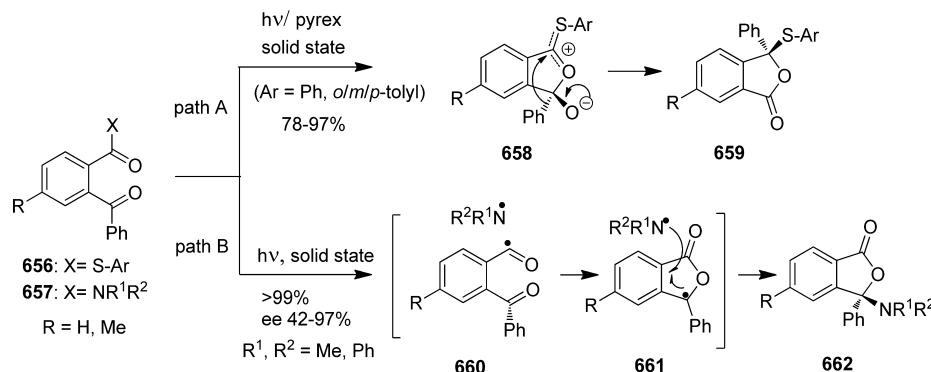
1.3.10. Miscellaneous. **1.3.10.1. Name Reactions in Phthalide Synthesis.** **1.3.10.1.1. Hauser Annulation.** Hauser annulation,^{3b,c} a well-known 1,4-quinol forming reaction, has been utilized for the synthesis of benzophthalides. LDA-mediated condensation of 3-(phenylsulfonyl)-isobenzofuranones 693 with butyrolactone 694 produced isonaphthofuranones 695 in 65–74% yield (Scheme 181).²¹⁷

1.3.10.1.2. Pummerer Rearrangement. It is the one in which an alkyl sulfoxide rearranges to α -acetoxy thio ether via a sulfenium ion intermediate in the presence of Ac₂O. Using the reaction, Hauser and Dorsch reported the preparation of phenylsulfanyl benzopyranonephthalide 699 (Scheme 182).²¹⁸ The starting sulfoxide 697 was prepared in four steps from chromone 696. Intramolecular Pummerer reaction of 697 in acetic anhydride resulted in 699, via sulfenium intermediate 698.

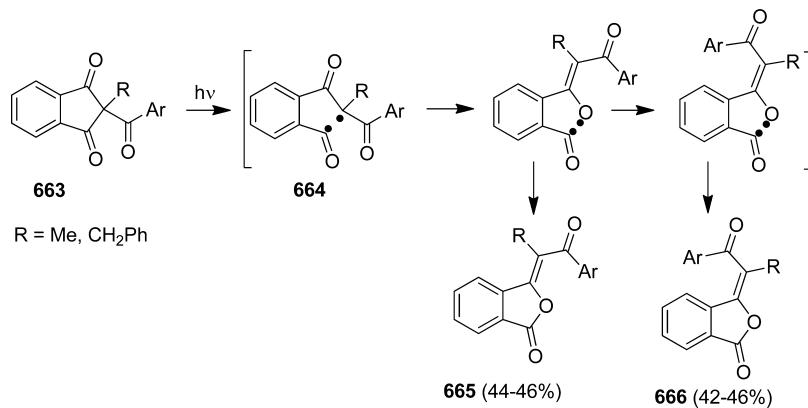
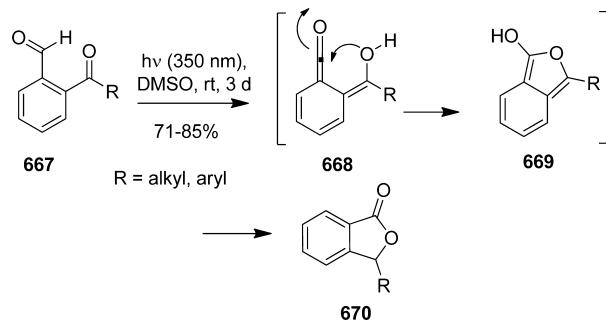
1.3.10.1.3. Fischer Indolization. Fischer indolization is an indole-forming reaction of arylhydrazones. This reaction can be applied for the synthesis of indole fused phthalides by using the hydrazones such as 700. Acid-catalyzed intramolecular cyclization of 700 led to furoindolone 701 (Scheme 183).^{219a,b} **N**-Protection and C3 bromination using NBS produced bromophthalide 702. 3-Phenylsulfonyl furoindolone derivative 703 was obtained by phenylsulfonylation of 702 using PhSO₂Na.

1.3.10.1.4. Baeyer–Villiger Oxidation. Suzuki et al. adopted Baeyer–Villiger oxidation for the synthesis of carbohydrate phthalide 708.²²⁰ Instead of commonly used phthalaldehydic acid precursors, benzocyclobutane derivative 706 was utilized for this purpose. Regioselective Baeyer–Villiger oxidation of

Scheme 172. Solid-State Photoreactions of Thioesters and Benzamides



Scheme 173. Synthesis of 3-Alkylidenephthalides via Norrish I Type Photoisomerization

Scheme 174. Light-Induced Isomerization of *o*-Formylarylketones to 3-Substituted Phthalides

706, accessible by the [2+2] cycloaddition of benzyne precursor 704 with ketene silyl acetal 705, with *m*-CPBA resulted in phthalide 707 in 95% yield (Scheme 184). Two subsequent steps, that is, thioether formation and *m*-CPBA oxidation, led to the formation of phthalide sulfone 708. Application of a similar sequence of reactions to a monomethoxy ketene acetal in place of 705 led to the synthesis of regioisomer of 708.

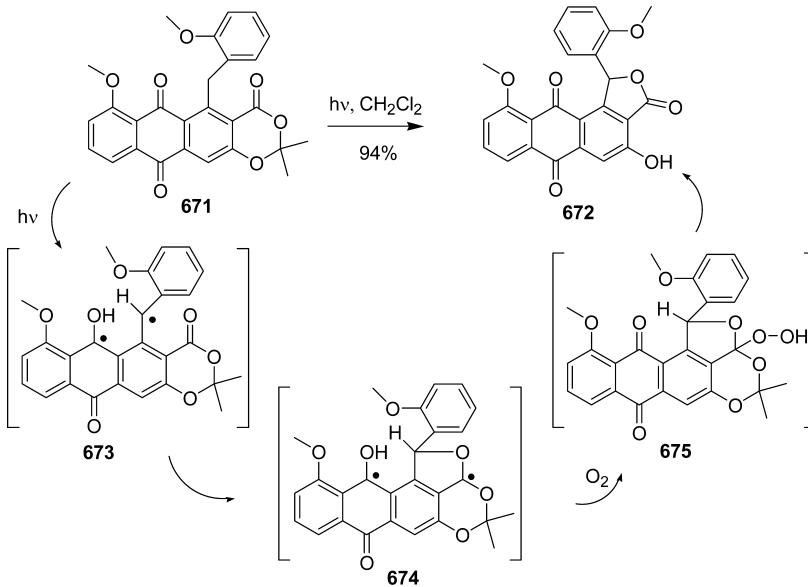
1.3.10.2. Synthesis of Dimeric Phthalides. The preparation of simplest dimeric phthalide 711 was first reported in 1961.²²¹ Action of triethyl phosphite on phthalic anhydride (235) in refluxing *o*-dichlorobenzene afforded biphenyl 711 in 70% yield (Scheme 185). It is presumed that the phosphorus atom of triethyl phosphite attacks the oxygen of the anhydride carbonyl giving intermediate 709, which subsequently generates a carbene 710 and a phosphate ester. The carbene then dimerizes to *trans*-biphenyl 711.

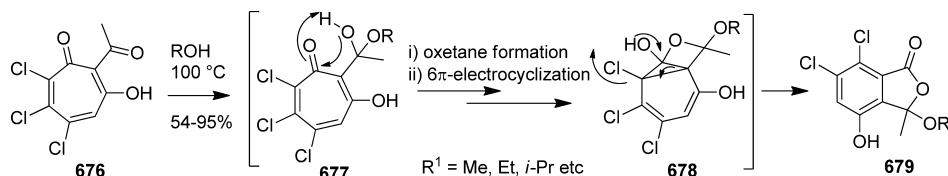
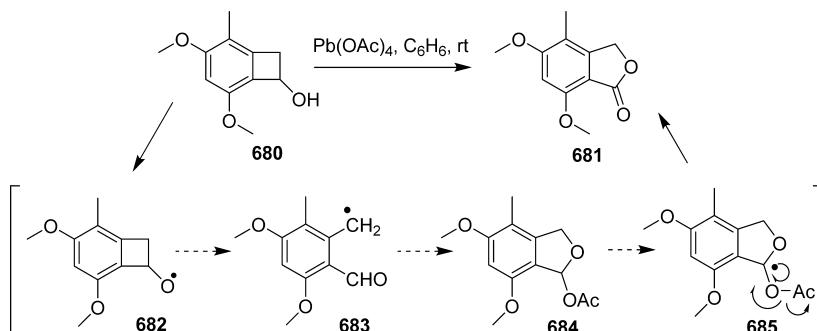
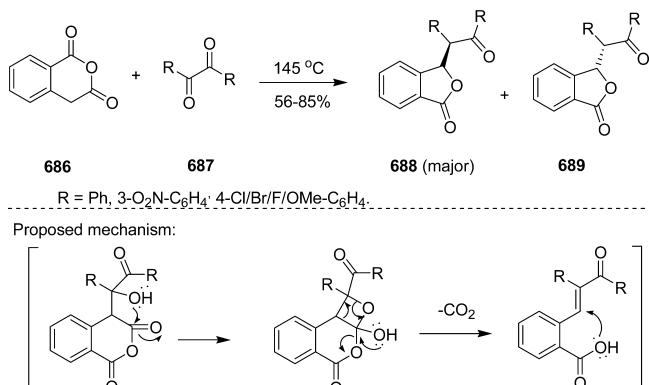
Later, an electrochemical route²²² was developed for the synthesis of 711. Electrochemical reduction of phthalyl dichloride 712 in the presence of NaClO₄ in dry DMF afforded *trans*-biphenyl 711 in 84% yield (Scheme 186). The reaction is initiated by the formation of carbanion 713 and its subsequent attack to another molecule of 712, forming 714 under the reaction conditions.

An analogue of 714, that is, *meso*-3,3'-dihydrobiphenyl, was obtained as the sole product during the photochemical decomposition of 3-(dithiocarbamyl)phthalides 372 (Scheme 89).^{133b}

On the way to the total synthesis of (\pm)-biphenyl, an anthraquinone natural product, synthesis of dimeric isobenzofuranone 719²²³ was secured on the basis of the Ullmann

Scheme 175. Photochemical Formation of Anthraquinone Phthalide



Scheme 176. Ring Contraction of Tropones Leading to 3-Substituted Phthalides**Scheme 177.** Ring Expansion of a Benzocyclobutanol to a Phthalide**Scheme 178.** Conversion of Homophthalic Anhydrides to Phthalides

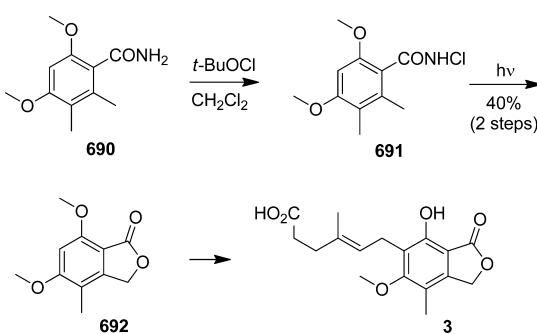
DMF afforded dimeric aldehyde 722. This, on treatment with TMSCN under acidic condition, gave dimeric cyanophthalide 723 (Scheme 188).

1.3.10.3. Synthesis of Thiophthalides. Thiophthalides have been considered as attractive 1,4-dipolar synthon equivalents, especially for the annulation with enones. Their synthesis is still continuing to develop.^{225a,b} A detailed systematic study on their preparation was reported by Mal et al.^{225c} Bromination of *ortho*-toluates 724 with NBS followed by treatment with urea furnished thiouronium salt 725, which was directly transmuted to thiophthalides 726 on heating at 80–90 °C with saturated aqueous NaHCO₃ (Scheme 189). The sequence is general and has been applied to a number of substituted thiophthalides.

Different 3-substituted thiophthalides (e.g., 728, 729, 730) were prepared from simple thiophthalides 727.²²⁶ Thus, thiophthalide 727, on treatment with PhSSPh or PhSSO₂Ph in the presence of LDA, afforded 3-phenylthiophthalide 728 (Scheme 190), which on H₂O₂–AcOH-mediated oxidation yielded 3-phenylsulfonylthiophthalide 729. NBS-mediated benzylic bromination of 727 furnished 3-bromophthalide 730, which was converted to 728 and 729 by the treatment with PhSH–NEt₃ and PhSO₂Na–DMF, respectively.

Recently, Tatsuta exploited the chemistry of dimeric thiophthalides.²²⁷ Oxidative dimerization of phenol 731, by silver trifluoroacetate, resulted in bisphenol 732, which on benzoylation produced the benzoate 733. Benzylic bromination of 733 with dibromo dimethylhydantoin followed by sequential treatment with thioacetate ion and NaOMe produced racemic bisthiophthalide 734. Resolution and subsequent three-step reaction sequence furnished chiral biaryl thiophthalide 737 (Scheme 191). It was utilized for the total synthesis of hibarimicinone, a complex bisantraquinone natural product.

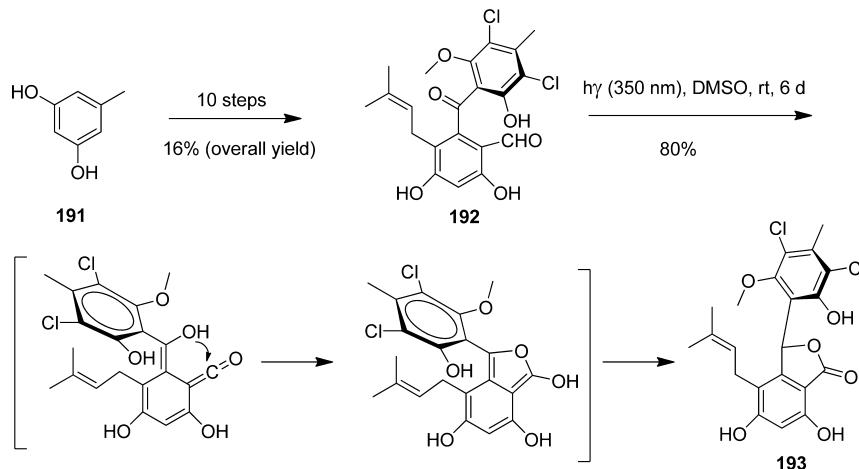
The synthesis of a sulfur analogue of NBP (2a), that is, thiophthalides 740 ($R = n\text{-Bu}$), is outlined in Scheme 192. Benzothiophene-1,3-dione 738 on reaction with the Grignard reagents afforded hydroxythiophthalides 739 in 33–73% yield. Treatment of 739 with hydriodic acid resulted in thiophthalides 740 in moderate yields via one-pot dehydration and reduction.²²⁸ The 3-pentylthiophthalide (740, $R = \text{pentyl}$) is shown to possess anti-ischemic activity greater than NBP (2a).

Scheme 179. Photolysis of Chloramide of *ortho*-Toluate

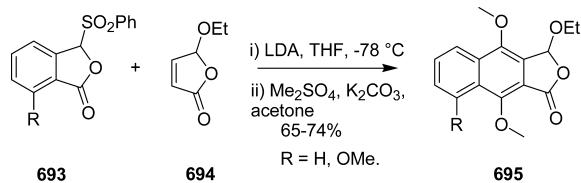
coupling of iodobenzene derivative 715. Lateral phenylsulfenation of dimeric *ortho*-toluate 716 furnished 717, which on cyclization in the presence of TFA gave isobenzofuranone 718. Oxidation of 718 by *m*-CPBA produced bis(sulfonylisobenzofuranone) 719 in quantitative yield (Scheme 187).

An *ortho*-lithiation approach was adopted by Brimble et al. for the synthesis of bis-cyanophthalide 723.²²⁴ The Pd-catalyzed formation of biphenyl 721 from 720 followed by its *ortho*-metalation with *t*-BuLi and subsequent formylation with

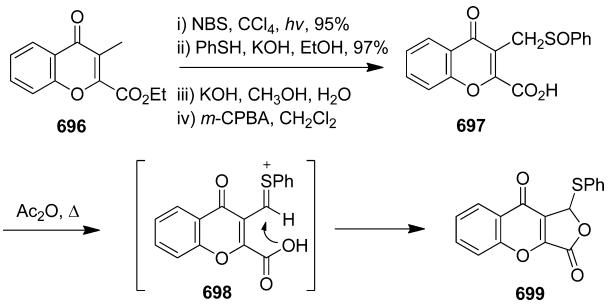
Scheme 180. Schmalz Synthesis of Pestalactone



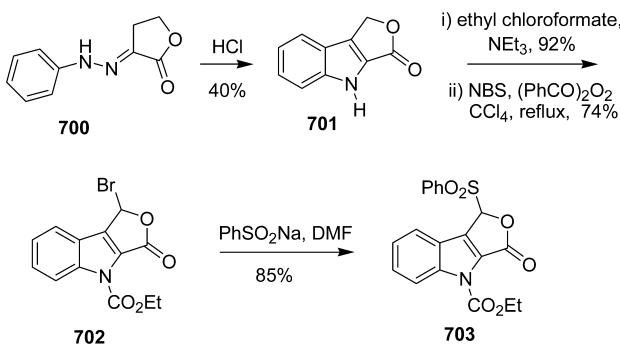
Scheme 181. Hauser Approach to Benzophthalides



Scheme 182. Hauser Approach to Chromonofuranones

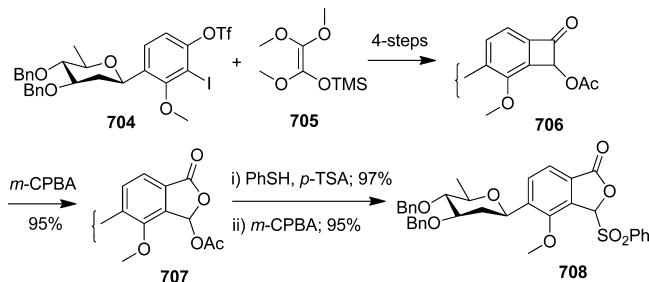


Scheme 183. Fischer Indolization Approach to Indole Analogues of Phthalide

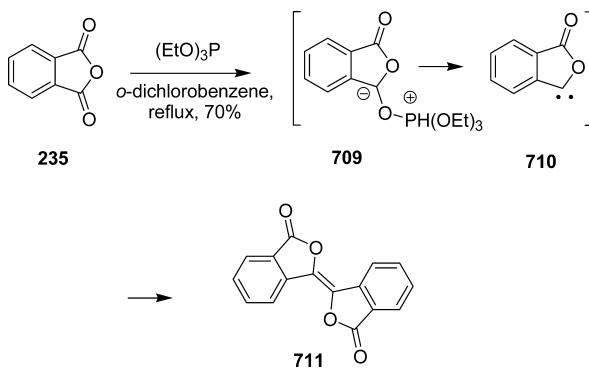


1.3.10.4. Phthalides to Enantiopure Phthalides. Chiral 3,3-disubstituted phthalides 744 and 746 were reported to be synthesized from the corresponding monosubstituted phthalides 741 by enantioselective and regiodivergent allylic alkylation reactions with MBH (Morita–Baylis–Hillman) adducts 742 (Scheme 193).²²⁹ Bifunctional chiral multifunctional tertiary amine-thiourea 743 or phosphine 745 acted as the catalysts. The stereoselectivity of the products arises due to

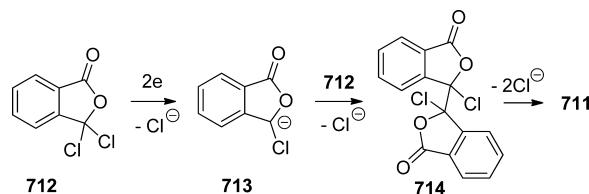
Scheme 184. Suzuki Synthesis of 3-Phenylsulfonylphthalide through Bayer–Villiger Oxidation



Scheme 185. Synthesis of Biphtalyl from Phthalic Anhydride



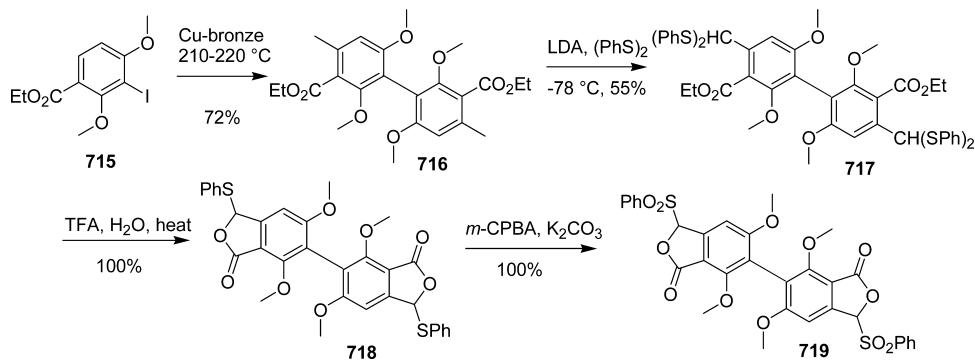
Scheme 186. Electrochemical Route to Biphtalyl



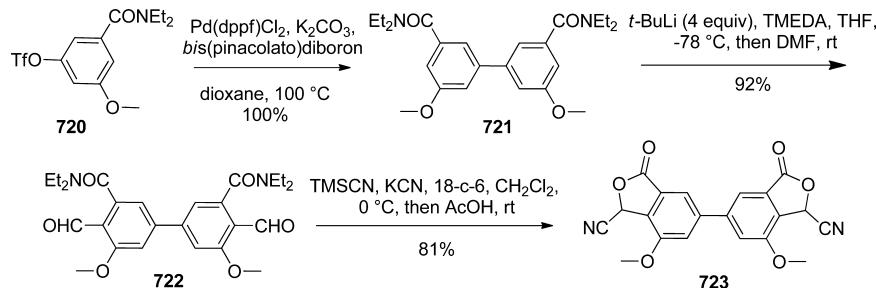
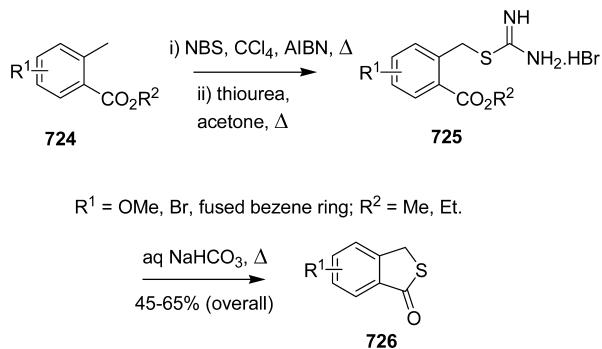
the hydrogen-bonding interactions between the thiourea moiety of the catalyst and the carbonyl group of the phthalides. Nonpolar aprotic solvents like toluene play a crucial role in promoting the H-bonding.

In a subsequent publication, the quinine-derived thiourea catalyst 749 was used to carry out a Mannich-type reaction.^{230a}

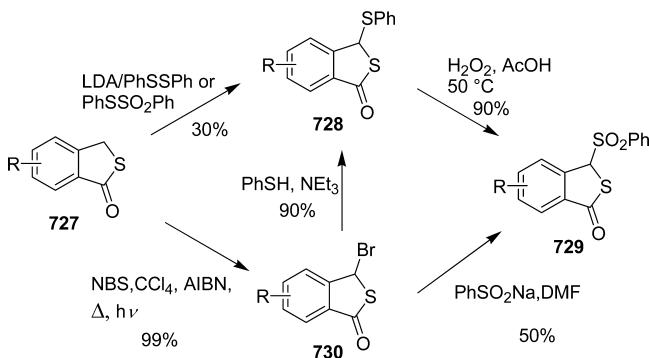
Scheme 187. Hauser Approach to Bis-phthalides



Scheme 188. Brimble Approach to Bis-cyanophthalide

Scheme 189. Mal Synthesis of Thiophthalides from *ortho*-Toluates

Scheme 190. Synthesis of 3-Functionalized Thiophthalides



The reaction of phthalide 747 with aryl imine 748 in the presence of catalyst 749 in toluene furnished optically active phthalides 750 in excellent yields with high diastereo- and enantioselectivities (Scheme 194). The same catalyst was also used for the asymmetric Michael addition of phthalide 747 with nitroolefins 751 to give the nitro-containing phthalide 752 in

very high enantio- and diastereoselectivity.^{230b} These highly functionalized Michael addition products, thus formed, were used for the synthesis of chiral bicyclic lactams. The same group also reported asymmetric Michael addition of phthalide 747 ($R^1 = \text{H}$) to chalcones using catalyst 753.^{230c}

In addition to the existing lithiation-based methods,^{229,231} hydrolysis of 3-cyanophthalide 754 under refluxing H_2SO_4 solution (50%) is also an important avenue to phthalide 3-carboxylic acid (755, Scheme 195).⁹⁰ Derivatization of 755 to phthalide 3-carboxylate 756 was accomplished with freshly distilled SOCl_2 in MeOH at room temperature.

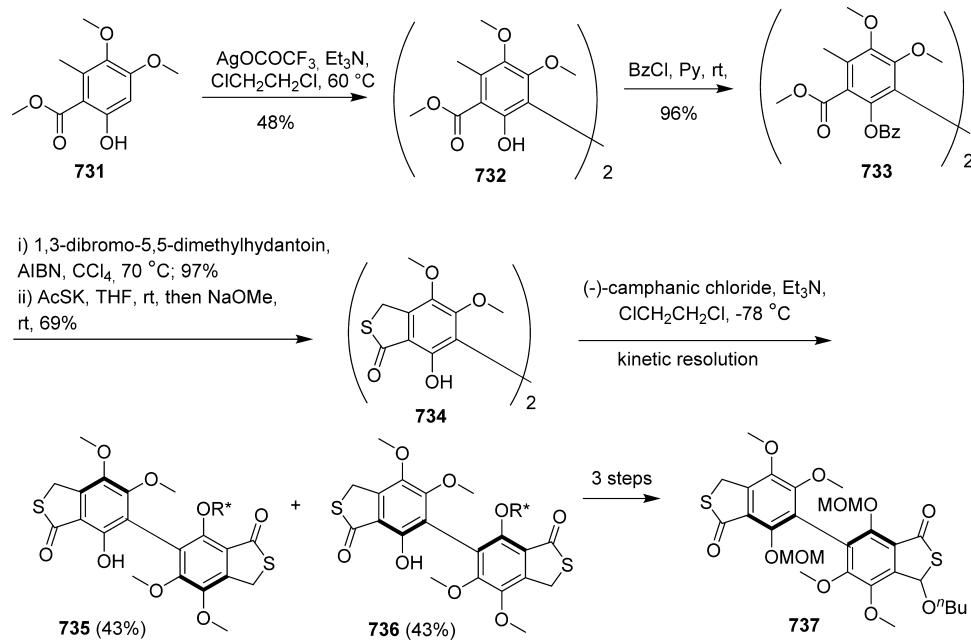
1.3.10.4.1. Total Synthesis of CJ Molecules (758–762). Alkylation of phthalides at C3 via lateral lithiation is a general process for the synthesis of 3-substituted phthalides. Mondal and Argade used this strategy in their synthesis of CJ-13015 (758), an anti-*Helicobacter pylori* agent (Scheme 196).^{232a} Such reactions involve $\text{S}_{\text{N}}2$ attack of the anions generated from 5,7-dimethylphthalide (757) with alkyl bromides. In 2010, the same group synthesized other *Helicobacter pylori* antibiotics, 759–762, by chemoselective coupling reaction of 757 with remotely functionalized long-chain alkyl iodides in the presence of NaHMDS.^{232b} Functional groups like ketone/ester, silyloxyketone, acetoxyketone, and spiroketal units, which are parts of the alkylating agents, survive the alkylation.

2. PHTHALANS

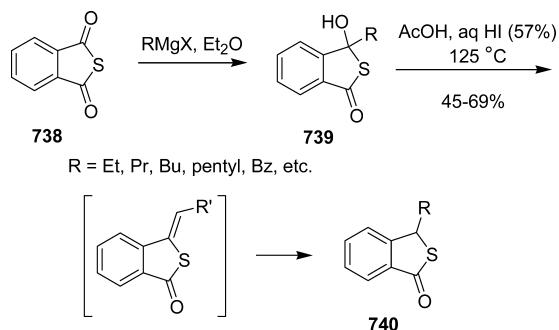
2.1. Introduction

The 1,3-dihydroisobenzofurans, commonly named as phthalans (e.g., 763, Figure 6), embody a large number of bioactive natural products.^{233a–i} Many of them display fascinating pharmacological activities such as antidepressive, antifungal, antisecretory, antihistaminic, etc.^{233j–o} Citalopram (764), a well-known and widely used antidepressant, belongs to this class. Phthalans have also been recognized as major building

Scheme 191. Tatsuta Approach to Chiral Biaryl Thiolactone



Scheme 192. Synthesis of Thiophthalides from Thiophthalic Anhydride



blocks in organic synthesis.^{233p,q} As noted earlier, phthalans serve as the synthetic precursors of phthalides.

2.2. Classification and Bioactivities

On the basis of the functionalities at C1, phthalans are categorized into three groups: (i) 1-alkyl/aryl/oxygenated phthalans, (ii) spirocyclic phthalans, and (iii) alkylidene phthalans.

2.2.1. 1-Alkyl/Aryl/Oxygenated Phthalans. The most prominent member of this class of phthalans is citalopram (764, Figure 6). It is a well-known antidepressant drug and used for the treatment of major depressive and general anxiety disorders in adults. The (*S*)-(+) enantiomer, known as escitalopram (765, Figure 7), seems to be more potent than the other (*S*)-(−) enantiomer. Since its development in 1989, citalopram has been used in more than 65 countries, with a total estimated worldwide exposure of 8 million people.^{6,234a} Several patents^{234b–j} have been filed describing the utility of the molecule. Some well-known members of this group are shown in Figure 7.

2.2.2. Spiroketal Phthalans. Papulacandins A–D,^{235a,b} 773a–d, and paecilospirone²³³ⁱ (774), featuring spiroacetal phthalans are the representative members of this category (Figure 8). Several new compounds structurally related to

papulacandins, such as L-687,781,^{235c} Mer-WF3010,^{235d} BU-4794F,^{235e} saricandin, and PF-1042,^{235f} have recently been isolated.

2.2.3. Alkylidenephthalans. The third group of phthalans, the group of compounds possessing alkylidene phthalan moiety, for example, 775 and 776 (Figure 9), is well-known as potential tyrosine kinase inhibitors.^{236a} In 2012, Perumal et al. discovered that 1-alkylidene-1,3-dihydroisobenzofurans^{236b} exhibit moderate antidepressant activity.

Besides the importance in the field of medicinal chemistry, phthalans are used in the agricultural, perfume, and colorant industries.²³⁷ Consequently, they have become an important class of targets for the chemical synthesis (Table 4).

2.3. Synthetic Routes to Phthalans

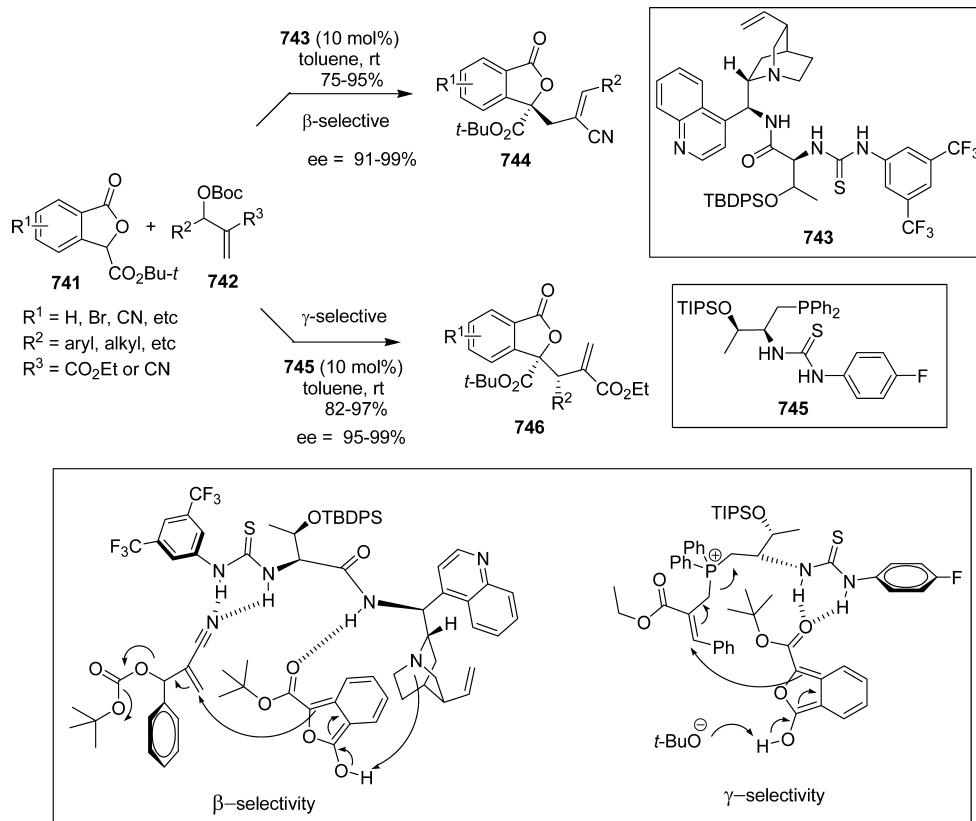
There are different routes reported in the literature for the synthesis of phthalan moieties and phthalan natural products. Among them, the following methodologies have been discussed in details in the subsequent sections: (i) cycloetherification of the *ortho*-substituted aromatics, (ii) [2+2+2] cyclotrimerization of alkynes, (iii) Diels–Alder reaction, (iv) oxa-Pictet–Spengler reaction, (v) Garratt–Braverman cyclization, (vi) cyclocarbonylation, (vii) transformations of phthalides, (viii) stereocontrolled benzylic functionalization of phthalans, (ix) hydrogenation of benzoisofurans, and (x) [8+2] intramolecular cycloaddition.

2.3.1. Cycloetherification of the *ortho*-Substituted Aromatics.

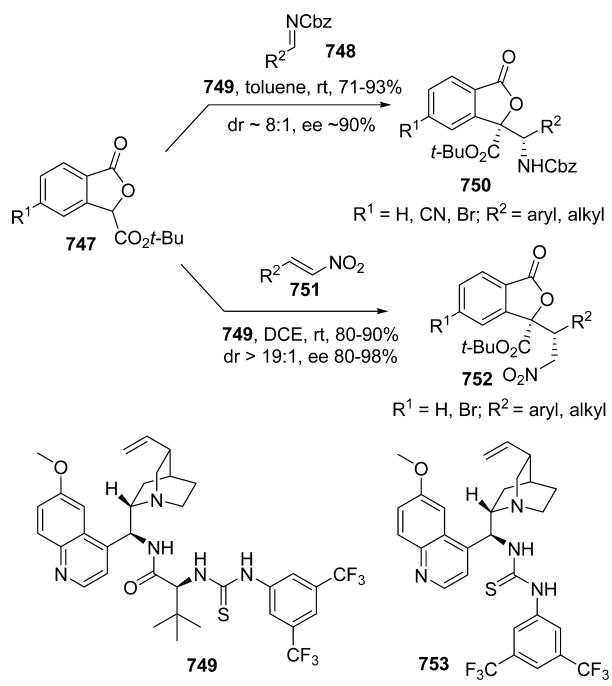
Among the established strategies, cycloetherification is the most widely employed method to access phthalan motifs. In general, an *ortho*-substituted benzyl alcohol or its derivative is used. The *ortho* substituent is an alkene, alkyne, alkyl ammonium salt, alkyl halide, or epoxide. Selected syntheses and methodologies of this category are presented below.

2.3.1.1. Methodology. Iodoetherification of 2-vinylbenzyl alcohols 777 was promoted by iodine-*t*-BuOK to give phthalans 778 (Scheme 197).²⁴⁴ Vinyl alcohols 777 were prepared from the corresponding 2-bromostyrenes.

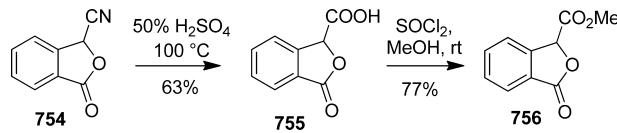
Scheme 193. Chiral 3,3-Disubstituted Phthalides via Enantioselective Alkylation of Phthalides



Scheme 194. Asymmetric Mannich Reaction and Michael Reaction for 3,3-Disubstituted Phthalides



Scheme 195. Synthesis of Phthalide-3-carboxylate



derivatives were utilized by Parham, Maddaluno, and Knochel for the construction of the phthalan skeletons.^{245b-d}

Capriati et al. have established an innovative synthetic route for phthalans. This is based upon ring closure of *ortho*-hydroxyalkyl-containing aryloxiranes.²⁴⁶ Reaction of *ortho*-lithiated aryloxirane intermediates, obtained from *ortho*-bromoaryloxiranes 782, with carbonyl compounds gave 783 (Scheme 199). In situ cyclization of the intermediate alkoxide 783 through nucleophilic ring-opening of the pendant epoxy function under acidic conditions afforded enantiomerically enriched hydroxyalkyl 1,3-dihydrobenzo[*c*]furan derivatives 784. Likewise, aminoalkylphthalans 785 were synthesized by the same group commencing from arylaziridines 300 (Scheme 68).¹¹¹

Intramolecular defluorinative cyclization of *o*-fluoromethylbromobenzene 786 based on one-pot three-step cascade reaction, that is, lithiation with *n*-BuLi, addition to a carbonyl compound, and cycloetherification, leads to phthalan 787 (Scheme 200). Under the reaction conditions, the use of *o*-bromo (or iodo) methylbromobenzene in place of 786 is reported to inefficient due to metalation at the benzylic position.²⁴⁷

In a more recent work,²⁴⁸ Capriati's group prepared enantiomerically enriched (er = 96:4) phthalan 790 by BF₃·Et₂O-induced 5-*exo* cyclization of 2-oxetanylbenzyl alcohol 789,

Thermal cyclization of *α*-hydroxybenzyl quaternary ammonium salts under basic conditions gives phthalans.^{245a} Thus, ammonium salt 780, derived from amine 779 via *ortho*-lithiation, on heating in DMF-containing NaOAc was transformed to phthalan 781 (Scheme 198). Similar benzene

Scheme 196. Synthesis of CJ-Molecules via Lateral Lithiation-Alkylation of Phthalides

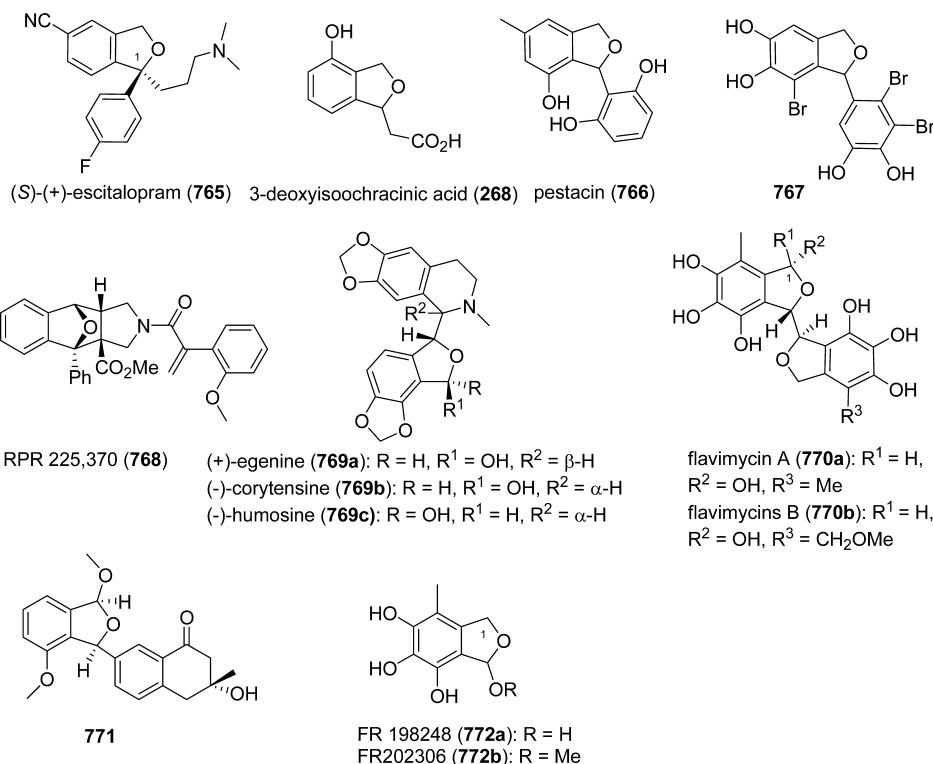
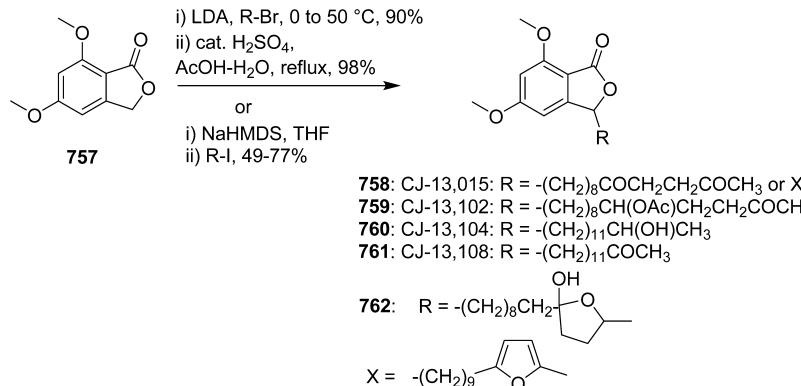


Figure 7. Selected bioactive phthalans.

which, in turn, was obtained from enantiomerically enriched phenyloxetane 788 ($er = 96:4$) exploiting, for the first time, the lithiation-directing ability of an oxetane ring (Scheme 201).

The lithio intermediates 791, derived from thianthrene 303 following Scheme 69, were converted to diols 792 through nucleophilic addition to ketones. Under acidic conditions (H_3PO_4), diols 792 cyclized to the phthalans 793 in excellent yields (Scheme 202).¹¹²

Sarkar and Panda developed a one-pot protocol for the highly efficient etherification of phthalyl alcohols 794 to phthalans 796.²⁴⁹ MnO_2 -promoted oxidation of benzyl alcohol 794 produced lactols 795, which undergo in situ deoxygenation by Et_3SiH and CF_3COOH to yield the phthalans 796 in very good yield (Scheme 203).

α,α' -Dihalo-*o*-xylenes 797 have been cyclized with solvent-free alumina in combination with microwave irradiation to furnish phthalans 798 (Scheme 204) in good yield.²⁵⁰ Addition of water (2 equiv) to alumina increased the yield of the

products. The oxygen atoms of the phthalan moieties originate from the surface layer of alumina and added water.

ortho-Substituted benzene derivative with an oxiranemethanol and an acrylate chain, that is, 799, gave phthalan 801 in reaction with a telluride ion.²⁵¹ Mechanistically, the telluride ion (Te powder + $HOCH_2SO_2Na \cdot 2H_2O$ + $NaOH$) reacts with epoxide 799 under phase-transfer conditions in toluene to give alkoxide 800, which undergoes intramolecular Michael addition with α,β -unsaturated ester to yield phthalan derivative 801 (Scheme 205). With optically active epoxides, diastereoselectivity was nominal.

Alkoxide ions generated by Henry reactions have been shown to undergo intramolecular Michael addition to form 1,3-disubstituted-1,3 dihydrobenzo[*c*]furans. In the presence of 1,1,3,3-*N,N,N,N*-tetramethylguanidine (TMG), *ortho*-formyl cinnamates 802 reacted with 2-nitropropane resulting in phthalide 803 (Scheme 206).^{252a} The reaction gave the products in good yields with various bifunctional *ortho*-formyl

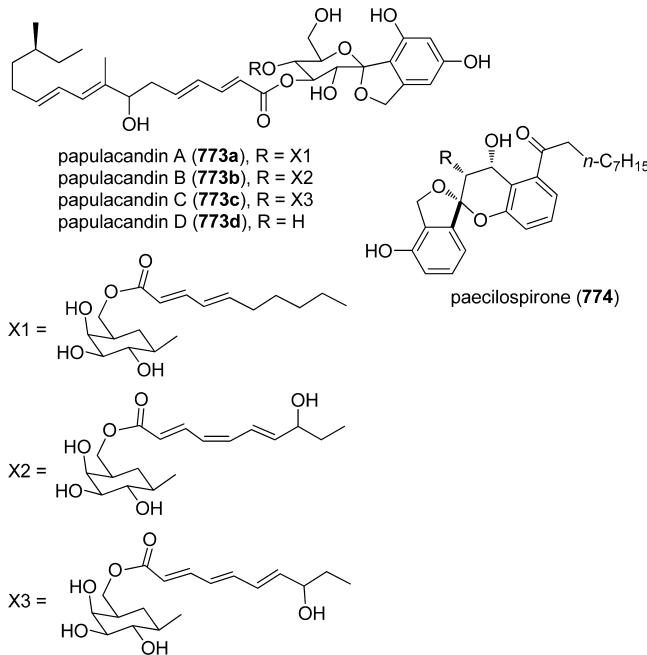


Figure 8. Representative members of spirocyclic phthalan natural products.

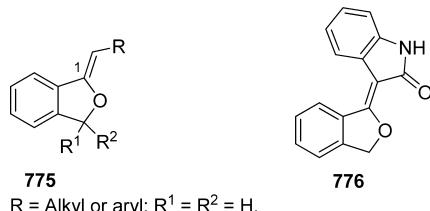
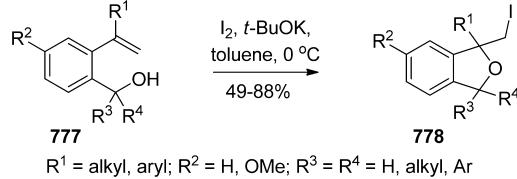


Figure 9. Alkylidenephthalans.

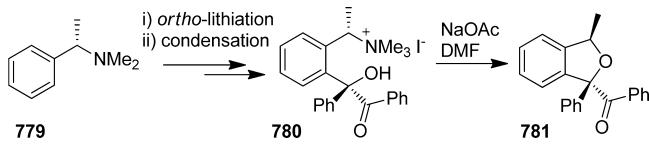
Table 4. Sources and Bioactivity of Selected Natural Phthalans

no.	structure and/or trivial names	sources	bioactivity
1 ²³⁸	(±)-3-deoxyisochracinic acid (268)	1-Alkyl/Aryl/Oxygenated Phthalans <i>Cladosporium</i> sp.	antibacterial activity, inhibiting the growth of <i>B. subtilis</i> , a known cause of food poisoning
2 ^{233a}	pestacin (766)	microorganism <i>Pestalotiopsis microspora</i>	antifungal, antimycotic, and potent antioxidant activity; 11 times greater than the vitamin-E derivative trolox
3 ²³⁹	7-bromo-1-(2,3-dibromo-4,5-dihydroxyphenyl)-5,6-dihydroxy-1,3-dihydroisobenzofuran (767)	brown alga <i>Leathesia nana</i>	potential usefulness for malignant tumors and cardiovascular disease
4 ²⁴⁰	RPR 225,370 (768)	NR	farnesyl transferase inhibitor with good cellular potency
5 ²⁴¹	(+)-eugenine (769a), (-)-corytensine (769b), (-)-humosine (769c)	769a, <i>Fumaria vailantii</i> Loisel (Fumariaceae); 769b and 769c, <i>Corydalis decumbens</i>	769a: anti-inflammatory activities
6 ²⁴²	flavimycins A (770a) and B (770b)	<i>Aspergillus flavipes</i>	inhibit <i>Staphylococcus aureus</i> peptide deformylase; flavimycins A have stronger antibacterial activity than B
7 ^{233e}	1,4-dimethoxy-3-(3R-hydroxy-3R-methyl-1-tetralone)-1(3H)-isobenzofuran (771)	broth of marine <i>Streptomyces</i> sp. M268	cytotoxic against human cancer cell, HL-60, A549, and BEL-7402
8 ^{233f,g,243}	FR198248 (772a) and FR202306 (772b)	<i>Aspergillus flavipes</i> F543 and <i>Aspergillus terreus</i> 13830	antibacterial activity and inhibitory activity against <i>Staphylococcus aureus</i> peptide deformylase; also exhibits anti-influenza activity
9 ^{235a,b,g}	papulacandins A–D (773a–d)	Spiroketal Phthalans fermentation broths of <i>Papularia sphaerosperma</i>	block the synthesis of β-(1,3)-D-glucan, an integral and essential component of the fungal cell wall; shown specific activity against several yeasts
10 ²³³ⁱ	paecilospirone (774)	marine fungus <i>Paecilomyces</i> sp.	antimitotic agent

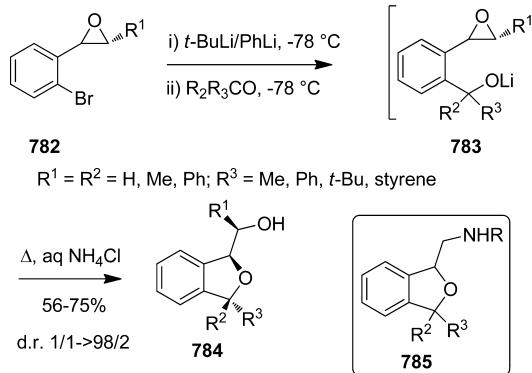
Scheme 197. Kobayashi Iodoetherification to Phthalans



Scheme 198. Phthalan Synthesis via Cycloetherification of an Ammonium Salt

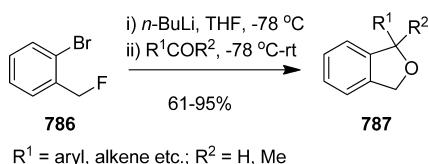


Scheme 199. Synthesis of Phthalans from *ortho*-Lithiated Aryloxiranes

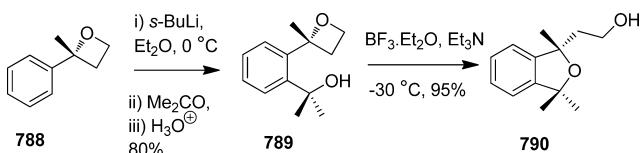


derivatives and cyclic secondary nitroalkanes. Tandem nucleophilic addition-intramolecular oxa-Michael addition was recently investigated to develop a generalized method for the synthesis of trifluoromethylphthalans.^{252b}

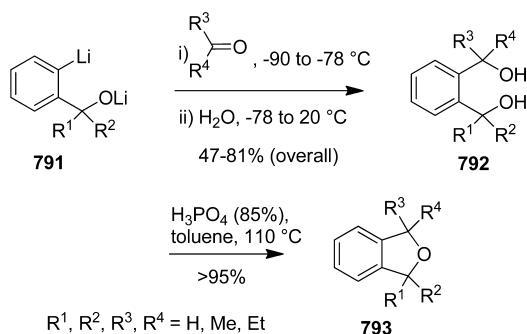
Scheme 200. Intramolecular Defluorinative Cycloetherification



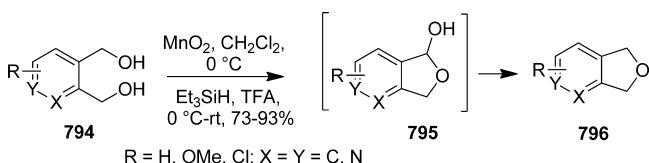
Scheme 201. Phthalans Synthesis from *ortho*-Lithiated Aryloxetanes



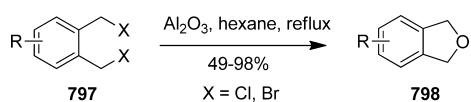
Scheme 202. Phthalans from 4-Heterosubstituted Dibenzothiin



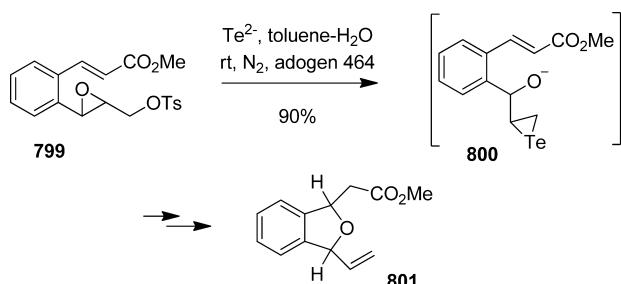
Scheme 203. Sarkar Deoxygenation Strategy for Phthalans



Scheme 204. Phthalans from 1,2-Dihalomethylbenzene Derivatives

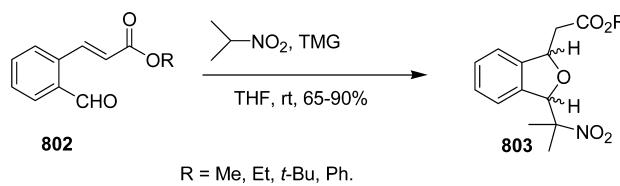


Scheme 205. Synthesis of Vinylphthalan via Telluride-Triggered Domino Reaction



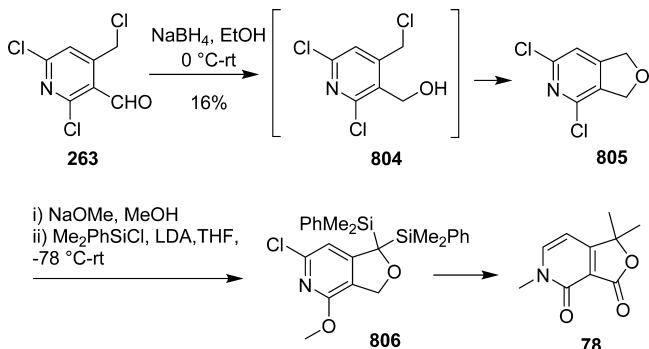
Cycloetherification was also effected during NaBH₄ reduction of an *ortho* chloromethylpyridine carboxaldehyde.¹⁰²

Scheme 206. Tandem “Henry-oxa-Michael” Route to 1,3-Disubstituted Phthalans



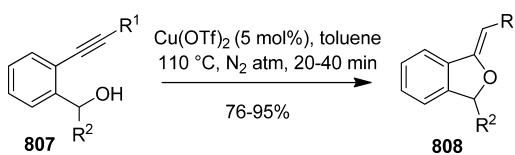
Chloro aldehyde 263 was converted to azaphthalan 805 on treatment with NaBH₄ through reduction-cyclization, albeit in low yield (16%). The improved yield (65%) of 805 was obtained when the alcohol 804 was allowed to react with DBU in refluxing toluene. The synthesis of 78 was achieved via regioselective gemdisilylation of 805 with Me₂PhSiCl to give 806 (Scheme 207).

Scheme 207. Synthesis of Gemdisilylated Phthalan



There are a large number of methods for the synthesis of alkylidene phthalans. Recently, Perumal et al. disclosed the copper(II)-catalyzed synthesis of such phthalans 808 via cycloisomerization of 2-ethynylbenzyl alcohols 807 in refluxing toluene (Scheme 208).^{253a} The results showed that alkynes

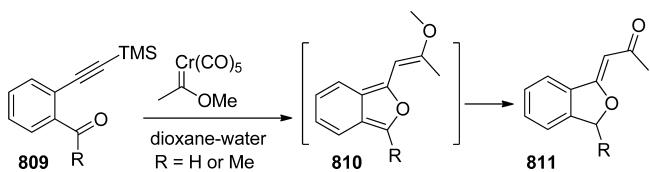
Scheme 208. Perumal Synthesis of Z-Alkylideneephthalans



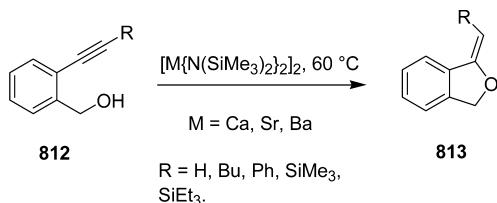
with electron-rich groups cyclized faster and afforded higher yields in a shorter reaction time. Substituents (i.e., *R*²) at the benzylic position have deleterious effects on the cyclization, contrary to the Thorpe–Ingold effect. In 2011, Gong et al. reported gold(I)-catalyzed cycloisomerization of substrates of type 807, furnishing similar phthalans in good overall yields along with 1*H*-isochromenes.^{253b}

Fluoride-induced (KF·2H₂O) cyclization of silylprotected aryl alkynes, having *ortho*-carbonyl functionality, to *Z*-alkylideneephthalans is also reported.²⁵⁴ An intriguing method is found in the Fischer carbene–chromium complex-mediated synthesis of *Z*-alkylideneephthalans 811 from 2-alkynylacetophenone derivatives 809 (Scheme 209).²⁵⁴

Alkaline earth metal bis(trimethylsilyl)amides have been known to promote intramolecular hydroalkoxylation of alkynyl

Scheme 209. Fischer Carbene-Catalyzed Phthalide Synthesis

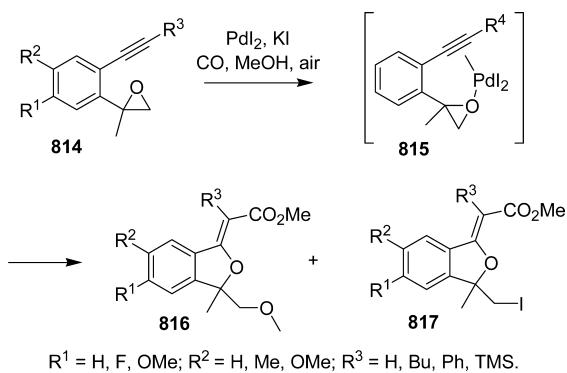
alcohols **812** to yield *E*-alkylidene phthalans **813** in regioselective manner (Scheme 210).²⁵⁵ The reactions with

Scheme 210. Barrett *E*-Alkylidene Phthalan Synthesis Catalyzed by Alkaline Earth Metals

substrates having R = H are much faster and higher yielding than those of substrates having R = Bu or Ph. In case of R = Me₃Si or Et₃Si, the reaction is even poorer, and often starting material is recovered.

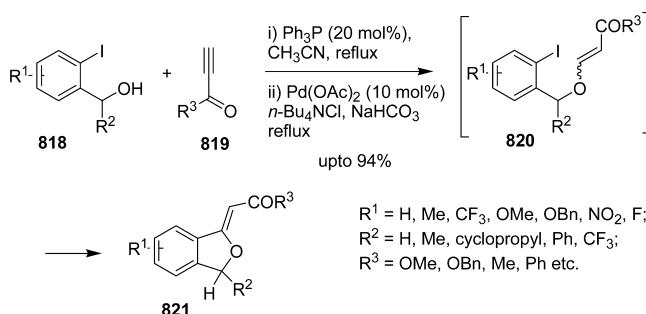
As noted by Villemin and Goussu, Z-phenylalkylidene phthalans are obtainable in greater than 82% yield by the reaction of 2-hydroxymethylidiphenylacetylene (**812**, R = Ph) with a catalytic amount of HgO and BF₃.²⁵⁶

The work of Costa et al. involved a one-step synthesis of highly functionalized alkylideneephthalans **816,817** from alkynylaryloxiranes **814** through a new sequential nucleophilic ring-opening–heterocyclization–oxidative carbonylation process, catalyzed by PdI₂, KI (Scheme 211).²⁵⁷ The reactions were

Scheme 211. *o*-Alkynyl Aryloxiranes En Route to Alkylideneephthalans

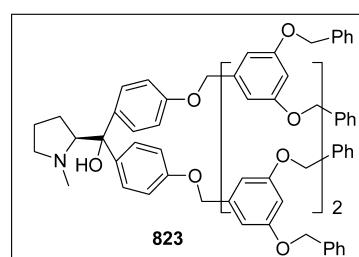
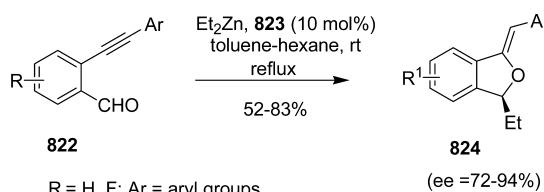
carried out at 80–100 °C under a 3:1 mixture of CO and air in MeOH or MeCN/MeOH. The cascade process was initiated by regioselective attack of methanol or iodide anions, to the less hindered carbon of the oxirane ring of the intermediate **815**.

Tandem Michael–Heck reaction of *o*-iodobenzyl alcohols **818** with electron-deficient acetylenes **819** can be promoted by Ph₃P and Pd(OAc)₂, *n*-Bu₄NCl to provide phthalans **821** (Scheme 212).¹⁰³ Substrates with varying substituents rapidly gave alkylideneephthalans in high yields, and with good stereoselectivities (*E/Z* ratios up to 1:22). The alkylidene phthalan **821** (R¹ = 7-OBn, R² = H, R³ = OBn) on

Scheme 212. Phosphine-Palladium-Catalyzed Synthesis of Alkylidene Phthalans

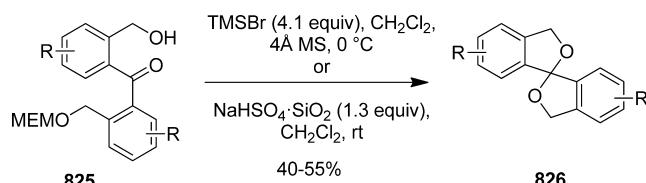
debenzylation and hydrogenation of the olefin by H₂, Pd/C generated the natural fungal metabolite 3-deoxyisochracinic acid (**268**).

Wang asymmetric synthesis of phthalans **824** entails tandem addition-intramolecular hydroalkoxylation of *o*-alkynylbenzaldehydes. The reaction of diethylzinc with 2-alkynyl aldehydes **822** in the presence of a dendritic ligand **823** afforded chiral 1,3-dihydroisobenzofurans **824** with good yields and complete *Z*-selectivities (Scheme 213).²⁵⁸ This method is, however, limited to substrates with aromatic Ar groups. These phthalans can be oxidized to enantiopure phthalides.

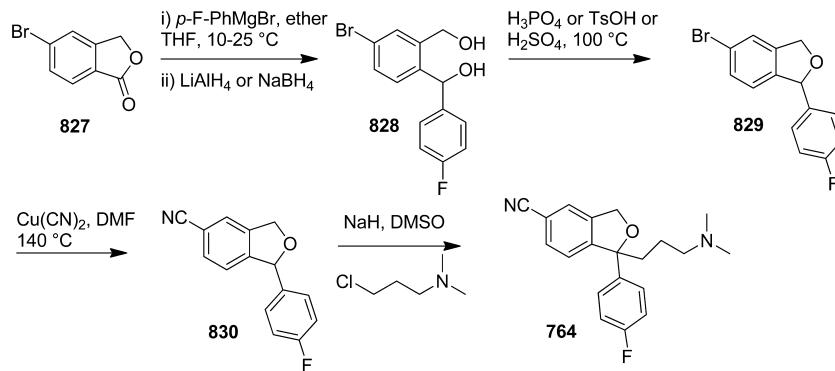
Scheme 213. Wang Tandem Addition-Cyclization Approach to *Z*-Alkylidene Phthalans

Spirophthalans such as **826** have been constructed by TMSBr or NaHSiO₄·SiO₂-catalyzed simultaneous deprotection and intramolecular spirocyclization of 2,2'-hydroxymethyl benzophenones **825** (Scheme 214).²⁵⁹

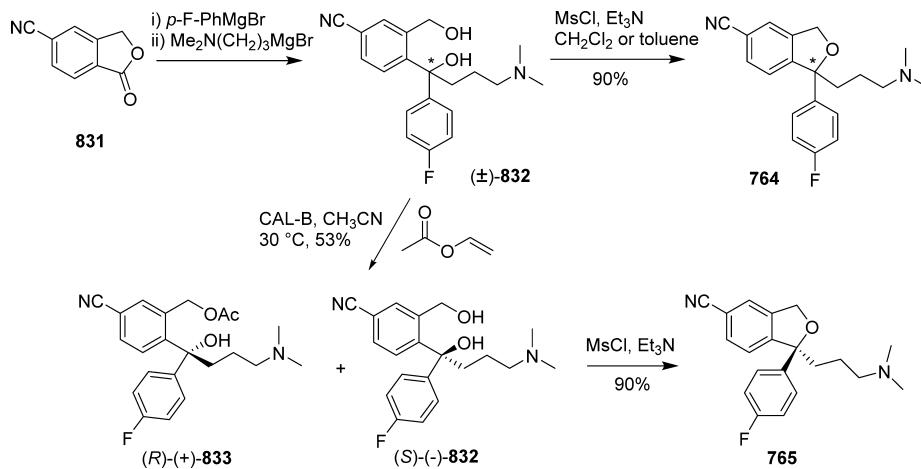
2.3.1.2. Applications in Total Synthesis. **2.3.1.2.1. Citalopram (764) and Escitalopram (765).** Since 1989, many syntheses of citalopram (**764**)^{234b–h} and escitalopram

Scheme 214. Brimble Approach to Spirophthalans

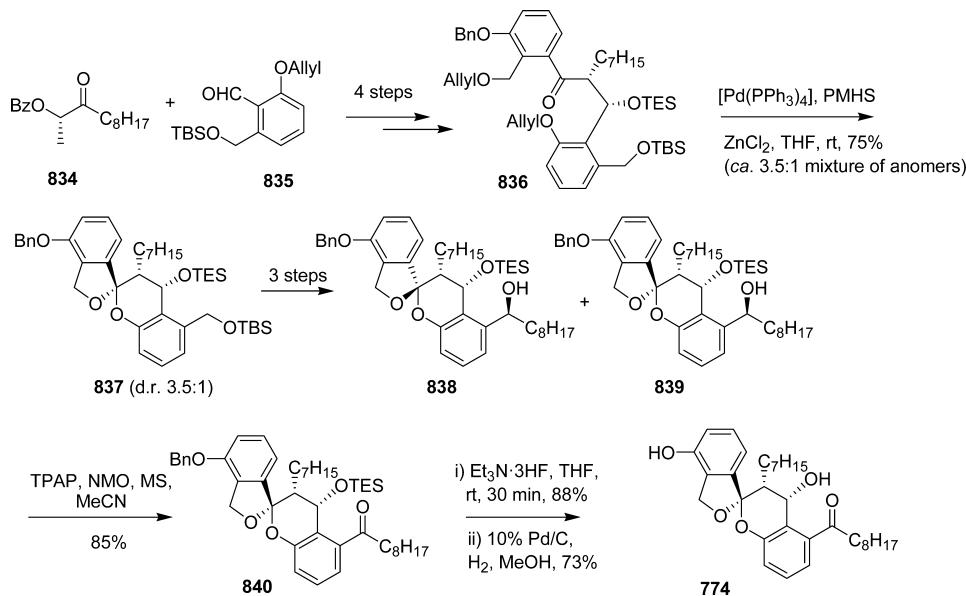
Scheme 215. First Synthesis of Citalopram



Scheme 216. Synthesis of Escitalopram



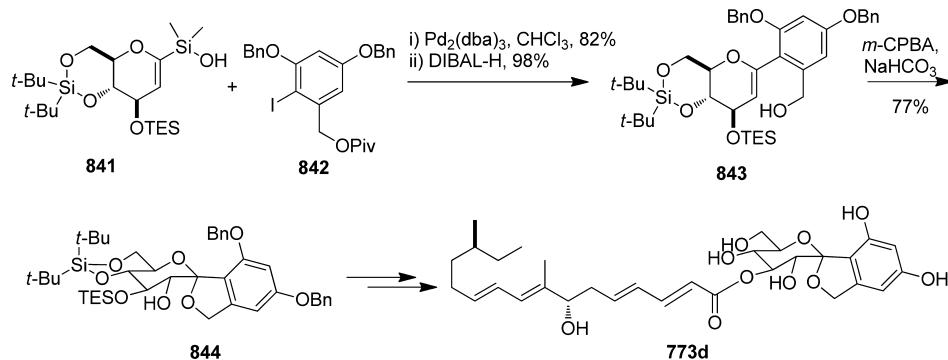
Scheme 217. Brimble Enantioselective Synthesis of Paecilospirone



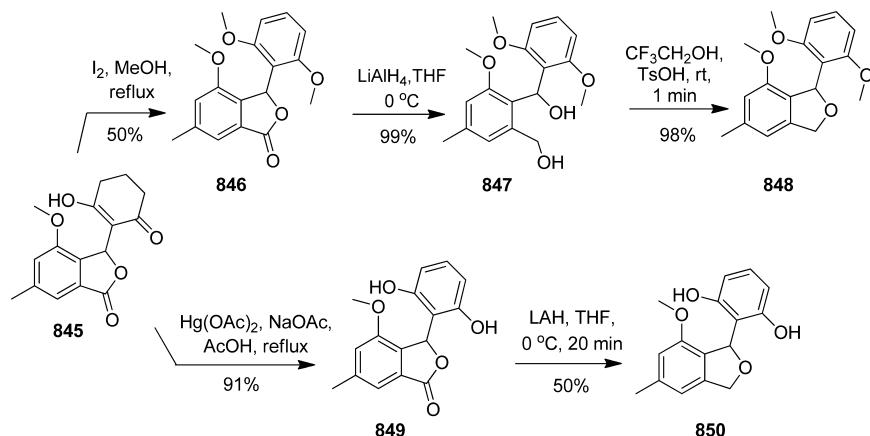
(765)^{234i,j} have been reported. The first synthesis²⁶⁰ of 764 involved the reaction of 5-bromophthalide 827 with 4-fluorophenylmagnesium bromide followed by LAH/NaBH₄ reduction to give benzyl alcohol 828. Subsequent acid-catalyzed cycloetherification furnished 5-bromo-1-(4-fluorophenyl)-phthalan 829. Finally, nucleophilic displacement of bromine of 829 with cyanide followed by NaH promoted lateral

alkylation with 3-(dimethylamino)propyl chloride afforded citalopram 764 (Scheme 215). Other methods^{234c,e,g,h} also used phthalides as starting materials but with different functional groups at the 5-position, for example, 5-carboxyphthalide, 5-cyanophthalide, 5-hydroxyphthalide, 5-aminophthalide, etc.

Scheme 218. Denmark Route to (+)-Papulacandin D



Scheme 219. Mal Synthesis of Pestacin Methyl Ethers



In an alternative route, citalopram (764) was prepared by the cycloetherification of diol intermediate 832 by the use of MsCl or TsCl , and triethyl amine.^{261a} The racemic diol 832 was obtained from 5-cyanophthalide 831 by 2-fold Grignard reaction (Scheme 216). In 2004, Gotor et al. reported an enantioselective synthesis of escitalopram (765) following an enzymatic kinetic resolution.^{261b} *Candida antarctica* lipase B (CAL-B) catalyzed the selective acetylation of the primary benzylic alcohol of *R*- $(+)$ enantiomer of 832 leaving the enantiomerically pure substrate (*S*)- $(-)$ -832 intact, which was then reacted with MsCl and triethylamine to yield the escitalopram (765) (90%).

More recently, a series of pharmacologically active chiral and (\pm)-4- and 5-substituted (CN, halogen, or substituted phenyl, etc.) citalopram analogues^{261c} were synthesized by Newman et al. The series was accessible by the combined use of 2-fold Grignard reactions and acid-catalyzed cycloetherification.

2.3.1.2.2. Paecilospirone (774). Brimble synthesis of spirophthalan paecilospirone (774) involved $\text{Pd}(0)$ -catalyzed double deallylation followed by spirocyclization (Scheme 217).²⁶² The synthesis was started with aldol condensation between ketone 834 and benzaldehyde 835 to provide ketone 836, via a four-step reaction sequence. $\text{Pd}(0)$ -catalyzed double deallylation and spirocyclization of 836 were effected by ZnCl_2 complex to obtain [5,6]-benzannulated spiroacetals 837 in 75% yield as an inseparable mixture of anomers. Selective TBS deprotection, benzylic oxidation using TPAP, and octylmagnesium bromide addition to resulting aldehyde produced an easily separable mixture of diastereomeric alcohols 838 and 839. The paecilospirone (774) was obtained from the major alcohol 839 by oxidation of benzylic alcohol followed by *O*-deprotection.

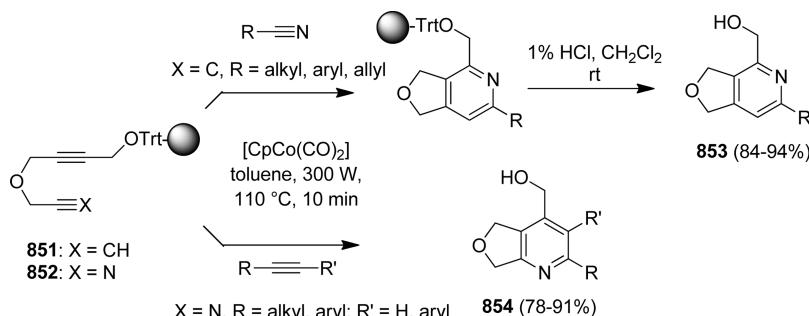
2.3.1.2.3. Papulacandin D (773d). The total synthesis of papulacandin D^{263a–d} (773d), the simplest member of the papulacandin family, has been reported by two different research groups. While Barrett and co-workers reported its first synthesis,^{263a} Denmark's route^{263b,e} comprised palladium-catalyzed cross-coupling of glucal silanol 841 with aryl iodide 842, and *m*-CPBA induced spiroketalization of the resulting alcohol 843 to afford phthalan 844. Compound 844 was subsequently elaborated to 773d in a few steps (Scheme 218).

2.3.1.2.4. Permethylated Pestacin (848) and Monomethyl Ether of Pestacin (850). Mal and Karmakar applied the trifluoroethanol– TsOH ^{264a}-mediated cycloetherification of phthalyl alcohols 847 in the synthesis of permethylated pestacin (848) (Scheme 219).^{264b} Compound 847 was prepared from phthalide 845 in two steps comprising an aromatization and LAH reduction. Monomethyl ether of pestacin 850 was also synthesized in two steps from 845 involving LAH-reduction of 849 and simultaneous cycloetherification in one pot.

2.3.2. Benzannulation/Cycloaddition. **2.3.2.1. [2+2+2] Cyclotrimerization of Alkynes.** The transition-metal catalyzed [2+2+2] cyclotrimerization is a fascinating strategy for the construction of substituted benzenes.¹⁹³ Vollhardt's^{265a} approach involving an intramolecular cyclotrimerization of a trialkyne has widely been used for the synthesis of several phthalan natural products. Among the numerous reports for phthalan synthesis,^{265b} one using Co/Rh-catalyzed [2+2+2] cyclotrimerization of 1,6-dynes and alkyne is described below.

Microwave-assisted synthesis of pyridophthalans by Co-catalyzed [2+2+2] chemo- and regioselective cyclotrimerizations was reported by Dieters et al.^{266a} Cyclotrimerization of

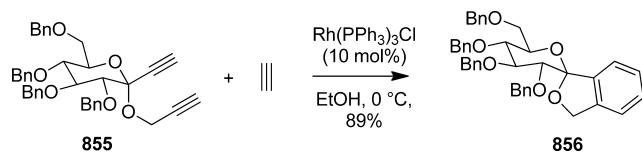
Scheme 220. Formation of Pyridophthalans under Microwave Irradiation



solid supported alkyne **851** in the presence of $[\text{CpCo}(\text{CO})_2]$ -catalyst under microwave irradiation in refluxing toluene, using different nitriles, afforded azaphthalans **853** in excellent yields (87–94%) and high purities (>90%) after cleavage from the resin (Scheme 220). Under similar reaction conditions, azaphthalide **854** were also synthesized starting from nitrile group tethered alkyne **852**. Such reactions were also carried out with Wilkinson catalyst $[\text{RhCl}(\text{PPh}_3)_3]$.^{266b}

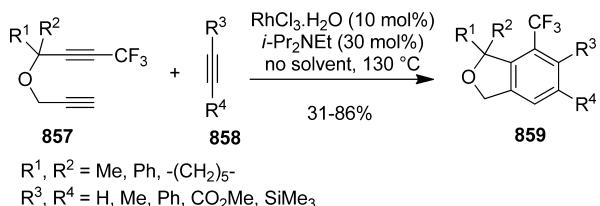
The $\text{RhCl}(\text{PPh}_3)_3$ -catalyzed [2+2+2] cycloaddition was applied in the synthesis of C-arylglycosidic phthalans.^{267a} Phthalan **856** was obtained in good yield by cycloaddition of **855** and acetylene in the presence of the Wilkinson catalyst (Scheme 221).^{267b}

Scheme 221. C-Arylglycosidic Phthalans via Rh-Catalyzed [2+2+2] Cyclotrimerization



RuCl_3 was also found effective for the [2+2+2] cycloaddition of trifluoromethyl-substituted unsymmetrical 1,6-diyne **857** and alkynes **858** to produce 1,1-disubstituted phthalans **859** with moderate regioselectivity (Scheme 222).²⁶⁸ Under these conditions, pyridine derivatives were also synthesized.

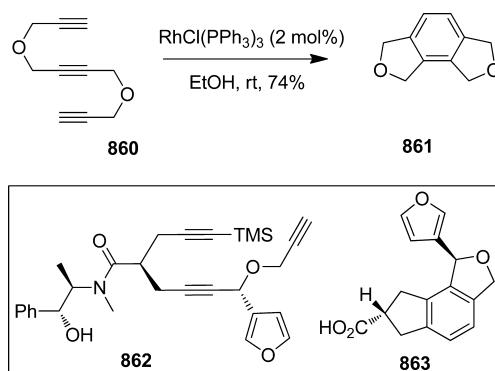
Scheme 222. [2+2+2] Cycloaddition of Various Fluoroalkylated Diynes



A completely intramolecular version of the cyclotrimerization was found in the work of Grigg et al. Use of ether-linked triynes (e.g., **860**) furnished the corresponding tricyclic phthalans (e.g., **861**) in good yield in the presence of Wilkinson's catalyst (Scheme 223).^{269a,b} Employment of ether-linked chiral triyne **862** allowed the formation of diterpenoid natural product, (+)-salvileucalin B, via phthalan **863**.^{269c}

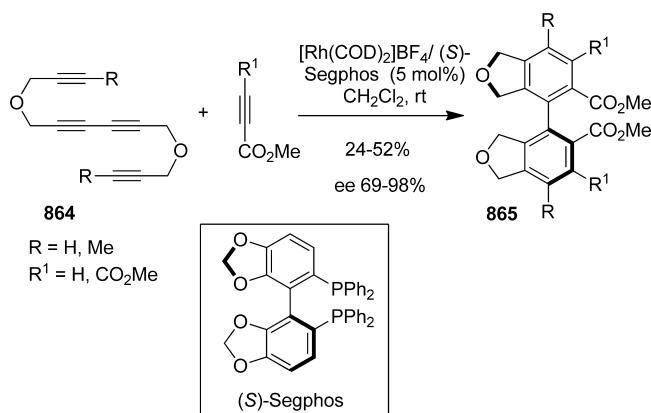
Because of frequent occurrence as key structural motifs in chiral ligands, catalysts, and biologically active compounds, the synthesis of axially chiral phthalans has drawn considerable

Scheme 223. Synthesis of Tricyclic Phthalans from Ether-Linked Triynes



attention of many research groups. Tanaka and co-workers showed that the synthesis of C2-symmetric axially chiral biaryls **865** can be achieved by using enantioselective double [2+2+2] cycloaddition starting from tetrynes **864** and two equivalents of an alkyne in the presence of a cationic rhodium(I)–Segphos complex (Scheme 224).²⁷⁰

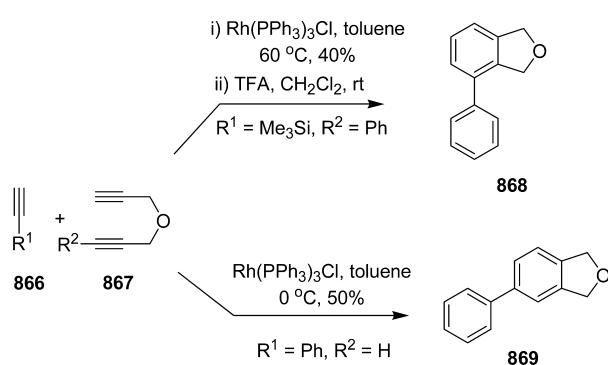
Scheme 224. Synthesis of Chiral Biaryl Phthalans



Phenylphthalans **868** and **869** are accessible by the modification of Witulski's method, which involves rhodium-catalyzed intermolecular [2+2+2] cycloaddition of **866** and **867** (Scheme 225).^{233k}

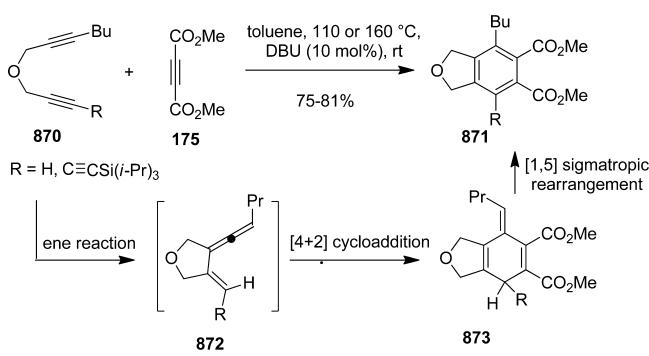
In 2010, Danheiser et al. disclosed a metal-free formal [2+2+2] cycloaddition strategy for the synthesis of phthalans.²⁷¹ This two-step synthesis involved an intramolecular propargylic ene-type reaction of 1,6-diyne **870** to generate vinylallenes of type **872** followed by an intermolecular Diels–

Scheme 225. Chemoselective Synthesis of Phenylated Phthalans



Alder reaction with an alkynyl dienophile 175. Isomerization of the resulting isotoluene-type intermediates 873 by a 1,5-sigmatropic rearrangement on exposure to DBU gave phthalans 871 (Scheme 226). A fully intramolecular version was also realized.

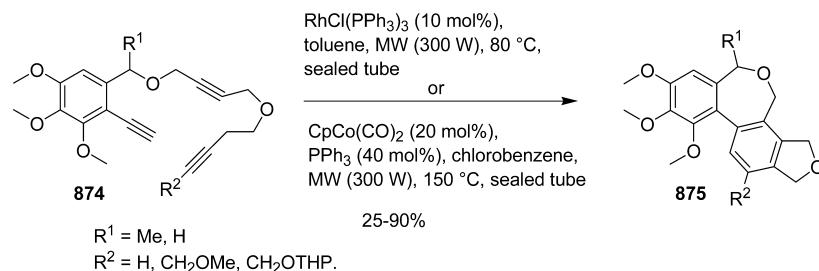
Scheme 226. Metal-Free [2+2+2] Cycloadditions of 1,6-Diyne with Alkynyl Dienophiles



Tetracyclic 6-oxa-allocolchicinoids of type 875, related to the natural product allocolchicine, were efficiently constructed by Schmalz and Prokop utilizing microwave-assisted intramolecular [2+2+2] cycloaddition.²⁷³ Triynes 874, when heated in a sealed tube under microwave irradiation in the presence of Rh(I) or Co(0)-catalyst, cyclized to tetracyclic phthalan 875 in moderate to good yields. These compounds are well-known for their prominent anticancer activity (Scheme 227).

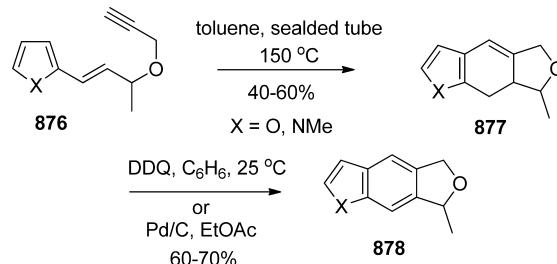
2.3.2.2. Diels–Alder Reaction. The Diels–Alder reaction has always been an attractive methodology for the synthesis of polycyclic organics. Likewise, the reaction is useful in fabricating various fused phthalan skeletons. Kanematsu reported the synthesis of furan and pyrrole fused phthalans via

Scheme 227. Microwave-Promoted Metal-Catalyzed Intramolecular [2+2+2] Cyclotrimerization



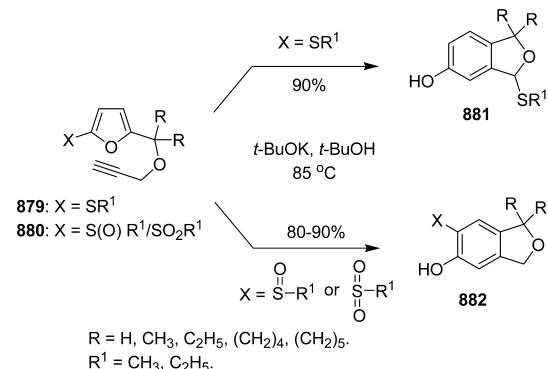
intramolecular Diels–Alder reactions.²⁷³ Thus, the propargyl ethers 876, when heated in toluene, provided the heterocycle fused dihydropthalans 877. DDQ or Pd-mediated aromatization of 877 gave the phthalans 878 (Scheme 228).

Scheme 228. Diels–Alder Reaction Route to Phthalans

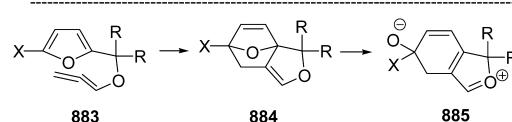


The access to 5-hydroxy-1,3-dihydroisobenzofurans is also possible via intramolecular cyclization of propargyloxymethylfurans in the presence of a catalytic amount of *t*-BuOK in *t*-BuOH.²⁷⁴ Wu et al. utilized the methodology for the synthesis of 3-thio substituted phthalans 881, starting from furan 879 bearing allenyl ether and methylthio group (Scheme 229).^{274a}

Scheme 229. Synthesis of Phthalans via Intramolecular Diels–Alder Reaction of Propargyloxymethylfurans



R = H, CH3, C2H5, (CH2)4, (CH2)5.
R1 = CH3, C2H5.

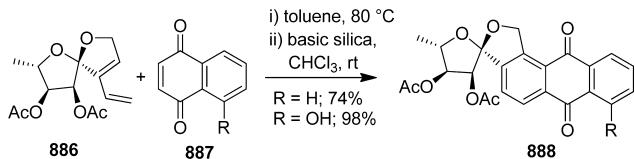


Interestingly, the starting furans containing alkyl sulfoxide or sulfones produced 6-thio-substituted phthalans 882. The reaction was believed to proceed via the isomerization of 2-propargyl furan to allene 883 followed by D–A reaction and subsequent cleavage of epoxy bridged Diels–Alder adduct 884

to **885**. An unusual 1,4-alkylthio rearrangement of **885** produced the product **881**, whereas 1,2-shift produced **882**. Furans containing trimethyl silyl group yielded a mixture of 6-silylphthalans and desilylated product via Brook rearrangement.

Formation of spirophthalan moiety at the anomeric center was established by Kaliappan et al.²⁷⁵ Diels–Alder reaction of various sugar-derived dienes (e.g., **886**) with suitable quinone dienophiles **887** followed by aromatization afforded spiro-C-aryl glycosides **888** in moderate to good yields (Scheme 230). This methodology was also applied to reactions between dienes having spiro-six-membered sugar derivatives and DMAD (175).

Scheme 230. Kaliappan Diels–Alder Approach to Spirophthalans

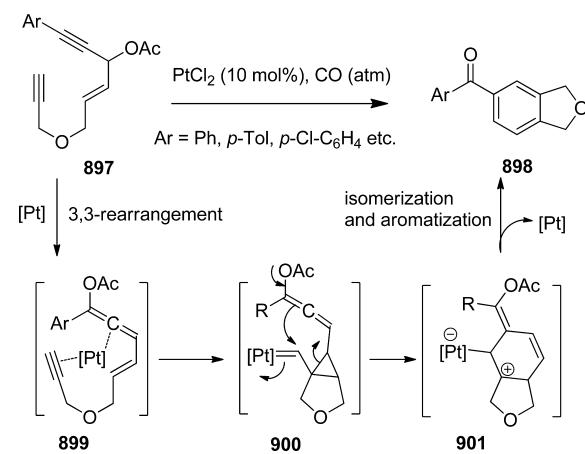


2.3.2.3. Metal Carbenoid Rearrangement. Contrary to Scheme 229, intramolecular cycloisomerization of propargyloxymethylfuran in the presence of a Pt(II) catalyst proceeds through a metal carbenoid intermediate.^{276a} Thus, the intramolecular cycloaddition of **889** in the presence of PtCl₂ or [PtCl₂(MeCN)₂] catalyst in refluxing acetone gave phenols **890** and **891** (Scheme 231). The reaction is initiated by the nucleophilic attack of the furan on (η^2 -alkyne)platinum(II) complex **889** to form cyclopropyl platinum carbenes **890**, which subsequently rearranges to epoxide **896**. 1,2-Rearrangement of the epoxide produced the mixture of phenols **890** and **891**. Similarly, AuCl₃-catalyzed synthesis of dihydroisobenzofurans was reported by Hashmi et al.^{276b}

PtCl₂-catalyzed intramolecular cycloaddition of propargyl acetates **897** produced phthalans **898**.²⁷⁷ Although the reaction appeared to proceed through an intramolecular Diels–Alder-type pathway, the proposed mechanism also discussed the possibility of formation of a metal carbene complex **900**, which then cycloisomerized to the product **898** via ionic intermediate **901** (Scheme 232).

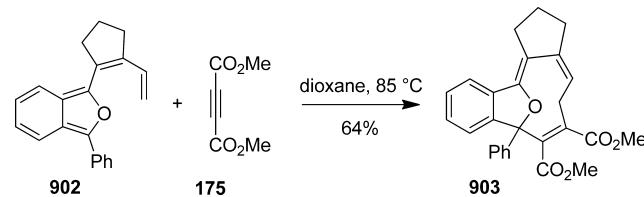
2.3.2.4. [8+2] Intramolecular Cycloaddition. Herndon et al. developed a novel method for the synthesis of furanophanes

Scheme 232. Phthalans through Rearrangement of Propargyl Acetates



(e.g., **903**), utilizing [8+2] cycloaddition between dienyl-isobenzofurans (e.g., **902**) and dimethyl acetylenedicarboxylate (175). The cycloaddition was successful with both alkyl- and aryl-substituted dienyl-isobenzofurans (Scheme 233).²⁷⁸

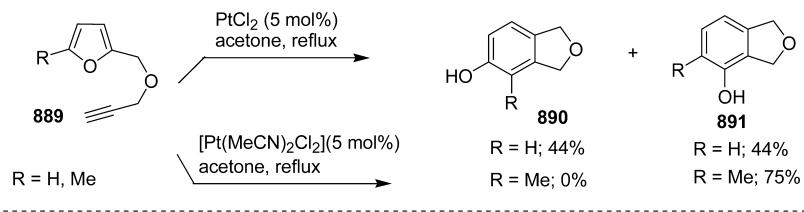
Scheme 233. Synthesis of Furanophane Derivatives via [8+2] Cycloaddition



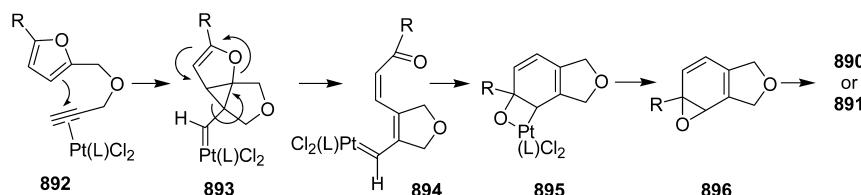
2.3.2.5. Electrocyclic Reaction. Trost's two-step protocol for the synthesis of azaphthalan involves ruthenium-catalyzed 6π electrocyclization reaction.²⁷⁹ Cycloisomerization of diynols **904** in the presence of [CpRu(CH₃CN)₃]PF₆ provided $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **905**. In the second step, oxime of **905** underwent 6π -electrocyclization to yield **906** (Scheme 234).

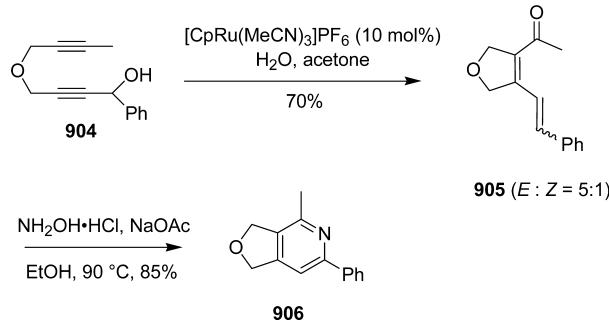
2.3.3. Miscellaneous. **2.3.3.1. Oxa-Pictet–Spengler reaction.** The oxa-Pictet–Spengler reaction is an acid-catalyzed condensation of an aryl alcohol with an aldehyde or ketone to yield polysubstituted isochromans and related oxygenated

Scheme 231. Echavarren Pt-Induced D–A Reaction of Enynes to Phthalans

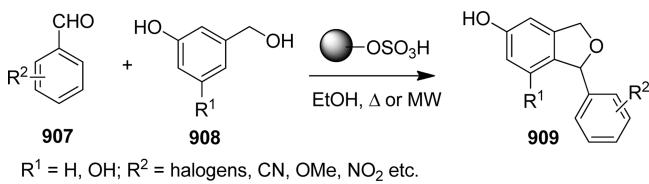


proposed mechanism:



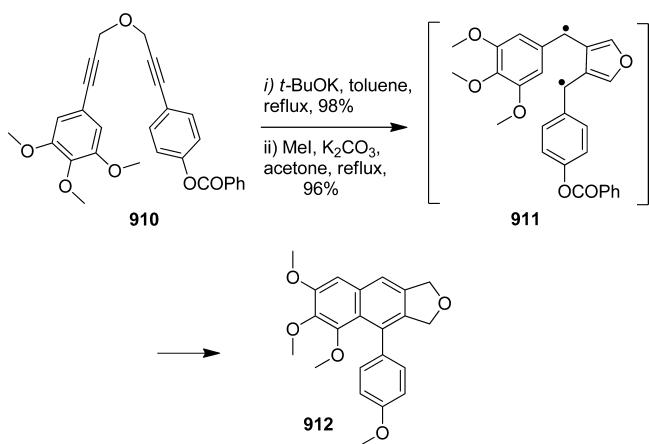
Scheme 234. Trost Synthesis of Pyridophthalans

heterocycles. The synthesis of hydroxyphthalans (e.g., 909) by this route was pioneered by Marra.^{280a} Recently, Khosropour reported the use of nanosilica sulfuric acid (NSSA), a mixture of chlorosulfonic acid and nano-SiO₂, as the catalyst for this reaction.^{280b} In the presence of heterogeneous catalyst NSSA, condensation of aromatic aldehydes 907 and 3-hydroxybenzyl alcohols 908 under conventional heating or microwave irradiation produced hydroxyphthalans 909 in moderate to good yields (Scheme 235). However, the yields of the products

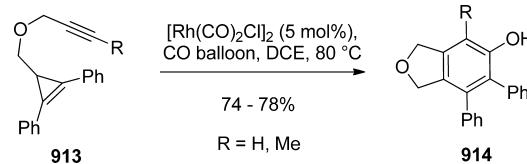
Scheme 235. Synthesis of 5-Hydroxyphthalans Catalyzed by NSSA

show strong dependency on the nature of substituents on aryl aldehydes. Sterically hindered or electron-deficient aryl aldehydes gave lower yields of the products.

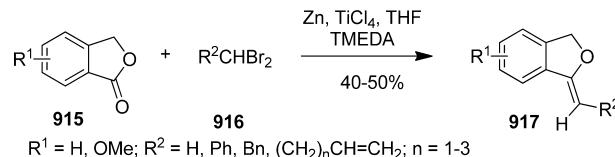
2.3.3.2. Garratt–Braverman (GB) Cyclization. Basak and co-workers reported base-mediated chemoselective cyclization of substituted bis-propargyl ether (e.g., 910) to the naphthofurans (e.g., 912) (Scheme 236).^{100a,b} The reaction is proposed to proceed through radical pathway involving diradical intermediate 911. The chemoselectivity of the GB-cyclization of 910 can be modulated by the substituents at the aryl ring.

Scheme 236. Basak GB-Approach to Phthalan

2.3.3.3. Cyclocarbonylation. The Rh(I)-catalyzed carbonylative cycloaddition of yne-cyclopropanes 913 has been shown to be an efficient way of preparing highly substituted phthalans 914.²⁸¹ The reaction takes place via a [3+2+1] carbonylative carbocyclization pathway (Scheme 237).

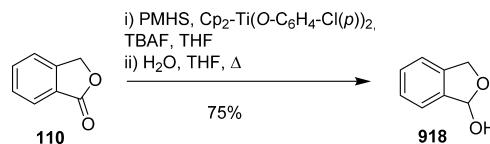
Scheme 237. Carbonylative Cycloaddition Route to Phthalans

2.3.3.4. Phthalides to Phthalans. **2.3.3.4.1. Condensation.** Organotitanium reagents are reported to convert phthalides to alkylidene phthalans without opening the lactone ring. The reagent, generated in situ from 1,1-dibromo compounds 916, TiCl_4 , and Zn dust, reacted with phthalides 915 in the presence of TMEDA to yield alkylidene phthalans 917 in moderate yields (Scheme 238).^{282a} In a similar type of reaction,

Scheme 238. Alkylidene Phthalan Synthesis via Organotitanium Catalyst

unsubstituted phthalide ($R^1 = \text{H}$) on reaction with $\text{PhCH}(\text{SPh})_2$ in the presence of a titanocene complex, $\text{Cp}_2\text{Ti}(\text{P}(\text{OEt})_3)_2$, afforded *Z*-benzylidene phthalan ($R^1 = \text{H}$, $R^2 = \text{Ph}$).^{282b}

2.3.3.4.2. Reduction. The unsubstituted phthalide 110 is reducible to the corresponding lactol 918 by reaction with $\text{Cp}_2\text{Ti}(o\text{-C}_6\text{H}_4\text{-Cl}(p))_2\text{-PMHS}$ in the presence of TBAF in THF (Scheme 239). The reaction also produced 1,2-benzenedimethanol.²⁸³

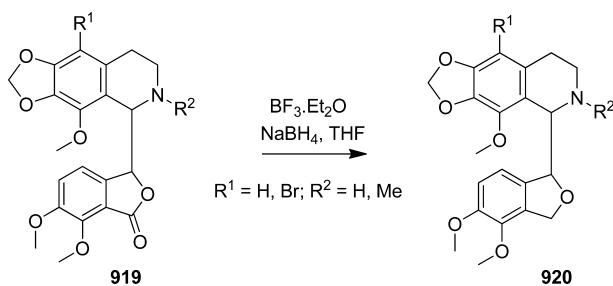
Scheme 239. Buchwald Approach to Lactol via Reduction of Phthalide

Super hydride (LiBHET_3) reduction of natural phthalides, bicuculline (33, Figure 4) and capnoidine (251, Scheme 53), in CH_2Cl_2 at -78°C afforded hydroxy phthalan alkaloid egenine (769a) in 86% yield.⁹⁶

Reduction of isoquinoline phthalides 919 with NaBH_4 in $\text{BF}_3\text{-Et}_2\text{O}$ is shown to be a method for the preparation of phthalans 920 (Scheme 240).²⁸⁴ Presumably, the reaction proceeds through the reaction of an in situ generated borane. LAH-mediated reduction also gives similar results, which are illustrated in the attempted synthesis of pestacine (766).^{264b}

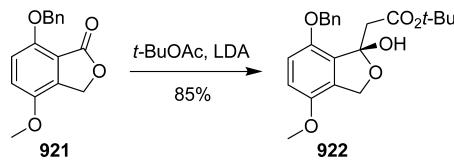
2.3.3.4.3. Nucleophilic Addition. The addition of phthalide 921 to the anion of *t*-BuOAc, generated by the action of LDA,

Scheme 240. NaBH₄-Mediated Reduction-Cyclization Route to Isoquinoline Phthalans



yielded 922 (Scheme 241).²⁸⁵ Such an addition was not realized with dianion of acetic acid probably because of the

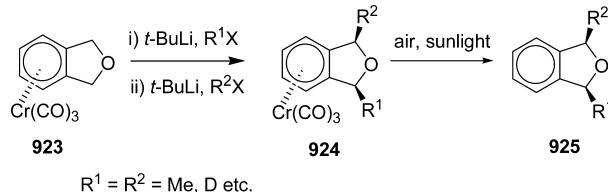
Scheme 241. Danishefsky Synthesis of Hydroxyphthalan



facile deprotonation of benzylic protons of 921. The methodology has formed the key step in the preparation of lactonamycin core.

2.3.3.5. Stereocontrolled Benzylic Functionalization of Phthalans. The most challenging aspect of the synthesis of phthalan derivatives is to control the stereochemistry of *cis*- or *trans*-1,3-disubstituted derivatives. Davies and co-workers first conceived the stereoselective synthesis of *cis*-1,3-disubstituted phthalans 925, starting from phthalan-Cr(CO)₃ complex 923 via 924, based on successive benzylic deprotonation, alkylation, and oxidative metal decomposition (Scheme 242).²⁸⁶ The

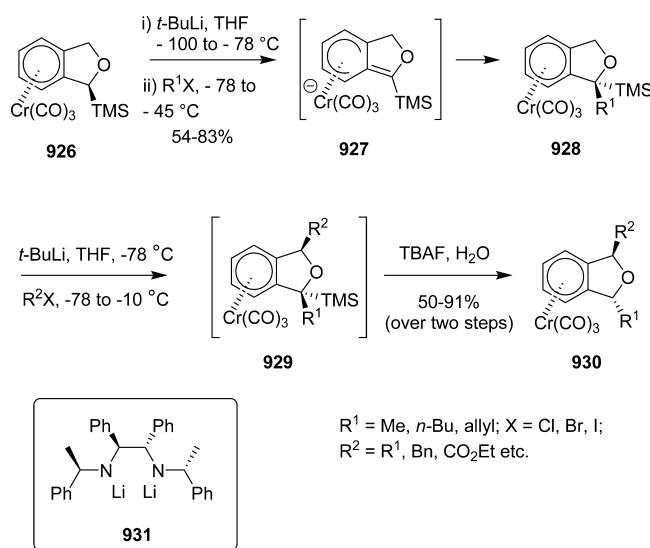
Scheme 242. Davis Stereoselective Synthesis of *cis*-1,3-Dialkylated Phthalans



success of the synthetic scheme relied upon the activation of the benzylic position by electron-withdrawing effect of the tricarbonyl group as well as steric bulk of the chromium complex, which led to the *cis*-configuration of the product.

trans-1,3-Disubstituted phthalans 930 were accessible by the innovative work of Schmalz.^{287a} Chromium complex of trimethylsilyl-substituted phthalan 926, upon alkylation using *t*-BuLi and alkyl halides, furnished 1,1-disubstituted compound 928 via *exo* attack of the approaching alkyl group on complex 927. A second alkylation produced intermediate 929, which on desilylation utilizing TBAF afforded the *trans*-1,3-disubstituted phthalide complex 930 as pure diastereomers (Scheme 243). The diastereoselectivity of the product came from the *exo*-protonation during desilylation. The enantioselective version of the methodology has been realized by the use of chiral diamide base 931, resulting in 99% enantiomeric purity.^{287a} Similar arenechromium tricarbonyl methodology was also

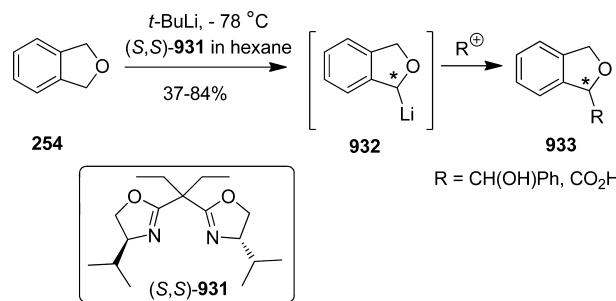
Scheme 243. Schmalz Synthesis of *trans*-1,3-Dialkylated Phthalans



described by Simpkins et al. for the synthesis of enantiopure thiophthalans by the use of 931 and LiCl.^{287b,c}

Under the influence of bis(oxazoline) 931, phthalan 254 was deprotonated at the benzylic-type by *t*-BuLi, and the resulting anion 932 was quenched with electrophiles like aldehydes and CO₂ to give enantiomerically enriched phthalan derivatives 933 (Scheme 244).²⁸⁸ It is reported that the asymmetric induction occurs at the post-lithiation stage.

Scheme 244. Synthesis of Chiral Phthalans by Lateral Lithiation

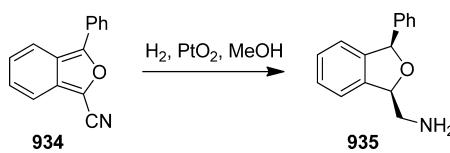


2.3.3.6. Hydrogenation of Benzoisofurans. A stereoselective synthesis of *cis*-1,3-disubstituted phthalan 935 was achieved by Davies et al. through H₂-PtO₂-mediated hydrogenation of 1-cyano-3-phenylisobenzofuran (934) (Scheme 245).²⁸⁶

3. CONCLUSION

In view of continued development on synthetic strategies in this field, we have attempted to present a comprehensive view

Scheme 245. Hydrogenation Approach to Phthalan



of the various synthetic avenues to phthalide and phthalan motifs, as well as their applications in the total synthesis of bioactive phthalide and phthalan natural products. Phthalides have been the subject of previous reviews, but, to date, a comprehensive review on the topic has not been available. Herein, we additionally overviewed the occurrence and biological activities of the majority of the natural products. The success stories of the drugs, *n*-butylphthalide (2a), mycophenolic acid (3), noscapine (36), and citalopram (764), have intensified the research in the area and resulted in a vast body of literature. In addition, synthetic utility of phthalides as building blocks for the quinonoid natural products like anthracyclines, angucyclines, and rheins has been venerable and has added a new dimension to research on phthalides and phthalans. Current isolation of new natural phthalides and phthalans would call for the development of novel stereoselective methodologies for the synthesis of phthalides and phthalans. Methods based on *ortho*-lithiations, cyclocarbonylations, transition metal-catalyzed orthoalkenylation, nucleophilic addition of organoboronic acids, [2+2+2] cycloadditions, and photochemical rearrangements are emerging to be the methods of choice. It is hoped that this Review will generate renewed academic interest in the chemistry of phthalides and phthalans, and will augment advancing the synthetic methods and total syntheses. This Review is expected to provide enough background information on this newer class of natural products, and allure the organic and medicinal chemists to solve the trivial and yet unsolved problems, the synthesis of pestacin, NG-121, etc.

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Notes

The authors declare no competing financial interest.

Biographies



Raju Karmakar was born in 1983 in Murshidabad, West Bengal, India. After completing his B.Sc. (Honours) (2004, first class, rank 4th) and M.Sc. (2006, first class, rank 2nd) degrees from the University of Kalyani, he joined a pharmaceutical company at Kolkata, India, where he spent one year. Thereafter, he joined the group of Professor D. Mal at the Indian Institute of Technology, Kharagpur, India, as a CSIR research fellow to earn his Ph.D. degree, which he received in April 2013. His research interests are total synthesis of angucycline antibiotics (completed first total synthesis of chlorocyclinone A) and isobenzofuran natural products. He has published six research publications in international journals. He has received the EliLilly

Outstanding Thesis Award in 2013. Currently, he is an Erasmus Mundus postdoctoral fellow at the Technical University of Braunschweig, Germany.



Pallab Pahari is a native of Midnapur, West Bengal, India. He obtained his Ph.D. in 2008 from the Indian Institute of Technology Kharagpur, India, under the supervision of Prof. Dipakranjan Mal. From 2007 to 2011, he was a postdoctoral fellow in the lab of Prof. Jürgen Rohr, University of Kentucky, KY. Currently, he is a scientist at CSIR-North East Institute of Science and Technology, Assam, India. His research interests include development of green chemical methodologies, synthesis of bioactive heterocycles, and isolation of bioactive natural products. He has published 25 research papers and three review articles in reputed international journals.



Dipakranjan Mal was born in 1952 and school-educated in Contai, West Bengal. He received his first class B.Sc.-Hons (1972) and M.Sc. (1975) degrees from the Calcutta University and began his research career as a CSIR junior research fellow in 1976 under the tutelage of Professor P. L. Majumder at the University College of Science, Kolkata. In mid-1976, he joined the University of Missouri at Kansas City where he received his Ph.D. degree (1981) on intramolecular hydrogen bonding in γ -hydroxycarboxylic acids under Professor Layton L. McCoy. After a postdoctoral stint (1981–1984) at Oregon Graduate Center with Professor Frank M. Hauser, he returned to India in 1984 and joined Bose Institute, Kolkata as a lecturer. Since 1987, he has been with the department of chemistry, Indian Institute of Technology Kharagpur, where he is now a full professor and the head of the department. His research interests are focused on the development of anionic and thermal domino strategies and total synthesis of angucyclines, anthracyclines, carbazoles, furocoumarins, and phthalide natural products. He has supervised 22 doctoral students and published over 100 research publications, including a review on the Hauser annulation published in *Chemical Reviews*. He has developed a video course on “Heterocyclic Chemistry”. He was a

recipient of the gold medal of R. K. Mission Vidyamandira, Belur Math, in 1973. He received the honor certificate of Phi Kappa Phi, U.S., in 1978. He is a life member of the Indian Chemical Society and the Chemical Research Society of India. He is also a member of the American Chemical Society. Recently, he was elected a Fellow of the West Bengal Academy of Science and Technology.

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DEDICATION

This Review is dedicated to my first research mentor, Professor Priyalal Majumder, Ex-Professor of Chemistry, Calcutta University, and Ex-Secretary, the Indian Chemical Society, who always inspires me to do something new in chemistry.

ABBREVIATIONS

Aq	aqueous
Bn	benzyl
BOM	benzyloxymethyl
CSA	camphor sulfonic acid
m-CPBA	meta-chloroperoxybenzoic acid
THF	tetrahydrofuran
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DMAP	4-(dimethylamino)pyridine
DIPEA	diisopropylethylamine
DTBB	4,4'-di- <i>tert</i> -butylbiphenyl
DMFDEA	N,N-dimethylformamide diethylacetal
DMAD	dimethyl acetylene dicarboxylate
DAST	diethylaminosulfur trifluoride
dppe	1,2-bis(diphenylphosphino)-ethane
dppf	1,2-bis(diphenylphosphino)-ferrocene
DABCO	1,4-diazabicyclo[2.2.2]octane
DEM	diethyl malonate
DMSO	dimethyl sulfoxide
DTBAD	di- <i>tert</i> -butyl azodicarboxylate
EOM	ethoxymethyl
HFIP	hexafluoroisopropanol
HMPT	hexamethylphosphorous triamide
IND	O-indolinylcarbamoyl
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LTMP	lithium tetramethylphosphoramide
MOM	methoxymethyl
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NHC	N-heterocyclic carbenes
NMP	N-methyl-2-pyrrolidone
NaHMDS	sodium hexamethyldisilazide
PIDA	phenyliodinium diacetate
PMB	p-methoxybenzyl
PMHS	polymethylhydrosiloxane
p-TSA	p-toluenesulfonic acid

TMEDA	N,N,N',N'-tetramethylethylenediamine
TIPS	triisopropylsilyl
TBDMS	<i>tert</i> -butyldimethylsilyl
TFA	trifluoroacetic acid
TBAF	tetrabutylammonium fluoride
TMU	1,1,3,3-tetramethylurea
TPAP	tetrapropylammonium perruthenate

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