frontiers
in Chemistry

Transition Metal-Mediated Annulation Approaches for Synthesis of Arylnaphthalene Lignan Lactones

Sooyoung Park[1†], Jin-Hee Kim[2†], Seok-Ho Kim[3*] and Dongyun Shin[1*]

[1] College of Pharmacy, Gachon University, Incheon, South Korea, [2] College of Pharmacy, Yonsei University, Incheon, South Korea, [3] Department of Pharmacy, College of Pharmacy and Institute of Pharmaceutical Sciences, CHA University, Pocheon-si, South Korea

Arylnaphthalene lignan lactones belong to a class of natural lignans, and more than 60 analogs have been isolated. Their pharmacological activities as well as unique structural features have attracted considerable attention from medicinal and synthetic chemists. Since the first synthesis in 1895, many synthetic methodologies with ionic or pericyclic reaction mechanisms have been reported. Transition metal catalysts sometimes provide exceptional synthetic versatility for the syntheses of natural compounds. Recently, transition metal-mediated methodologies were investigated for the construction of basic scaffolds of arylnaphthalene lignan lactones. Five kinds of transition metal catalysts containing gold, manganese, nickel, palladium, and silver have been explored. Most of the metal catalysts successfully created arylnaphthalene lactones by intermolecular or intramolecular annulative cyclization. In this review, all reports of transition metal-mediated annulative construction of arylnaphthalene lignan lactones were compiled, and synthetic approaches, mechanistic aspects, and successful applications were discussed.

Keywords: transition metal, arylnaphthalene, catalysis, lignan, synthesis, lactone

INTRODUCTION

Natural arylnaphthalene lignan lactones are classified as lignans and isolated from a variety of dietary or medicinal plants, such as *Phyllanthus, Justicia, Haplophyllum*, and *Cleistanthus* (Anjaneyulu et al., 1981; Batsuren et al., 1981; Khalid and Waterman, 1981; Ulubelen, 1985; Lin et al., 1995). They show broad pharmacological activities, including cytotoxic (Day et al., 2002; Yu et al., 2010; He et al., 2012; Deng et al., 2014; Luo et al., 2014; Ren et al., 2014, 2019; Won et al., 2015; Woo et al., 2017; Woodard et al., 2018; Yi et al., 2018; Young et al., 2018), antiplatelet (Chen et al., 1996; Weng et al., 2004), neuroprotective (Gu et al., 2016), antiviral (Asano et al., 1996; Cow et al., 2000), antifungal (Windayani et al., 2014), and anti-HIV (Chang et al., 1995; Zhang et al., 2017) activities. From the biosynthetic viewpoint, oxygenated phenylpropanoids, which are synthesized from phenylalanine or tyrosine, are condensed to bicyclic diphenyl furofurans. Reductive ring opening and oxidative cyclization delivers dibenzylbutyrolactones and final intramolecular Friedel–Crafts type cyclization produced arylnaphthalene lignan lactones (Teponno et al., 2016). Structurally, these compounds can be divided into Type I and Type II arylnaphthalene lignan lactones based on the position of lactones and phenyl groups (**Figure 1**). Thus far, more than 60 arylnaphthalene congeners and glycosylated products are reported. Diverse
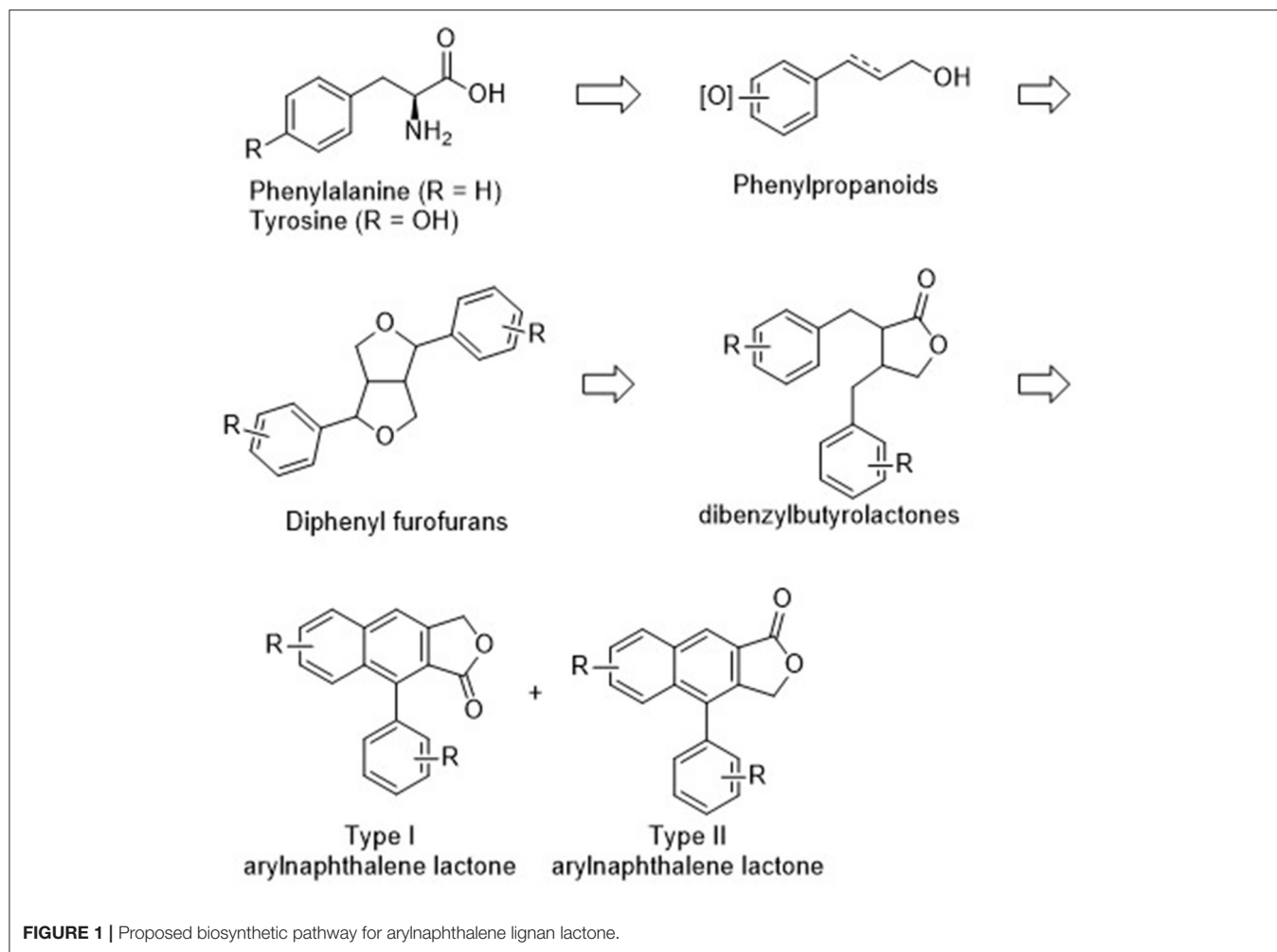
FIGURE 1 | Proposed biosynthetic pathway for arylnaphthalene lignan lactone.

and significant pharmacological activities make them more attractive, and representative natural examples are listed in **Figure 2**.

Since the report of early efforts on the synthesis of arylnaphthalene lignan lactone in 1895 by Michael and Bucher (1895) and in 1910 by Bucher (1910) using the thermal cyclative condensation reaction of arylpropiolic acids, many synthetic methodologies for arylnaphthalene lignan lactones and their applications for natural arylnaphthalene lignan lactones have been investigated. Representative synthetic methodologies include intramolecular Diels–Alder type ring formation of arylpropiolic anhydride by Stevenson's group (Brown and Stevenson, 1964, 1965; Maclean and Stevenson, 1966; Holmes and Stevenson, 1970, 1971; Block and Stevenson, 1971, 1973; Stevenson and Block, 1971; Stevenson and Holmes, 1971; Stevenson and Weber, 1989, 1991; Anastas and Stevenson, 1991; Park et al., 2014), intermolecular Diels–Alder reaction of isobenzofurans and dimethyl acetylenedicarboxylate (De Silva et al., 1980; Plaumann et al., 1980), sequential Blaise reaction-intramolecular [4 + 2] reaction of 2-alkynylbenzonitriles (He et al., 2014), and Garratt–Braverman cyclization of substituted bis-propargyl ethers (Mondal et al., 2011, 2012). Photo-assisted

cyclization methods provide arylnaphthalene lignan lactones efficiently (Block and Stevenson, 1971, 1973; Arnold et al., 1973; Yamamoto et al., 2015). Tandem conjugate addition-aldol reaction protocol (Ogiku et al., 1990; Kamal et al., 1994), benzoin condensation-thermal cyclization (Hayat et al., 2015), and electrophilic aromatic substitution protocols (González et al., 1978; Ogiku et al., 1995) have also been reported. Recently, synthetic approaches and biological activities of arylnaphthalene lignan lactones were reviewed by Zhao et al. (2018).

Transition metals have proven to be very useful in modern organic synthesis. The transition metal catalyzed reaction is particularly important for the formation of carbon–carbon bonds, and enables formation of bonds that are not possible with conventional methods. It also allows the formation of complex structures in a single reaction. In this review, all the research articles in which transition metals were utilized for the synthesis of arylnaphthalene lignan lactones are comprehensively discussed and the main advantages in each method are elucidated. There are five transition metals involved in the synthesis of arylnaphthalene lignan lactones, and each one is discussed in terms of the reaction mechanism and its applications for synthesis of arylnaphthalene lignan lactones.

FIGURE 2 | Selected natural arylnaphthalene lignan lactones.
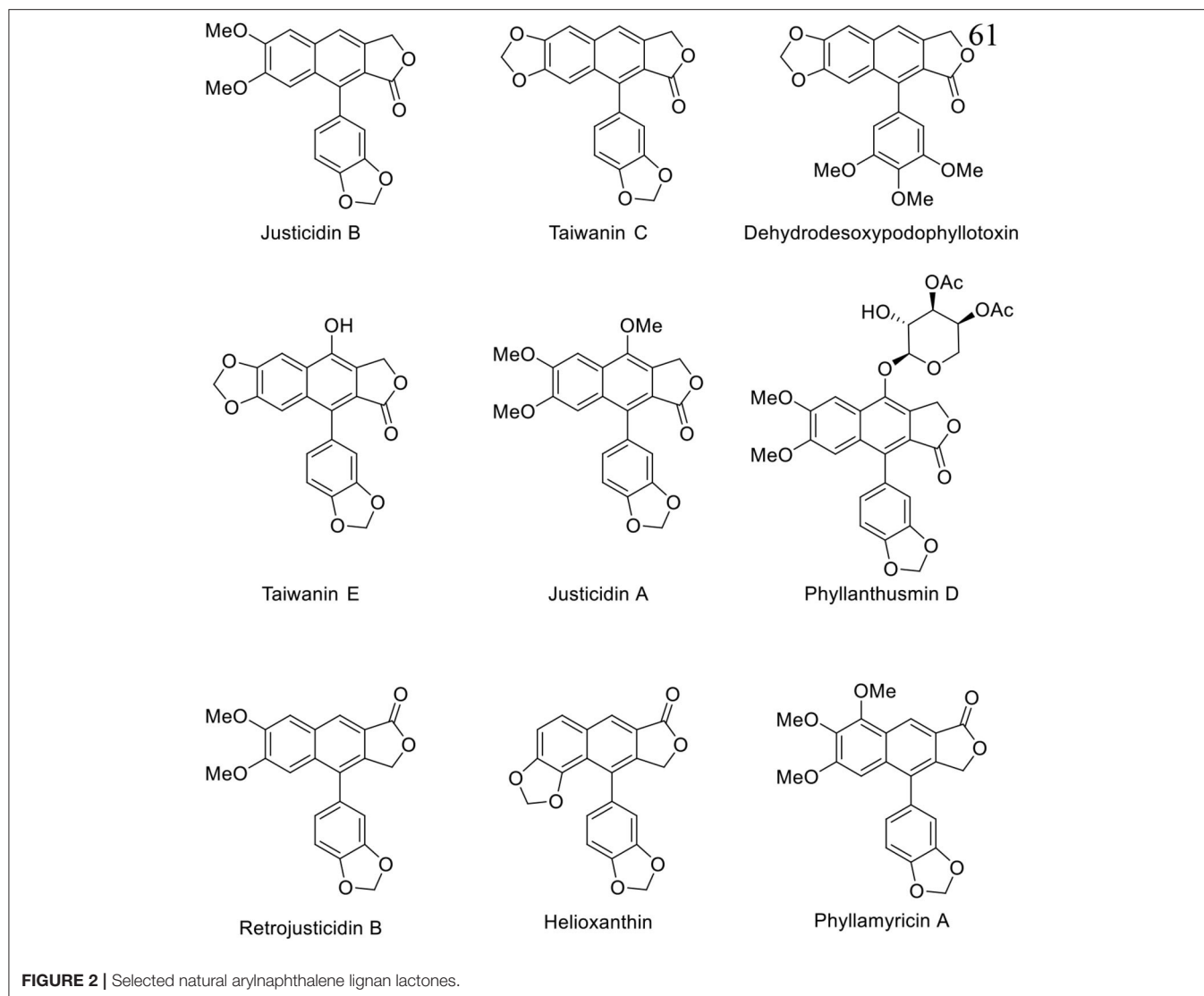
TRANSITION METAL-MEDIATED SYNTHESIS OF ARYLNAPHTHALENE LIGNAN LACTONES

Gold-Catalyzed Cyclization

Recently, extensive studies have been devoted to gold-catalyzed reactions in organic synthesis (Hashmi, 2007; Li et al., 2008). Balamurugan's group focused on the intramolecular cyclization of alkynyl ester **1** by an Au catalyst in combination with AgSbF$_6$ for the synthesis of an arylnaphthalene lignan lactone lignan scaffold (Gudla and Balamurugan, 2011). Catalysis of the cyclization begins with coordination of the distant carbonyl and alkyne group of **1** to a proximal position by the Au catalyst. Vinyl cation **2** was produced by subsequent attachment of the alkyne on the carbonyl group. Arylnaphthalene lignan lactone precursor **4** was synthesized by the removal of water and Au catalyst from **3** that was obtained from the electrophilic benzannulation reaction of **2** (**Scheme 1**).

Application of this methodology to the synthesis of natural arylnaphthalene lignan lactone is summarized in **Scheme 2**. The key intermediate **1** was obtained from propargyl alcohol in four steps. Sonogashira coupling of propyn-1-ol **5** with substituted aryl iodide provided **6** and **7** was obtained by the substitution reaction. Boron trifluoride-mediated epoxide opening provided **8** and **1** was obtained by Swern oxidation. The ketone **1** can also be obtained by epoxidation of cinnamyl alcohol **9**, propargylation, Cu(OTf)$_2$-mediated Meinwald rearrangement and Sonogashira coupling with substituted aryl iodide albeit in low yield. The Au-catalyzed cyclization of **1a-1c** was achieved in yields of 84, 68, and 73%, respectively. Regiocontrolled oxidation of **4** by CrO$_3$/H$_5$IO$_6$ in acetonitrile (Yamazaki, 1999) afforded 4.5:1 mixture of type II and isomeric type I arylnaphthalene lignan lactone. The advantage of this synthetic approach is the highly mild reaction condition performed at room temperature and easy derivatization with late-stage introduction of the aryl group from intermediate **10**. Two years later, Balamurugan's group

SCHEME 1 | Mechanism of Au-catalyzed intramolecular cyclization of alkynyl ester.
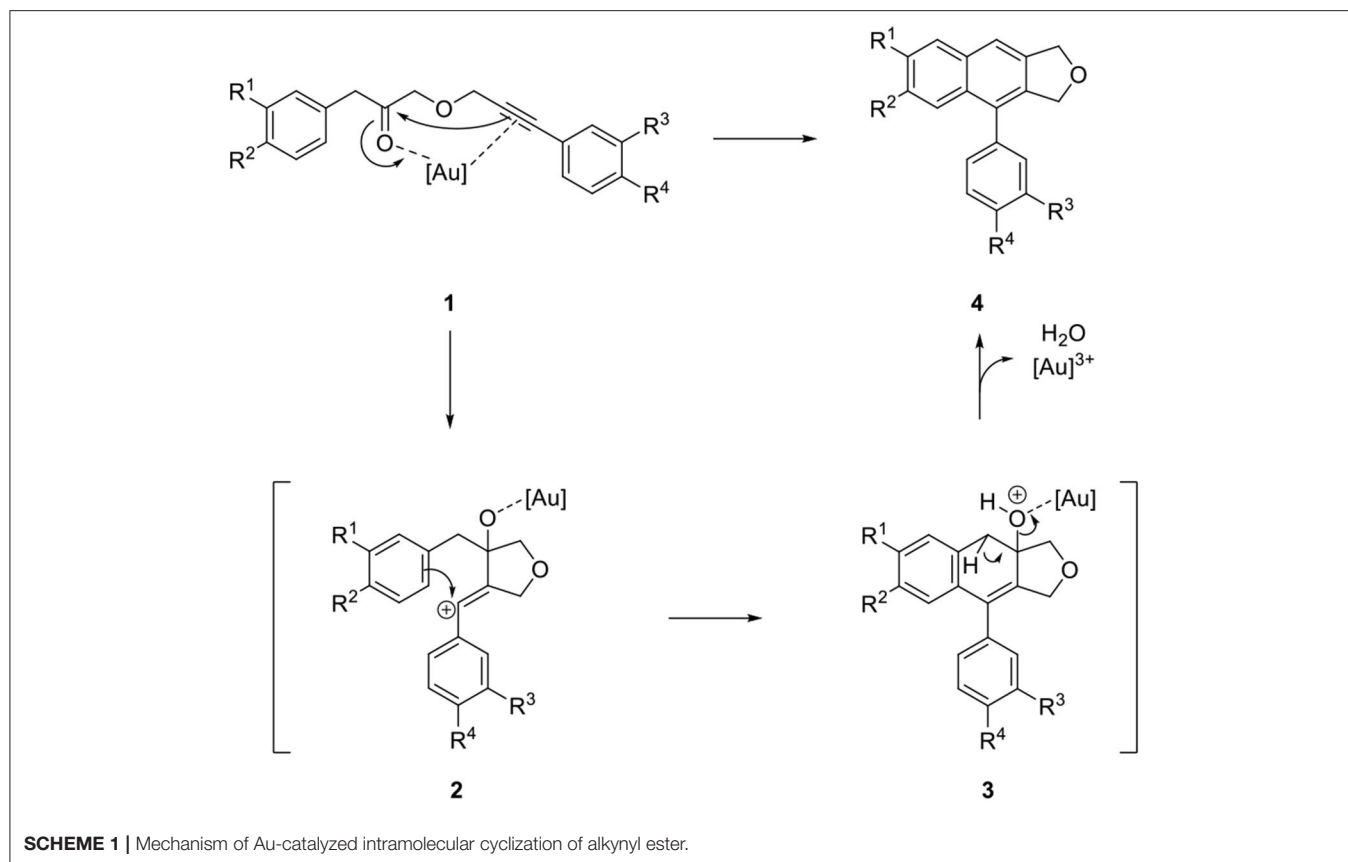
developed the one-pot sequential Meinwald rearrangement of **11** and cyclization of ketone **1** to provide **4** in yields of 79–93% (Gudla and Balamurugan, 2013).
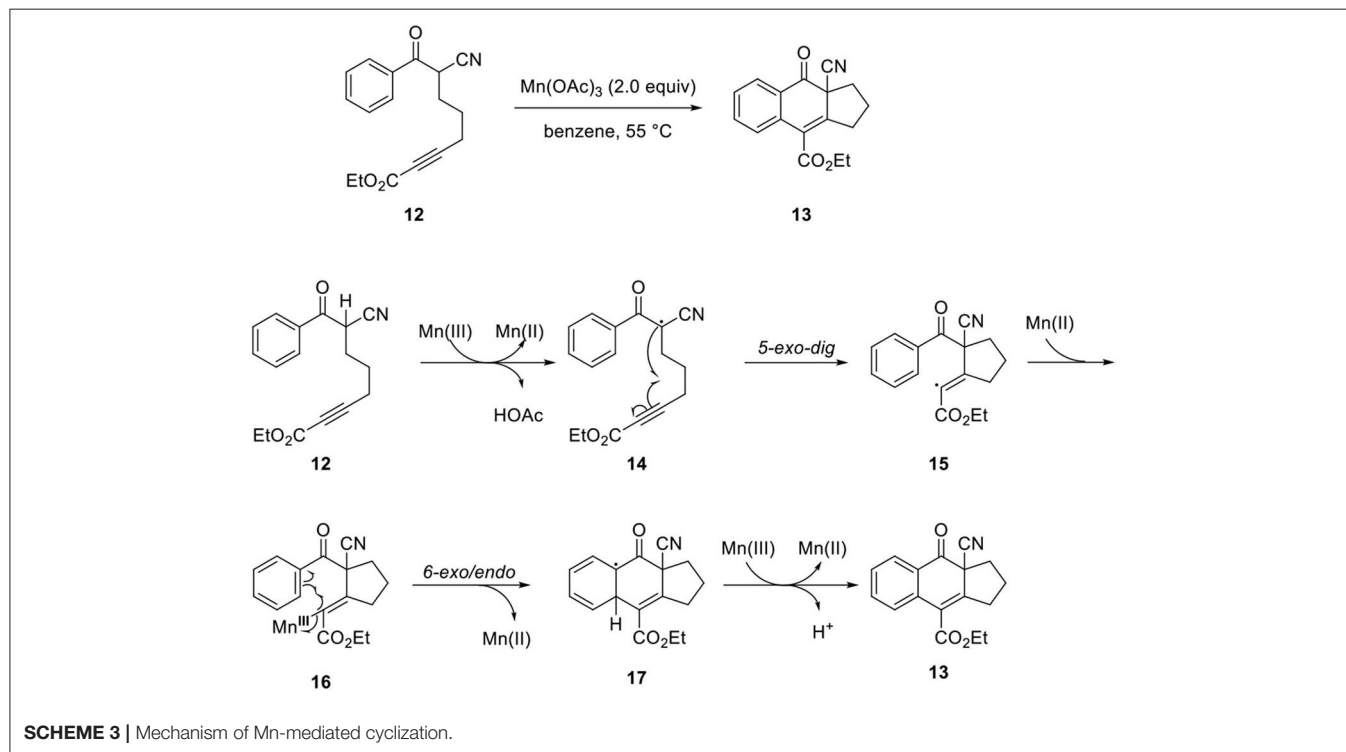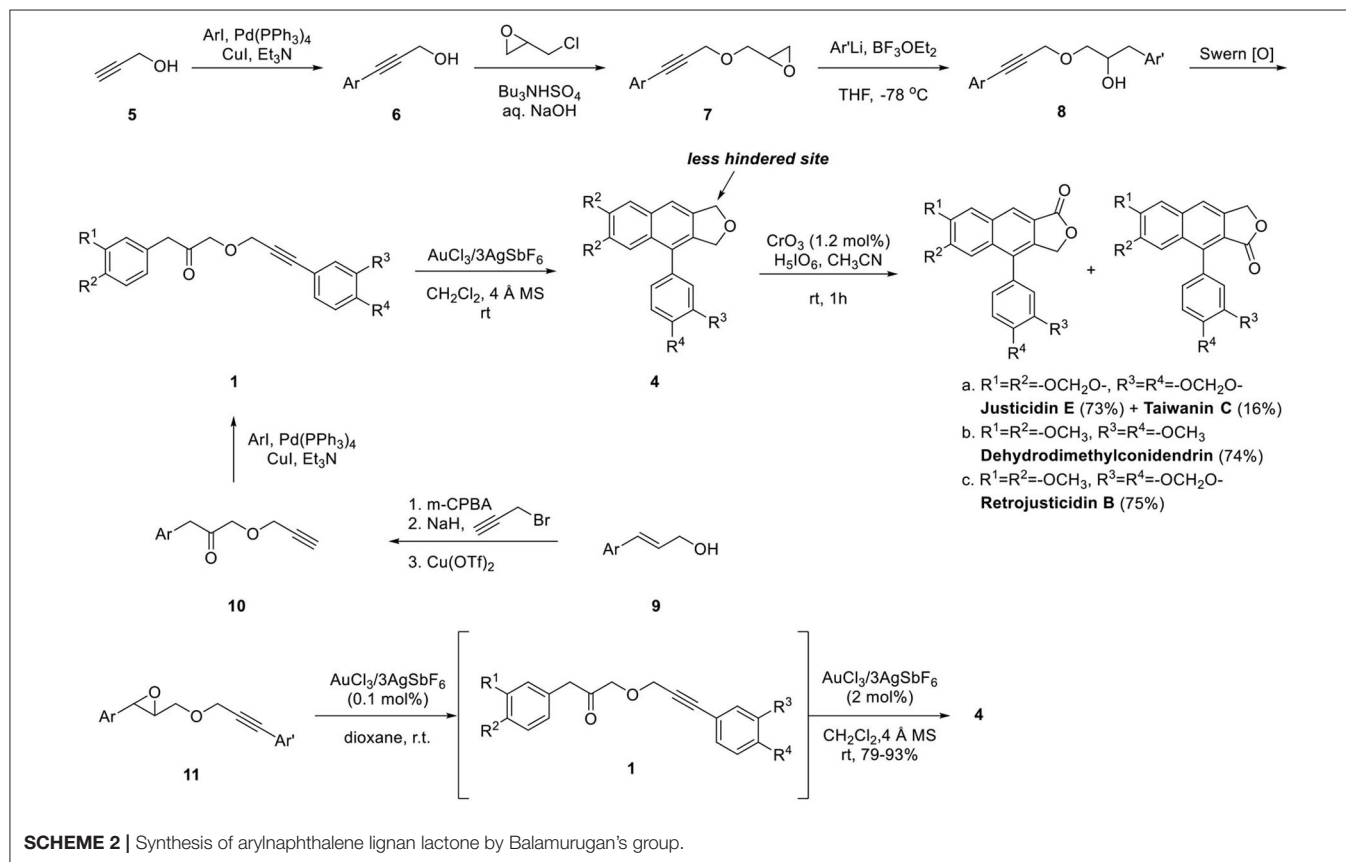
Manganese-Catalyzed Cyclization

Shia's group studied Mn(OAc)$_3$-mediated cyclization to synthesize arylnaphthalene lignan lactone (Wong et al., 2014; Kao et al., 2015). Initially, they investigated the feasibility of the oxidative cyclization of model system **12**. The reaction proceeded under mild condition compared to the dehydro-Diels–Alder reaction, which requires high reaction temperatures of 160–300°C. The mild reaction conditions allow diverse functional groups, including Trimethylsilyl (TMS), ester, ketone, amide, phosphonate, and halogen. The reaction mechanism was proposed as follows. Abstraction of α-H in **12** produced Mn(III) enolate, and electron transfer generated Mn(II) and radical species **14**. Then, the radical was added to the alkyne by 5-exo-dig type cyclization to provide **15**. Next, the vinyl radical reacted with Mn(II) to form Mn(III)-vinyl complex **16**, and naphthalene core **13** can be constructed by vinyl radical addition to benzene by 6-exo/endo type cyclization, and another electron transfer from **17** to Mn(III) ultimately generates an aromatic ring with loss of H$^+$ (**Scheme 3**).
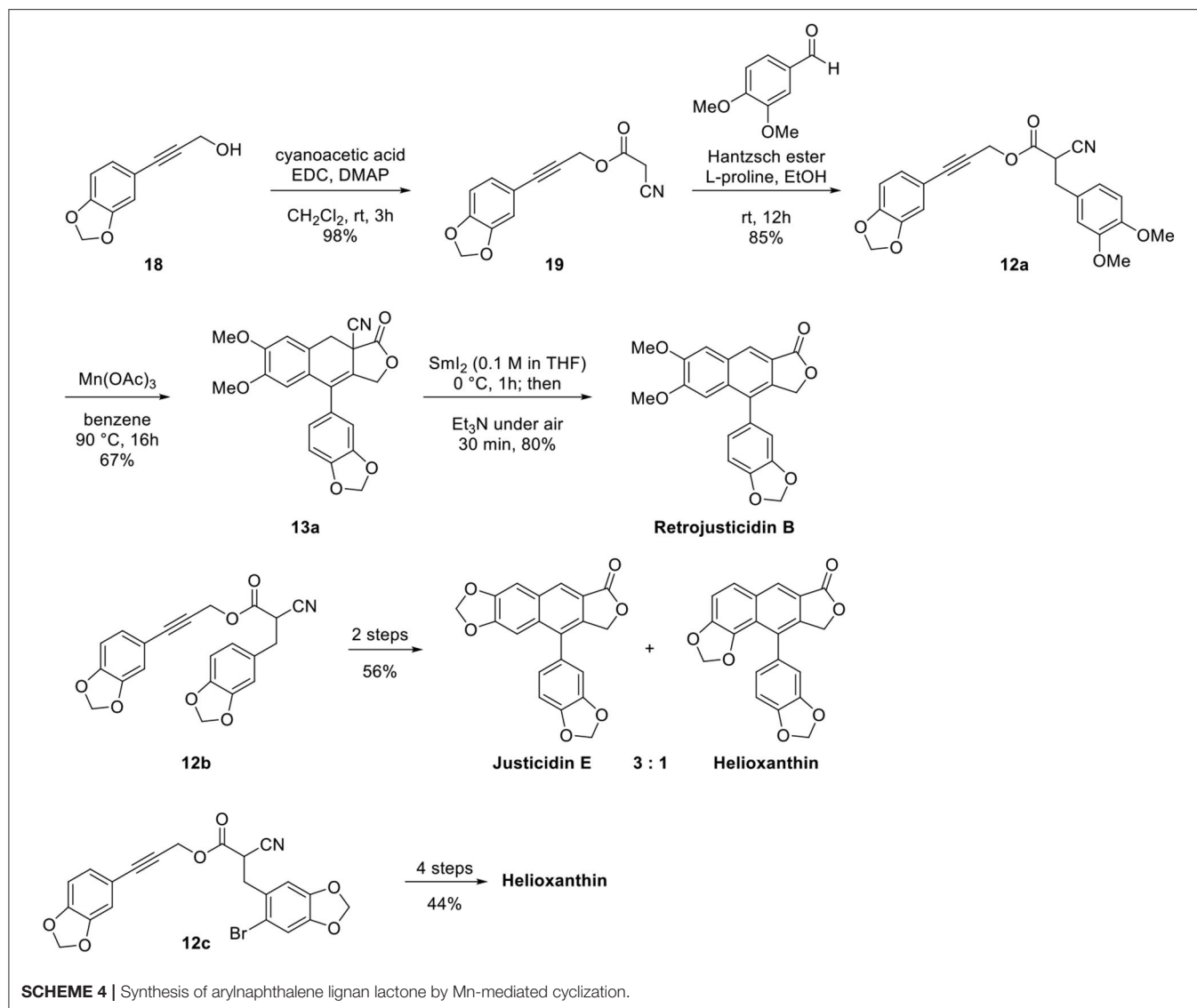
With these successful results in hand, they turned their attention to the natural products synthesis as shown in **Scheme 4**. Cyclization precursor **12a** was synthesized by esterification

of substituted phenyl propargyl alcohol **18** with cyanoacetic acid, one-pot Knoevenagel condensation with benzaldehyde, and Hantzsch ester mediated reduction. Mn(OAc)$_3$-catalyzed cyclization provided inseparable 3:1 mixtures of **13a** and its regioisomer (67:22%). Samarium iodide mediated reductive decyanation and air oxidation afforded retrojusticidin B at 80% yield. Synthesis of justicidin E and helioxanthin was also achieved from **13b** following the same procedure affording a 59:20% mixture. Regioselective synthesis of helioxanthin was accomplished from **13c** by introducing Br in the 2-position of piperonal to minimize regioisomer formation. The main advantage of this reaction may be functional group tolerance; however, the regioselectivity is not satisfactory unless Br is introduced in the 2-position to inhibit adverse cyclization, where Mn(OAc)$_3$ is used in stoichiometric amount (2.0 equivalents).

Nickel-Catalyzed Cyclization

Peng's group developed a nickel-catalyzed cyclization to afford dihydronaphthalene and tetrahydronaphthalene in a diastereodivergent manner (Xiao et al., 2018a). Following on, they investigated the construction of an arylnaphthalene core for the synthesis of dehydrodesoxypodophyllotoxin (Xiao et al., 2018c). Key reaction is summarized in **Scheme 5** although detailed stereochemical outcomes are not indicated here (Xiao et al., 2018b). Ni(I) is reduced to Ni(0) by Zinc(0) metal and the single electron transfer process produced alkyl radical **21**

SCHEME 2 | Synthesis of arylnaphthalene lignan lactone by Balamurugan's group.

a. $R^1=R^2=$-OCH$_2$O-, $R^3=R^4=$-OCH$_2$O-
Justicidin E (73%) + **Taiwanin C** (16%)
b. $R^1=R^2=$-OCH$_3$, $R^3=R^4=$-OCH$_3$
Dehydrodimethylconidendrin (74%)
c. $R^1=R^2=$-OCH$_3$, $R^3=R^4=$-OCH$_2$O-
Retrojusticidin B (75%)

SCHEME 3 | Mechanism of Mn-mediated cyclization.

SCHEME 4 | Synthesis of arylnaphthalene lignan lactone by Mn-mediated cyclization.

from **20**. The secondary radical of **21** was added to the alkene in 5-*exo-trig* type producing **22** and then, the primary radical formed the Ni(III) species **2** following the known Ni^I-Ni^{III} redox process via **23** and **24**. Finally, reductive elimination provided **26** and regenerated the Ni(I) species.

The synthesis of arylnaphthalene lignan lactones begins with oxazolidinone imide formation, as shown in **Scheme 6**. Oxazolidinone imide **28** was obtained by the Horner–Emmons reaction of 6-bromopiperonal **27** with triethyl phosphonoacetate, saponification, and imide formation by reaction of *in situ* generated pivaloyl anhydride and oxazolidinone. Gilman reagent was added to the β-position of enone diasteroselectively at a ratio of 97:3 affording **29** and subsequent reduction of the imide by NaBH$_4$, oxidation with Pyridinium ChloroChromate (PCC) and acetal formation afforded **30**. Enol ether **31** was generated in the presence of TMSOTf as Lewis acid. **32** was obtained as a 1.2:1 mixture by bromination with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD) (Kato et al., 1976, 1984) and

concomitant mixed acetal formation with allyl alcohol. Ni-catalyzed reductive cyclization afforded tetrahydronaphthalene lactol ether **33** with *cis* and *trans* mixture of 41 and 35% yield, respectively. Then, acetal **33** was hydrolyzed and oxidized to lactone by PCC to produce *cis*-**34** and *trans*-**34** in 68 and 62% yield, respectively. Dehydrodesoxypodophyllotoxin was obtained by radical halogenation, elimination reaction, and further oxidation from *trans*-**34**. Dihydronaphthalene lactone can be obtained from *cis*-**34** by phenylselenylation at −78°C, *m*-CPBA oxidation, and selenoxide elimination. This Ni-mediated reductive cyclization is advantageous in terms of diastereodivergent synthesis for tetrahydronaphthalene containing diversity-oriented library synthesis.

Palladium-Mediated Cyclization

Pd-catalyzed copolymerization of diynes and arynes is well-known for the construction of an aromatic ring depending on the metal species (Peña et al., 1998). In continuation of

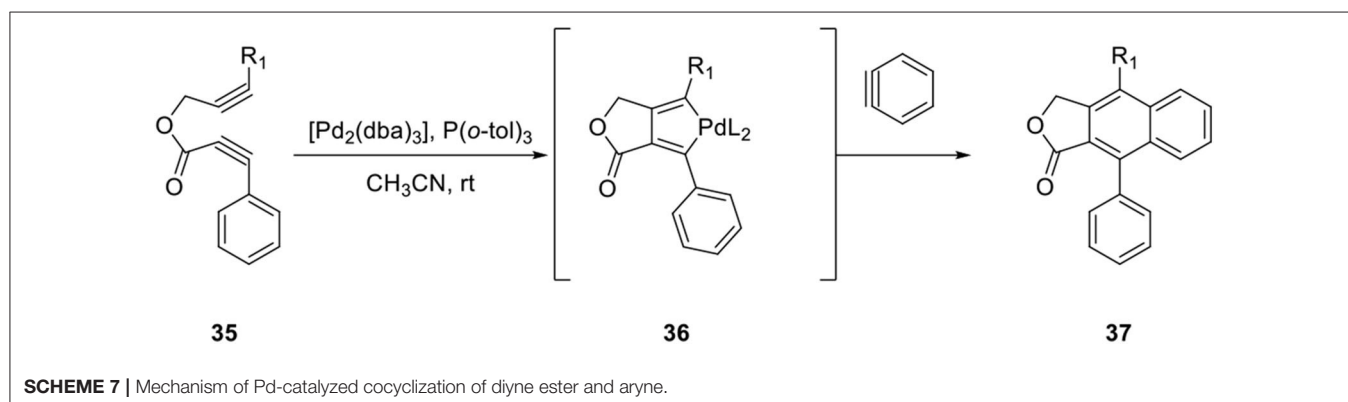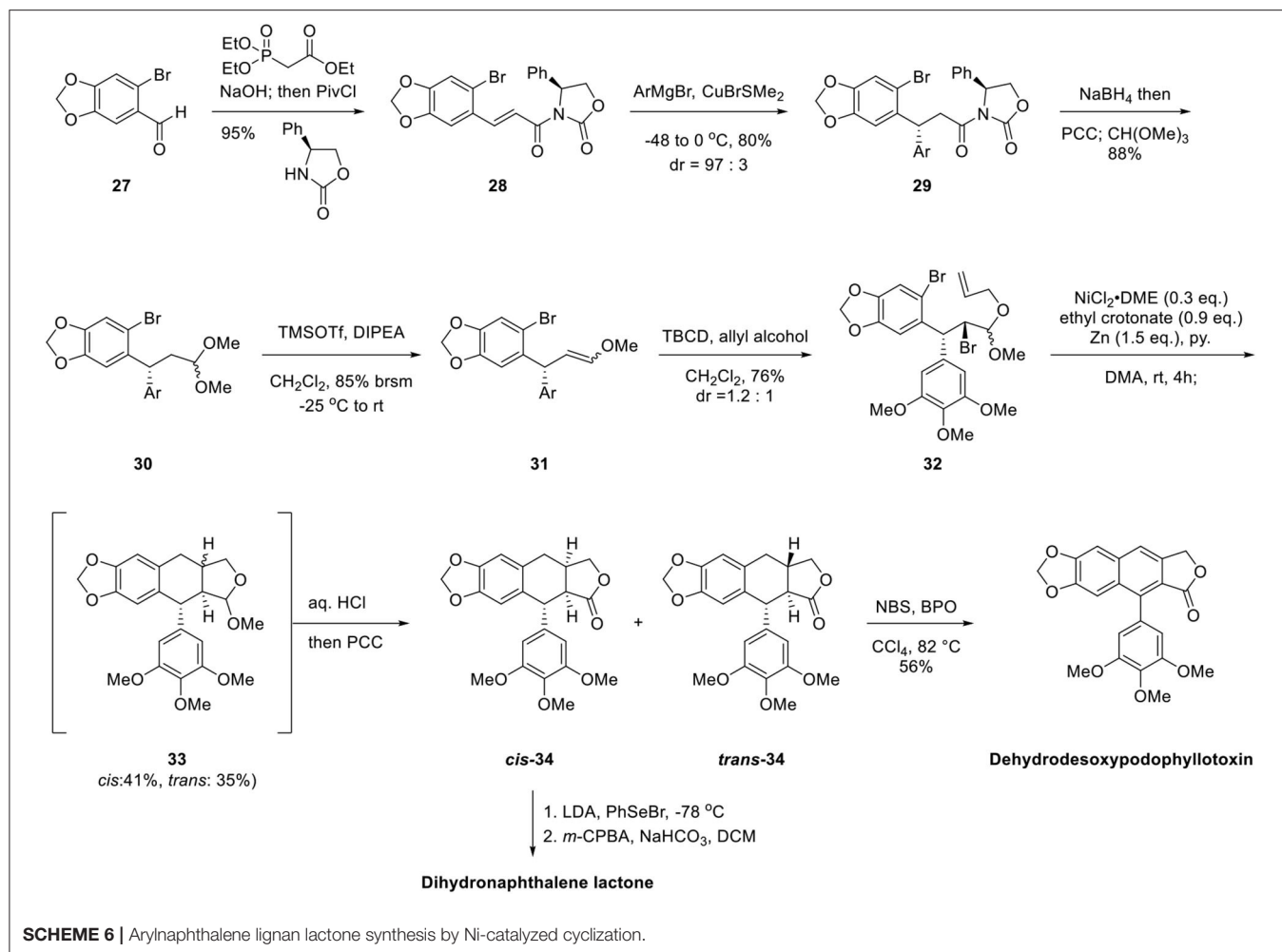**SCHEME 5 |** Mechanism of Ni-catalyzed cyclization reaction.
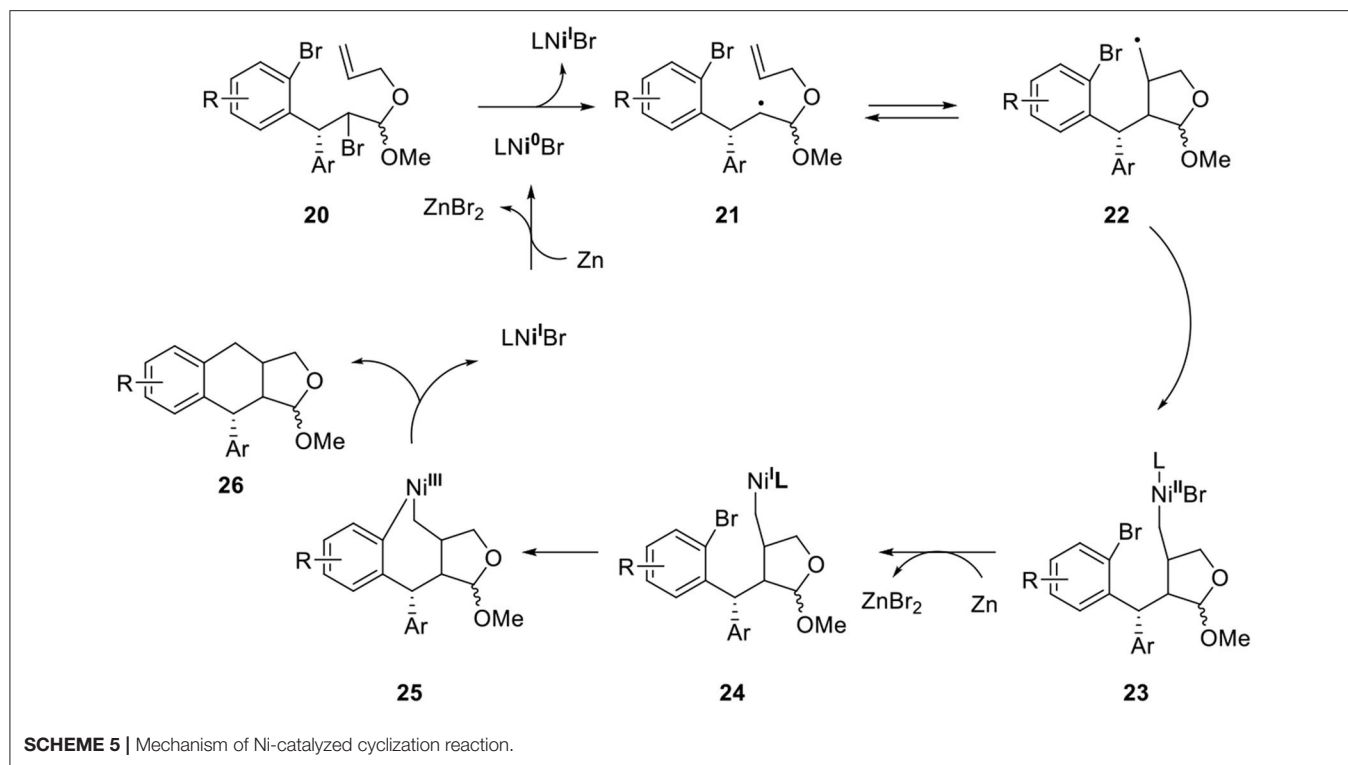
arylnaphthalene lignan synthesis efforts (Mori et al., 1999; Sato et al., 1999), Mori et al. developed a new method for construction of the naphthalene ring by a Pd-catalyzed cocyclization of diyne esters and arynes (Sato et al., 2004). A plausible reaction mechanism can be explained by the formation of palladacycle intermediate **36** from diyne ester **35** and further reaction with benzyne to provide arylnaphthalene lignan lactone **37** (Peña et al., 1998; **Scheme 7**).

As depicted in **Scheme 8**, synthesis of diyne ester **40** was commenced with Pd-catalyzed coupling of *N*-methoxy-*N*-methylcarbamoyl chloride with protected propargyl alcohol **38** (Murakami et al., 1998). After deprotection of **39** in the acidic condition, the resulting alcohol was coupled with 3-[benzo(d)(1,3)dioxol-5-yl]propiolic acid, which was prepared by sequential Corey–Fuchs olefination, carboxylation under *n*-BuLi, and methyl chloroformate, and hydrolysis of methyl ester to afford diyne ester **40**. Aryne precursor **41** was synthesized by silylation of 2-bromophenol, lithiation at low temperature with silyl group migration, and triflation of *in situ* generated phenol. Arylnaphthalene lignan lactone **42** was obtained with diyne ester **40** and aryne precursor **41** in the presence of CsF and Pd catalyst in 61% yield with only 5 mol% loading of Pd catalyst. However, the functional group interconversion of Weinreb amide of **42** was difficult compared to the ease of core ring formation. Direct reduction of amide with LiAl(OtBu)₃H (Paris et al., 1998) and L-Selectride with MeOTf (Tsay et al., 1990) were attempted but were unsuccessful. Finally, it was converted to aldehyde with an additional four steps. Lactol **43** was obtained by methanolysis of lactone **42** and concomitant transesterification and partial reduction with DIBAL at low temperature. Reduction of lactol **43**

with NaBH₄ afforded diol, which underwent transesterification to provide primary alcohol and aldehyde **44** was obtained upon PCC oxidation. Then, the aldehyde was converted to taiwanin C by the Tsuji–Wilkinson decarbonylation reaction with rhodium catalyst (Tsuji and Ohno, 1965). Taiwanin E was obtained by Baeyer–Villiger oxidation and hydrolysis of the ester.

In 2007, Sato et al. (2007) applied the aforementioned methodology for the synthesis of arylnaphthalene lignan lactone. As shown in **Scheme 9**, Pd-catalyzed copolymerization of diyne ester **45** and aryne precursor **41** was also successful despite a multistep of reactions for conversion of Weinreb amide **46** to lactol **47** and aldehyde **48**. The aldehyde group of **48** was converted to O-triflate **49** by a three-step sequence of Baeyer–Villiger oxidation, hydrolysis, and triflation of the resulting phenolic hydroxyl group. Finally, the triflate was eliminated by Pd-catalyzed hydrogenation to give arylnaphthalene lignan lactone. The desired dehydrodesoxypodophyllotoxin was synthesized from **46** in low yields of 17% through eight steps. In these two syntheses, constructions of the core ring were highly efficient and regioselective. Further manipulation of the functional groups successfully delivered natural arylnaphthalene lactone products.
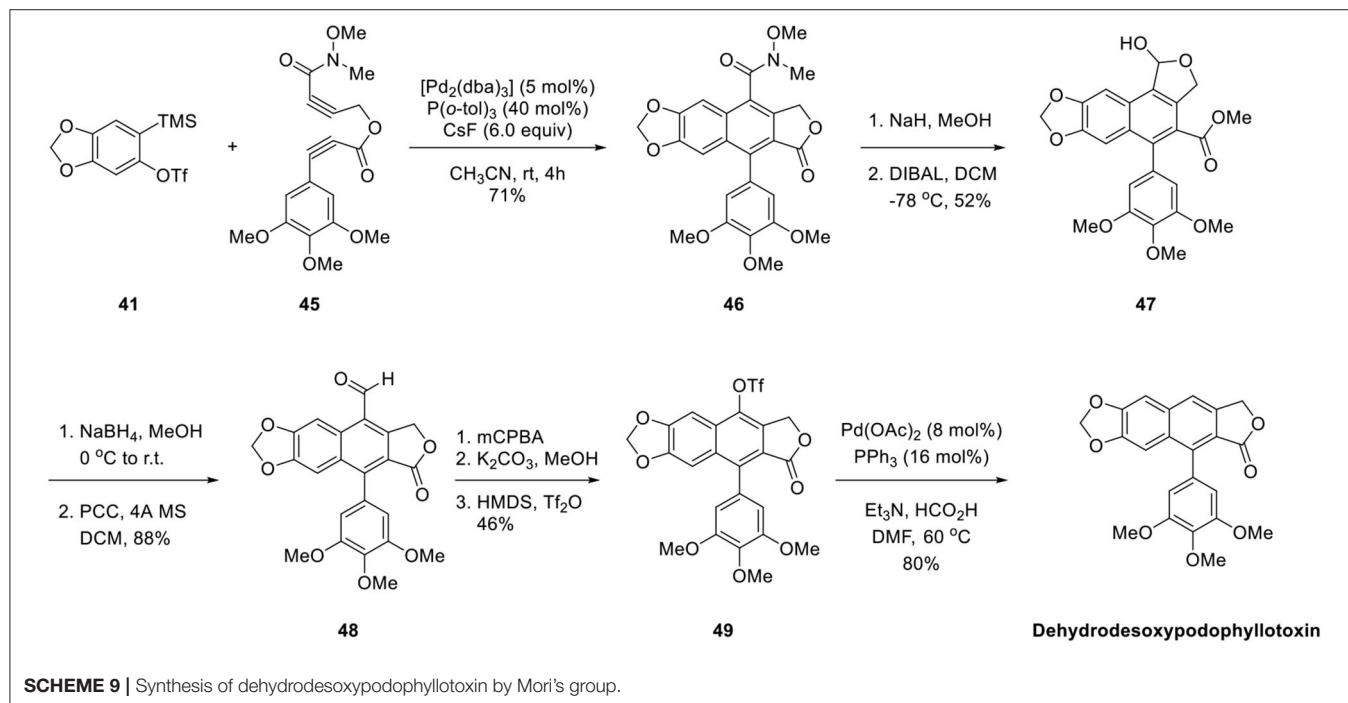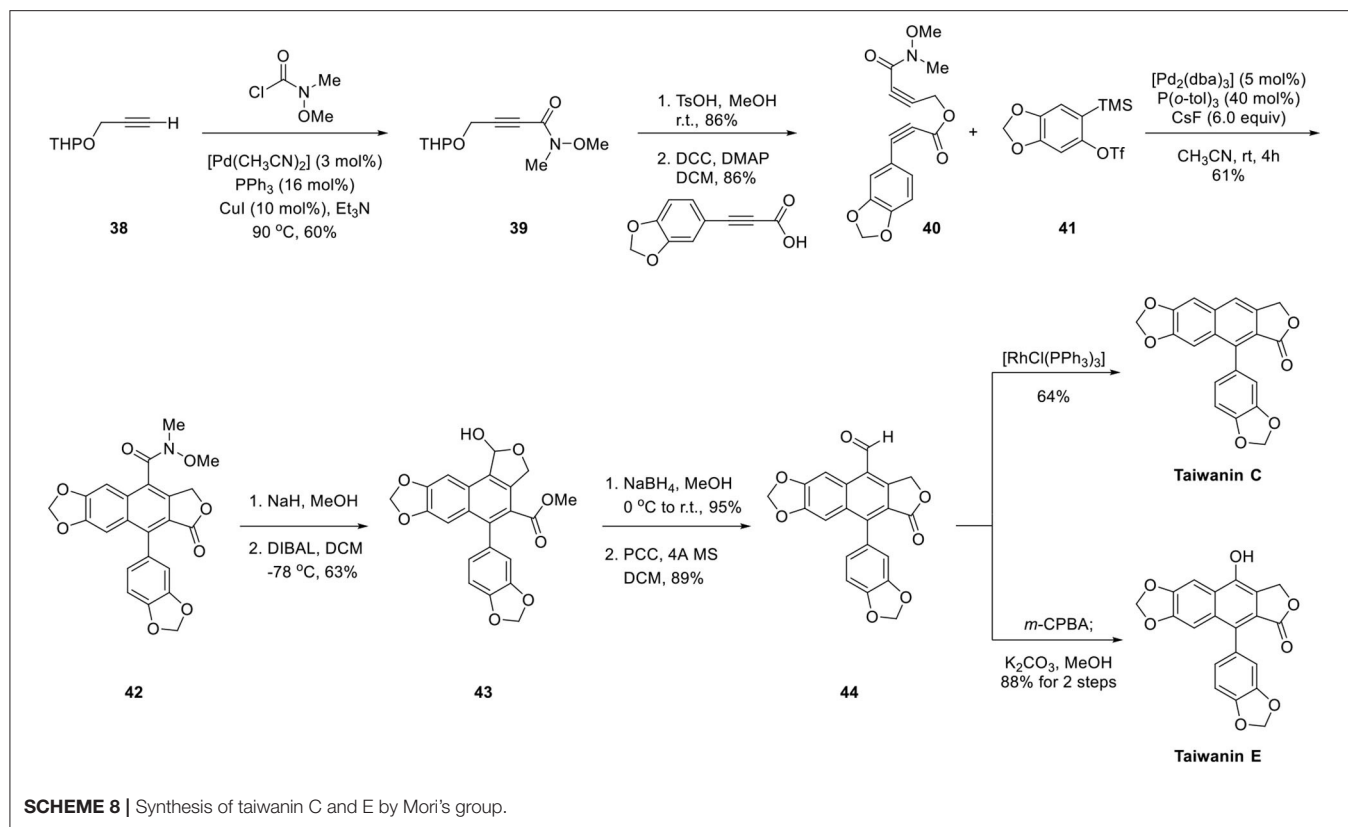
In 2013, Patel and Argade (2013) further developed Pd-catalyzed [2 + 2 + 2] cocyclization of aryne **50** and unsymmetrical conjugated diene **51** using palladium catalyst with *N*-heterocyclic carbene ligand. Initial trial of aryne **50** and diene **51** in the absence of catalyst resulted in only [2 + 2] cycloaddition adduct in which the less substituted olefin of **51** reacted with aryne **50**. It was assumed that the desired [2 + 2 + 2] cycloadduct was not generated because of two

SCHEME 6 | Arylnaphthalene lignan lactone synthesis by Ni-catalyzed cyclization.

SCHEME 7 | Mechanism of Pd-catalyzed cocyclization of diyne ester and aryne.

electro-positive carbons in diene. Therefore, Argade's group systematically studied metal-mediated [2 + 2 + 2] cocyclization to construct a 6-membered ring. The reaction was ultimately optimized to 62% yield with Pd₂(dba)₃ and IMes.HCl as the ligands. The mechanistic pathway involves oxidative addition of Pd to aryne **50** and the less hindered alkene of **51** to form a five-membered palladacycle intermediate **52**, and insertion of

more substituted bonds to form a seven-membered palladacycle **53** via rearrangement. Finally, **55** was obtained by reductive elimination of **53** and spontaneous air oxidation of **54** during workup (**Scheme 10**).

By applying this methodology, the authors successfully achieved total synthesis of Type I and Type II arylnaphthalene lignan lactones, justicidin B and retrojusticidin B, respectively, as

SCHEME 8 | Synthesis of taiwanin C and E by Mori's group.

SCHEME 9 | Synthesis of dehydrodesoxypodophyllotoxin by Mori's group.

presented in **Scheme 11**. The synthesis begins with methanolysis of citraconic anhydride **56** in acidic condition and then allylic bromination to afford **57** (Kar and Argade, 2002). Unsymmetrical

diene **58** was synthesized by further reaction with Wittig reagent (Patel and Argade, 2007). Arylnaphthalene lignan lactone **60** was obtained in 66% yield by Pd-promoted copolymerization

SCHEME 10 | Mechanism of Pd-catalyzed cocyclization of aryne and unsymmetrical diene.
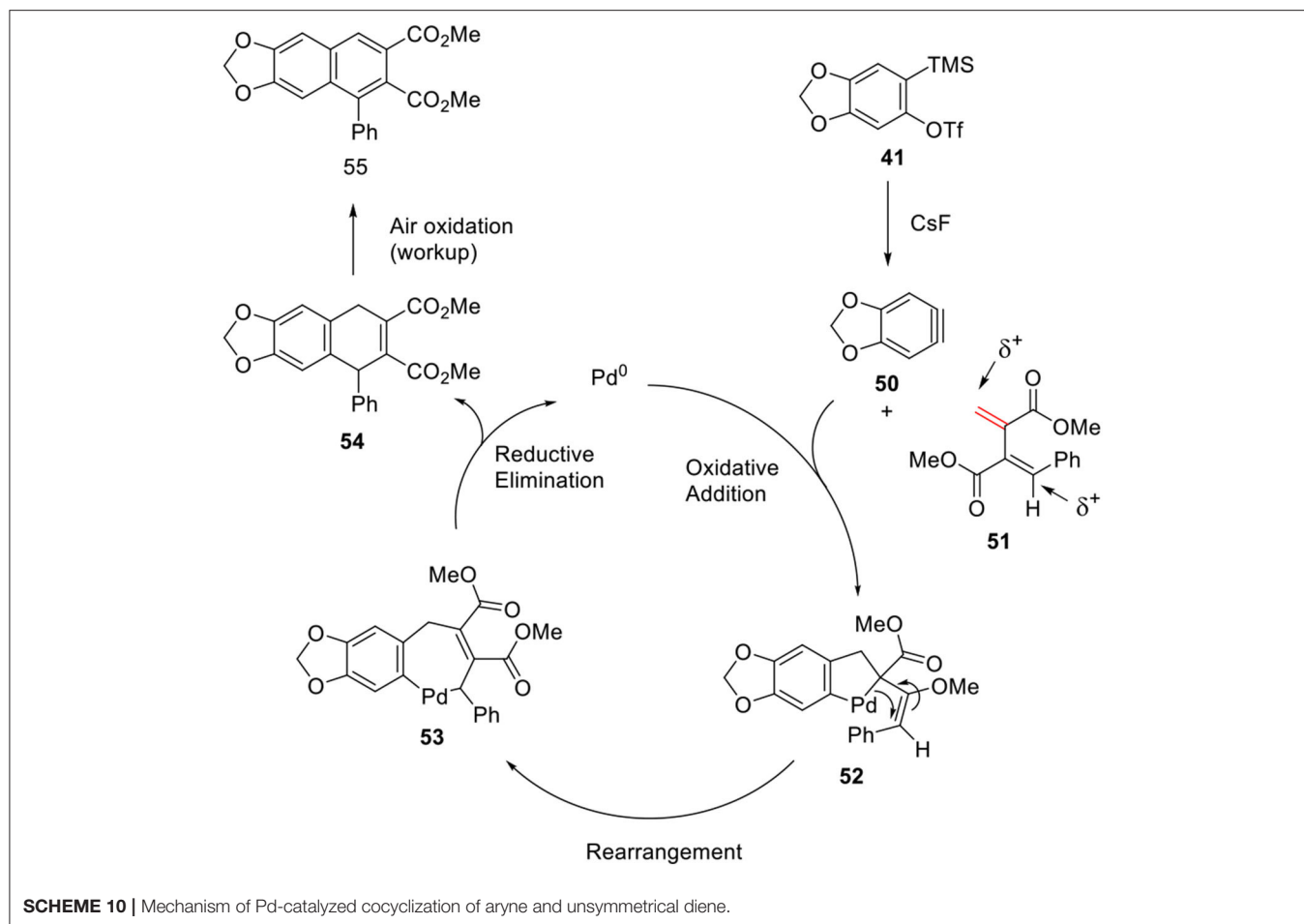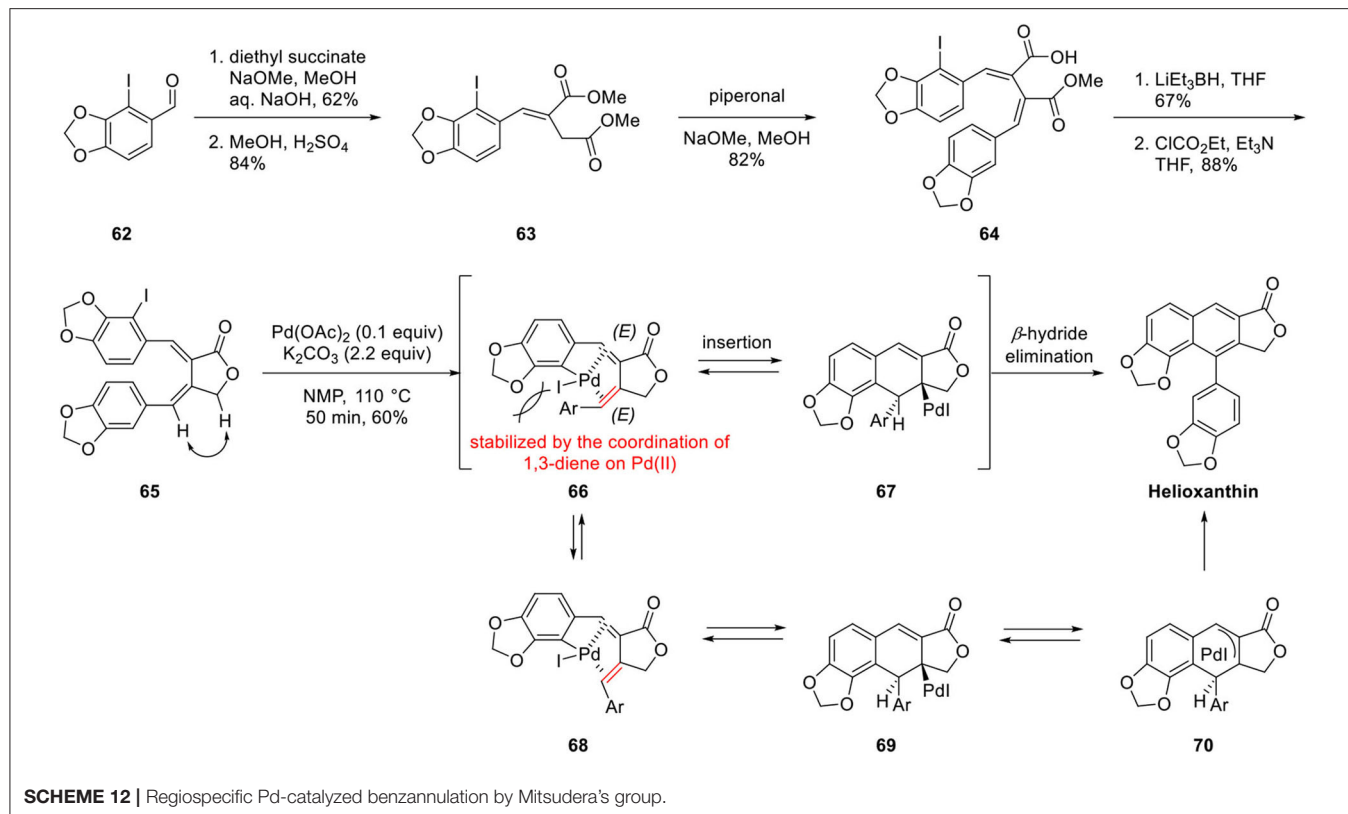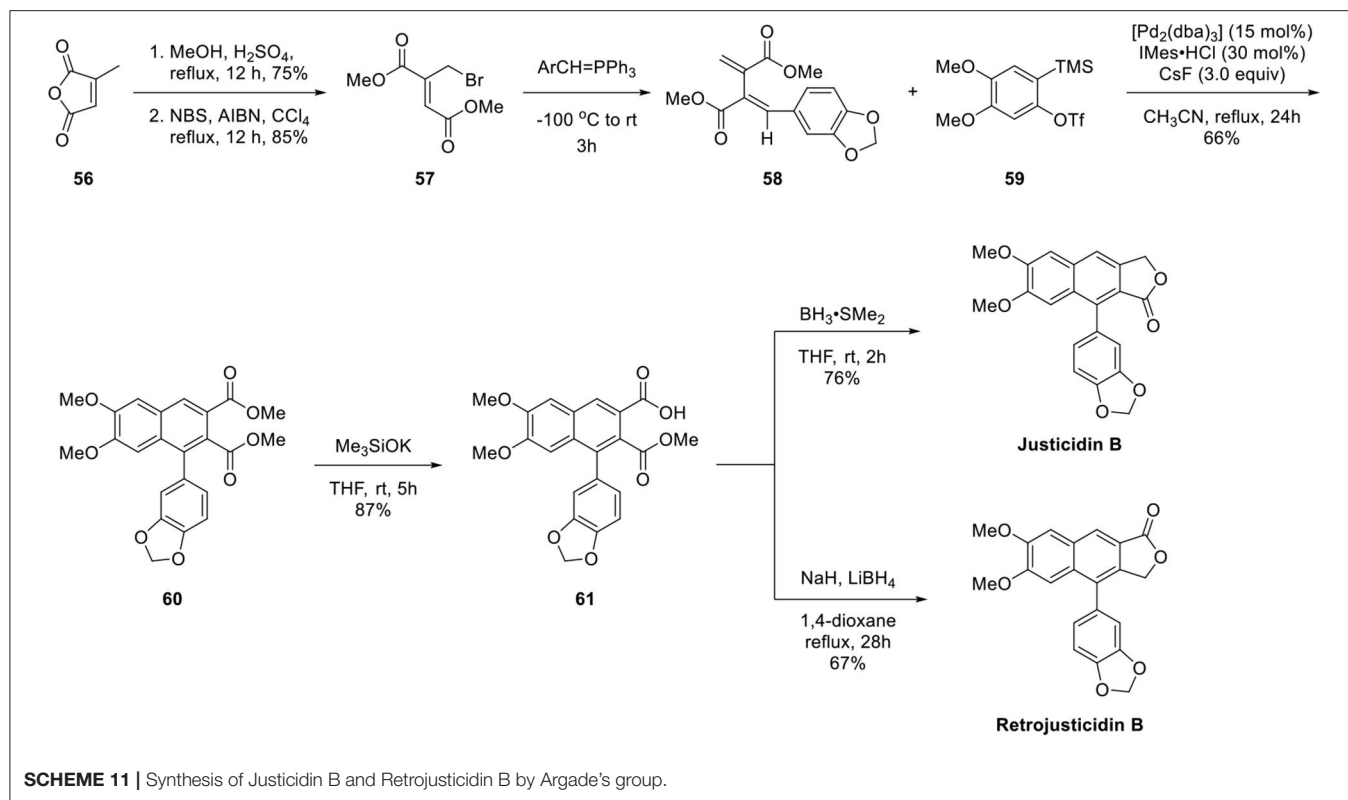
of **58** and **59**. Regioselective hydrolysis of less-hindered ester afforded **61**. Justicidin B was obtained by borane reduction of carboxylic acid and lactonization. Retrojusticidin B was obtained in 67% yield by selective ester group reduction in the presence of carboxylate salt with 28% yield of justicidin B as a regioisomer.
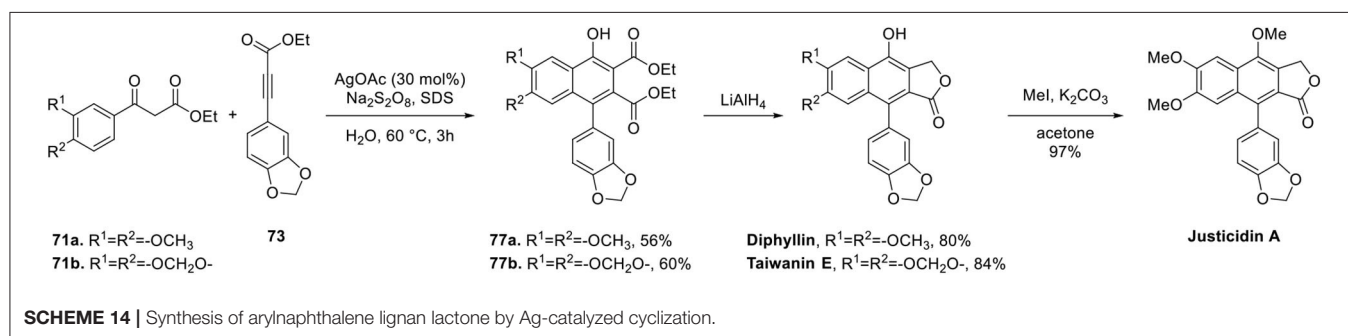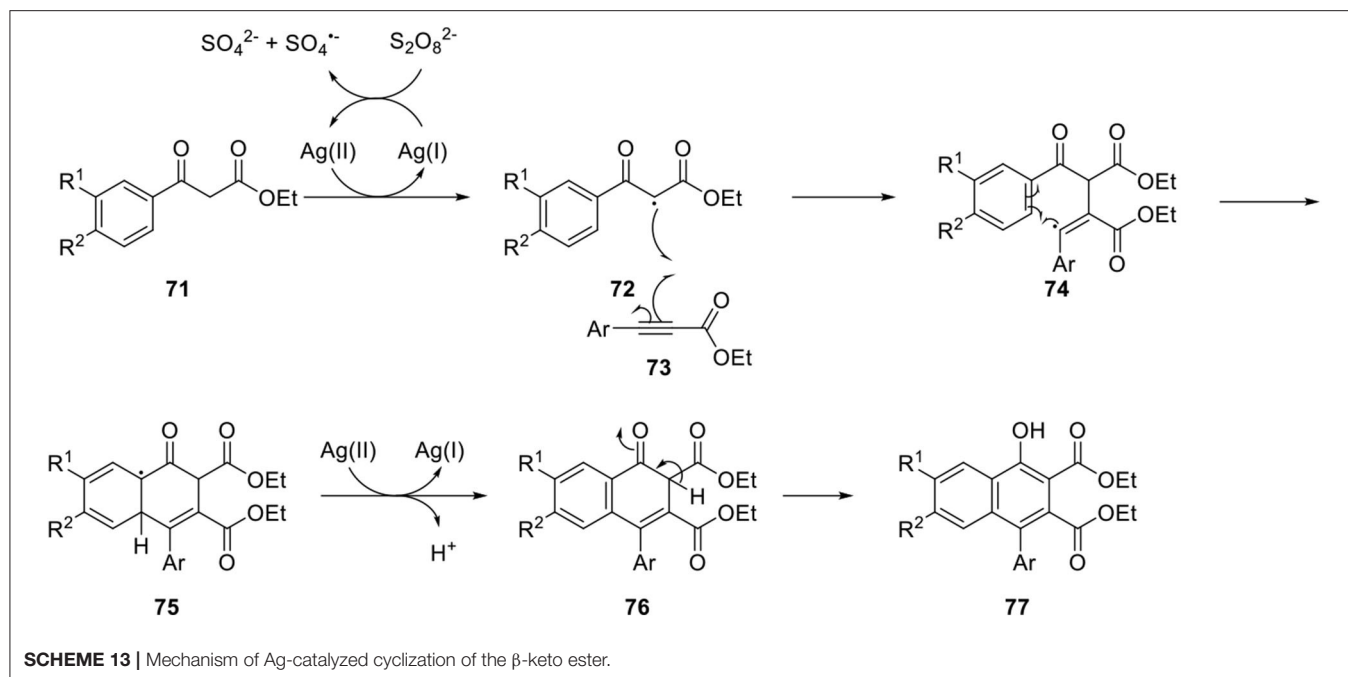
Mitsudera's group studied the construction of arylnaphthalene lignan lactone by a regiospecific Pd-catalyzed benzannulation of α, β-bisbenzylidene-γ-lactone for the synthesis of helioxanthin (Mizufune et al., 2001; **Scheme 12**). Structurally, helioxanthin is a 7,8-substituted naphthalene lignan lactone compound, whereas most natural arylnaphthalene lignan lactones bear 6,7-oxygen substituents. Therefore, regioselectivity is the most significant issue in this synthesis. Benzannulation precursor **65** was synthesized by Stobbe condensation of diethyl succinate with 2-iodopiperonal **62** and Fischer esterification to afford **63**. Stobbe reaction of **63** with piperonal afforded **64**, and lactone **65** was obtained by Super-Hydride-mediated ester reduction and concomitant lactonization. The geometry of the alkene was confirmed by analysis of the NOESY spectrum. With this substrate in hand, helioxanthin was obtained by benzannulation in 60% yield. The reaction mechanism can be explained as described below. Oxidative addition of Pd to aryl iodide **65** provided intermediate **66,** which is stabilized by a

coordination of 1,3-diene to Pd even in the presence of steric hindrance generated by the aryl group of the diene. Then *syn* insertion of the palladium complex to the alkene provided σ-dihydronaphthalene palladium complex **67** and *syn* β-hydride elimination afforded helioxanthin. In the other process, the geometry of alkene can be isomerized to (*Z*) in **68** specified in red color in **Scheme 6**. In that case, the β-hydride, which is positioned *anti* to Pd in **69** is eliminated by *anti* β-hydride elimination process by way of π-allylpalladium complex **70**. In this synthesis, construction of the naphthalene ring is proceeded in relatively mild condition with only the catalytic amount of Pd catalyst in a concise, efficient manner with opposite regioselectivity usually obtained as a minor product using the Diels–Alder approach.

Silver-Catalyzed Cyclization

Narender et al. developed a novel route for regioselective synthesis of 4-aryl substituted α-naphthols by silver(I) catalyzed C-H functionalization of β-keto esters **71** and aryl propiolates **73** in an environmentally friendly manner (Naresh et al., 2015). The reaction mechanism was proposed to begin with disproportionation of persulfate dianion to persulfate radical anion producing Ag(II) ion. Then, β-ketoester **71** is oxidized

SCHEME 11 | Synthesis of Justicidin B and Retrojusticidin B by Argade's group.

SCHEME 12 | Regiospecific Pd-catalyzed benzannulation by Mitsudera's group.

SCHEME 13 | Mechanism of Ag-catalyzed cyclization of the β-keto ester.

SCHEME 14 | Synthesis of arylnaphthalene lignan lactone by Ag-catalyzed cyclization.

by the Ag(II) ion to a highly stable radical species **72**, and the radical is added to propiolate **73** to produce vinyl radical **74**, which is stabilized by the neighboring aryl group (Yan et al., 2015). Finally, the radical **74** underwent addition to the benzene ring and synthesis of 4-arylnaphthol **77** was achieved by additional oxidation of **75** by Ag(II) ion, and tautomerization of **76** (**Scheme 13**).

Successful and efficient applications for the synthesis of arylnaphthalene lignan lactone is summarized in **Scheme 14**. The reaction of substituted ethyl benzoyl acetate **71** and substituted ethyl phenylpropiolate **73** in the presence of silver acetate and $Na_2S_2O_8$ furnished 4-aryl α-naphthol **77a** and **77b** in 56 and 60% yield, respectively. Surfactant (sodium dodecyl sulfate) was used to enhance water solubility and yield and reduced the use of organic solvent. Lithium Aluminum Hydride (LAH)-mediated reduction of ester located next to phenol and the spontaneous lactonization afforded diphyllin and taiwanin E in 80 and 84% yield, respectively. Justicidin A was also obtained by methylation of diphyllin in quantitative yield. This Ag-catalyzed cyclization

proceeded in an atom economic manner, broad substrate scope, excellent regioselectivity, and environmental friendliness albeit with high loading of Ag catalyst.

CONCLUSION

Arylnaphthalene lignan lactones continuously intrigue synthetic organic chemists and medicinal chemists owing to their structural uniqueness and pharmacological activity as well as the possibility as privileged structures. This review focused on transition metal catalyzed approaches for the synthesis of arylnaphthalene lignan lactones, especially on the construction of arylnaphthalene cores by metal catalyst incorporating gold, manganese, nickel, palladium, and silver. Compared with the non-metal catalyzed synthesis of arylnaphthalene lignan lactones, synthetic methodologies using transition metal catalysts provide distinct advantages in terms of mild reaction conditions, chemical yields, and functional group tolerance. In addition,

single step construction of a complex core structure through multiple bond formation is scientifically meaningful and provides utility in chemical library synthesis for drug discovery.

AUTHOR CONTRIBUTIONS

DS conceptualized the manuscript. SP researched publications related to the review article. SP and J-HK prepared the schemes and figures. S-HK and DS wrote the draft of the manuscript and

prepared the final version of the manuscript with considerable corrections. All authors approved the manuscript in its final form for publication.

FUNDING

REFERENCES

Anastas, P. T., and Stevenson, R. (1991). Synthesis of natural lignan arylnaphthalene lactones, daurinol and retrochinensin. *J. Nat. Prod.* 54, 1687–1691. doi: 10.1021/np50078a035

Anjaneyulu, A. S. R., Ramaiah, P. A., Row, L. R., Venkateswarlu, R., Pelter, A., and Ward, R. S. (1981). New lignans from the heartwood of cleistanthus collinus. *Tetrahedron* 37, 3641–3652. doi: 10.1016/S0040-4020(01)98 893-3

Arnold, B. J., Mellows, S. M., and Sammes, P. G. (1973). Photochemical reactions. Part I. A new route to tetradehydropodophyllotoxin, taiwanin E, and related compounds. *J. Chem. Soc. Perkin Trans.* 1, 1266–1270. doi: 10.1039/p19730001266

Asano, J., Chiba, K., Tada, M., and Yoshii, T. (1996). Antiviral activity of lignans and their glycosides from *Justicia procumbens. Phytochemistry* 42, 713–717. doi: 10.1016/0031-9422(96)00024-6

Batsuren, D., Batirov, K., Malikov, V. M., Zemlyanskii, V. N., and Yagudaev, M. R. (1981). Arylnaphthalene lignans of *Haplophyllum dauricum*. The structure of daurinol. *Chem. Nat. Compd.* 17, 223–225. doi: 10.1007/BF00568506

Block, E., and Stevenson, R. (1971). Synthesis of model aryltetralin ligands: adducts of o-methylbenzophenone with unsymmetrical dienophiles. *J. Chem. Soc. D Chem. Commun.* 13, 711–712. doi: 10.1039/c29710000711

Block, E., and Stevenson, R. (1973). The irradiation of 2-methylbenzophenone in the presence of dienophiles. *J. Chem. Soc. Perkin Trans.* 1, 308–313. doi: 10.1039/p19730000308

Brown, D., and Stevenson, R. (1964). Action of N,N-dicyclohexylcarbodiimide on phenylpropiolic acids: synthesis of dehydro-otobain. *Tetrahedron Lett.* 5, 3213–3216. doi: 10.1016/0040-4039(64)83136-1

Brown, D., and Stevenson, R. (1965). Synthesis of dehydrootobain. *J. Org. Chem.* 30, 1759–1763. doi: 10.1021/jo01017a012

Bucher, J. E. (1910). The acids of the phenylpropiolic series and their condensation to naphthalene derivatives. *J. Amer. Chem. Soc.* 32, 212–221. doi: 10.1021/ja01920a008

Chang, C.-W., Lin, M.-T., Lee, S.-S., Liu, K. C. S. C., Hsu, F.-L., and Lin, J.-Y. (1995). Differential inhibition of reverse transcriptase and cellular DNA polymerase-α activities by lignans isolated from Chinese herbs, *Phyllanthus myrtifolius* Moon, and tannins from *Lonicera japonica* Thunb and *Castanopsis hystrix. Antiviral Res.* 27, 367–374. doi: 10.1016/0166-3542(95)0 0020-M

Chen, C.-C., Hsin, W.-C., Ko, F.-N., Huang, Y.-L., Ou, J.-C., and Teng, C.-M. (1996). Antiplatelet arylnaphthalide lignans from *Justicia procumbens. J. Nat. Prod.* 59, 1149–1150. doi: 10.1021/np960443+

Cow, C., Leung, C., and Charlton, J. L. (2000). Antiviral activity of arylnaphthalene and aryldihydronaphthalene lignans. *Can. J. Chem.* 78, 553–561. doi: 10.1139/v00-059

Day, S.-H., Lin, Y.-C., Tsai, M.-L., Tsao, L.-T., Ko, H.-H., Chung, M.-I., et al. (2002). Potent cytotoxic lignans from *Justicia procumbens* and yheir effects on nitric oxide and tumor necrosis factor-α production in mouse macrophages. *J. Nat. Prod.* 65, 379–381. doi: 10.1021/np0101651

De Silva, S. O., Denis, C. S., and Rodrigo, R. (1980). A regiocontrolled synthesis of some arylnaphthalide ligans. *J. Chem. Soc.Chem. Commun.* 21, 995–997. doi: 10.1039/c39800000995

Deng, Y., Chu, J., Ren, Y., Fan, Z., Ji, X., Mundy-Bosse, B., et al. (2014). The natural product phyllanthusmin C enhances IFN-γ production by human NK

cells through upregulation of TLR-mediated NF-κB signaling. *J. Immunol.* 193, 2994–3002. doi: 10.4049/jimmunol.1302600

González, A. G., Pérez, J. P., and Trujillo, J. M. (1978). Synthesis of two arylnaphthalene lignans. Part 18 in the series Constituents of the Umbelliferae. *Tetrahedron* 34, 1011–1013. doi: 10.1016/0040-4020(78)88156-3

Gu, M.-Y., Kim, J., and Yang, H. O. (2016). The neuroprotective effects of justicidin A on amyloid beta25–35-induced neuronal cell death through inhibition of Tau hyperphosphorylation and induction of autophagy in SH-SY5Y cells. *Neurochem. Res.* 41, 1458–1467. doi: 10.1007/s11064-016-1857-5

Gudla, V., and Balamurugan, R. (2011). Synthesis of arylnaphthalene lignan scaffold by gold-catalyzed intramolecular sequential electrophilic addition and benzannulation. *J. Org. Chem.* 76, 9919–9933. doi: 10.1021/jo201918d

Gudla, V., and Balamurugan, R. (2013). Synthesis of 1-arylnaphthalenes by gold-catalyzed one-pot sequential epoxide to carbonyl rearrangement and cyclization with arylalkynes. *Chem. Asian J.* 8, 414–428. doi: 10.1002/asia.201200817

Hashmi, A. S. K. (2007). Gold-catalyzed organic reactions. *Chem. Rev.* 107, 3180–3211. doi: 10.1021/cr000436x

Hayat, F., Kang, L., Lee, C. Y., and Shin, D. (2015). Synthesis of arylnaphthalene lignan lactone using benzoin condensation, intramolecular thermal cyclization and Suzuki coupling. *Tetrahedron* 71, 2945–2950. doi: 10.1016/j.tet.2015.03.023

He, X.-L., Zhang, P., Dong, X.-Z., Yang, M.-H., Chen, S.-L., and Bi, M.-G. (2012). JR6, a new compound isolated from *Justicia procumbens*, induces apoptosis in human bladder cancer EJ cells through caspase-dependent pathway. *J. Ethnopharmacol.*144, 284–292. doi: 10.1016/j.jep.2012.09.010

He, Y., Zhang, X., and Fan, X. (2014). Synthesis of naphthalene amino esters and arylnaphthalene lactone lignans through tandem reactions of 2-alkynylbenzonitriles. *Chem. Commun.* 50, 5641–5643. doi: 10.1039/C4CC01738B

Holmes, T. L., and Stevenson, R. (1970). Synthesis of helioxanthin. *Tetrahedron Lett.* 11, 199–202. doi: 10.1016/0040-4039(70)80025-9

Holmes, T. L., and Stevenson, R. (1971). Arylnaphthalene lignans: synthesis of helioxanthin. *J. Chem. Soc. C Org.* 11, 2091–2094. doi: 10.1039/j39710002091

Kamal, A., Daneshtalab, M., and Micetich, R. G. (1994). A rapid entry into podophyllotoxin congeners: Synthesis of justicidin B. *Tetrahedron Lett.* 35, 3879–3882. doi: 10.1016/S0040-4039(00)76691-3

Kao, T. T., Lin, C. C., and Shia, K. S. (2015). The total synthesis of retrojusticidin B, justicidin E, and helioxanthin. *J. Org. Chem.* 80, 6708–6714. doi: 10.1021/acs.joc.5b00866

Kar, A., and Argade, N. P. (2002). A facile synthesis of natural products chaetomellic acid A and 1,7(Z)- nonadecadiene-2,3-dicarboxylic acid. *J. Org. Chem.* 67, 7131–7134. doi: 10.1021/jo020195o

Kato, T., Ichinose, I., Kamoshida, A., and Kitahara, Y. (1976). Cyclization of polyenes. Biogenetic-type synthesis of snyderols. *J. Chem. Soc. Chem. Commun.* 13, 518–519. doi: 10.1039/c39760000518

Kato, T., Mochizuki, M., Hirano, T., Fujiwara, S., and Uyehara, T. (1984). Selective brominative cyclization of polyenes assisted by acetonitrile. Application to the synthesis of acoratriene. *J. Chem. Soc. Chem. Commun.* 16, 1077–1078. doi: 10.1039/c39840001077

Khalid, S. A., and Waterman, P. G. (1981). Alkaloid, lignan and flavonoid constituents of *Haplophyllum tuberculatum* from Sudan. *Planta Med.* 43, 148–152. doi: 10.1055/s-2007-971491

Li, Z., Brouwer, C., and He, C. (2008). Gold-catalyzed organic transformations. *Chem. Rev.* 108, 3239–3265. doi: 10.1021/cr068434l

Lin, M.-T., Lee, S.-S., and Liu, K. C. S. C. (1995). Phyllamyricins A-C, three novel lignans from *Phyllanthus myrtifolius*. *J. Nat. Prod.* 58, 244–249. doi: 10.1021/np50116a013

Luo, J., Hu, Y., Kong, W., and Yang, M. (2014). Evaluation and structure-activity relationship analysis of a new series of arylnaphthalene lignans as potential anti-tumor agents. *PLoS ONE* 9:e93516. doi: 10.1371/journal.pone.0093516

Maclean, I., and Stevenson, R. (1966). Synthesis of (±)-otobain. *J. Chem. Soc. C Org.* 1717–1719. doi: 10.1039/J39660001717

Michael, A., and Bucher, J. E. (1895). Ueber die Einwirkung von Essigsäureanhydrid auf Säuren der Acetylenreihe. *Ber. Deutsch. Chem. Ges.* 28, 2511–2512. doi: 10.1002/cber.18950280337

Mizufune, H., Nakamura, M., and Mitsudera, H. (2001). The first regiospecific synthesis of helioxanthin by novel palladium-catalyzed benzannulation reaction of alpha,beta-bisbenzylidene-gamma-lactone. *Tetrahedron Lett.* 42, 437–439. doi: 10.1016/S0040-4039(00)01982-1

Mondal, S., Maji, M., and Basak, A. (2011). A Garratt–Braverman route to aryl naphthalene lignans. *Tetrahedron Lett.* 52, 1183–1186. doi: 10.1016/j.tetlet.2011.01.011

Mondal, S., Mitra, T., Mukherjee, R., Addy, P. S., and Basak, A. (2012). Garratt–Braverman cyclization, a powerful tool for C–C bond formation. *Synlett* 23, 2582–2602. doi: 10.1055/s-0032-1317321

Mori, S., Takechi, S., Shimizu, S., Kida, S., Iwakura, H., and Hajima, M. (1999). Convergent synthesis of S-8921, a new potent hypocholesterolemic arylnaphthalene lignan analog. *Tetrahedron Lett.* 40, 1165–1168. doi: 10.1016/S0040-4039(98)02554-4

Murakami, M., Hoshino, Y., Ito, H., and Ito, Y. (1998). Palladium-catalyzed coupling reactions of *N*-methoxy-*N*-methylcarbamoyl chloride for the synthesis of *N*-methoxy-*N*-methylamides. *Chem. Lett.* 27, 163–164. doi: 10.1246/cl.1998.163

Naresh, G., Kant, R., and Narender, T. (2015). Silver(I)-catalyzed regioselective construction of highly substituted alpha-naphthols and its application toward expeditious synthesis of lignan natural products. *Org. Lett.* 17, 3446–3449. doi: 10.1021/acs.orglett.5b01477

Ogiku, T., Seki, M., Takahashi, M., Ohmizu, H., and Iwasaki, T. (1990). A new 2-step synthesis of 1-arylnaphthalene lignans from cyanohydrins. *Tetrahedron Lett.* 31, 5487–5490. doi: 10.1016/S0040-4039(00)97879-1

Ogiku, T., Yoshida, S., Ohmizu, H., and Iwasaki, T. (1995). Efficient synthesis of 1-arylnaphthalene lactones and related-compounds from cyanohydrins. *J. Org. Chem.* 60, 4585–4590. doi: 10.1021/jo00119a041

Paris, M., Pothion, C., Heitz, A., Martinez, J., and Fehrentz, J.-A. (1998). Synthesis of *N*- and side chain protected aspartyl and glutamyl aldehyde derivatives. Reinvestigation of the reduction of Weinreb amides. *Tetrahedron Lett.* 39, 1341–1344. doi: 10.1016/S0040-4039(97)10813-9

Park, J. E., Lee, J., Seo, S. Y., and Shin, D. (2014). Regioselective route for arylnaphthalene lactones: convenient synthesis of taiwanin C, justicidin E, and daurinol. *Tetrahedron Lett.* 55, 818–820. doi: 10.1016/j.tetlet.2013.12.014

Patel, R. M., and Argade, N. P. (2007). Facile SN2′coupling reactions of Wittig reagents with dimethyl bromomethylfumarate: synthesis of enes, dienes, and related natural products. *J. Org. Chem.* 72, 4900–4904. doi: 10.1021/jo070728z

Patel, R. M., and Argade, N. P. (2013). Palladium-promoted 2+2+2 cocyclization of arynes and unsymmetrical conjugated dienes: synthesis of justicidin B and retrojusticidin B. *Org. Lett.* 15, 14–17. doi: 10.1021/ol3028658

Peña, D., Escudero, S., Pérez, D., Guitián, E., and Castedo, L. (1998). Efficient palladium-catalyzed cyclotrimerization of arynes: synthesis of triphenylenes. *Angew. Chem. Int. Ed.* 37, 2659–2661. doi: 10.1002/(SICI)1521-3773(19981016)37:19<2659::AID-ANIE2659>3.0.CO;2-4

Plaumann, H. P., Smith, J. G., and Rodrigo, R. (1980). Potential isobenzofurans: their use in the synthesis of naturally occurring 1-arylnaphthalide lignans. *J. Chem. Soc. Chem. Commun.* 8, 354–355. doi: 10.1039/c39800000354

Ren, Y., Carcache de Blanco, E. J., Fuchs, J. R., Soejarto, D. D., Burdette, J. E., Swanson, S. M., et al. (2019). Potential anticancer agents characterized from selected tropical plants. *J. Nat. Prod.* 82, 657–679. doi: 10.1021/acs.jnatprod.9b00018

Ren, Y., Lantvit, D. D., Deng, Y., Kanagasabai, R., Gallucci, J. C., Ninh, T. N., et al. (2014). Potent cytotoxic arylnaphthalene lignan lactones from *Phyllanthus poilanei*. *J. Nat. Prod.* 77, 1494–1504. doi: 10.1021/np5002785

Sato, Y., Ohashi, K., and Mori, M. (1999). Synthesis of biaryls using nickel-catalyzed [2+2+2] cocyclization. *Tetrahedron Lett.* 40, 5231–5234. doi: 10.1016/S0040-4039(99)00945-4

Sato, Y., Tamura, T., Kinbara, A., and Mori, M. (2007). Synthesis of biaryls via palladium-catalyzed 2+2+2 cocyclization of arynes and diynes: application to the synthesis of arylnaphthalene lignans. *Adv. Synth. Catal.* 349, 647–661. doi: 10.1002/adsc.200600587

Sato, Y., Tamura, T., and Mori, M. (2004). Arylnaphthalene lignans through Pd-catalyzed 2+2+2 cocyclization of arynes and diynes: total synthesis of taiwanins C and E. *Angew. Chem. Int. Ed.* 43, 2436–2440. doi: 10.1002/anie.200453809

Stevenson, R., and Block, E. (1971). Lignan lactones. Synthesis of (±)-collinusin and justicidin B. *J. Org. Chem.* 36, 3453–3455. doi: 10.1021/jo00821a038

Stevenson, R., and Holmes, T. L. (1971). Arylnaphthalene lignans. Synthesis of justicidin E, taiwanin C, dehydrodimethylconidendrin, and dehydrodimethylretrodendrin. *J. Org. Chem.* 36, 3450–3453. doi: 10.1021/jo00821a037

Stevenson, R., and Weber, J. V. (1989). Improved methods of synthesis of lignan arylnaphthalene lactones via arylpropargyl arylpropiolate esters. *J. Nat. Prod.* 52, 367–375. doi: 10.1021/np50062a024

Stevenson, R., and Weber, J. V. (1991). Synthesis of lignan aryldihydronaphthalene lactones by cyclization of cinnamyl arylpropiolate esters-revised structure of beta apopolycamatin. *J. Nat. Prod.* 54, 310–314. doi: 10.1021/np50073a042

Teponno, R. B., Kusari, S., and Spiteller, M. (2016). Recent advances in research on lignans and neolignans. *Nat. Prod. Rep.* 33, 1044–1092. doi: 10.1039/C6NP00021E

Tsay, S.-C., Robl, J. A., and Hwu, J. R. (1990). New method for the selective reduction of amides. *J. Chem. Soc. Perkin Trans.* 1, 757–759. doi: 10.1039/p19900000757

Tsuji, J., and Ohno, K. (1965). Organic syntheses by means of noble metal compounds XXI. Decarbonylation of aldehydes using rhodium complex. *Tetrahedron Lett.* 6, 3969–3971. doi: 10.1016/S0040-4039(01)89127-9

Ulubelen, A. (1985). Alkaloids from *Haplophyllum buxbaumii*. *Phytochemistry* 24, 372–374. doi: 10.1016/S0031-9422(00)83563-3

Weng, J.-R., Ko, H.-H., Yeh, T.-L., Lin, H.-C., and Lin, C.-N. (2004). Two new arylnaphthalide lignans and antiplatelet constituents from *Justicia procumbens*. *Arch. Pharm.* 337, 207–212. doi: 10.1002/ardp.200300841

Windayani, N. R., Rukayadi, Y., Hakim, E. H., Ruslan, K., Syah, Y. M. (2014). Antifungal activity of lignans isolated from *Phyllanthus myrtifolius* Moon against. *Fusarium oxysporum*. *Phytochemistry* 12, 33–39.

Won, S.-J., Yen, C.-H., Liu, H.-S., Wu, S.-Y., Lan, S.-H., Jiang-Shieh, Y.-F., et al. (2015). Justicidin A-induced autophagy flux enhances apoptosis of human colorectal cancer cells via class III PI3K and Atg5 pathway. *J. Cell Physiol.* 230, 930–946. doi: 10.1002/jcp.24825

Wong, Y.-C., Kao, T.-T., Huang, J.-K., Jhang, Y.-W., Chou, M.-C., and Shia, K.-S. (2014). Manganese(III)-catalyzed oxidative cyclization of aryl 1-cyanoalk-5-ynyl ketone systems: a convenient and general approach to cyclopenta[b]naphthalene derivatives. *Adv. Synth. Catal.* 356, 3025–3038. doi: 10.1002/adsc.201400257

Woo, J. K., Jung, H. J., Park, J. Y., Kang, J. H., Lee, B. I., Shin, D., et al. (2017). Daurinol blocks breast and lung cancer metastasis and development by inhibition of focal adhesion kinase (FAK). *Oncotarget* 8, 57058–57071. doi: 10.18632/oncotarget.18983

Woodard, J. L., Huntsman, A. C., Patel, P. A., Chai, H.-B., Kanagasabai, R., Karmahapatra, S., et al. (2018) Synthesis and antiproliferative activity of derivatives of the phyllanthusmin class of arylnaphthalene lignan lactones. *Bioorg. Med. Chem.* 26, 2354–2364. doi: 10.1016/j.bmc.2018.03.033

Xiao, J., Cong, X.-W., Yang, G.-Z., Wang, Y.-W., and Peng, Y. (2018a). Divergent asymmetric syntheses of podophyllotoxin and related family members via stereoselective reductive Ni-catalysis. *Org. Lett.* 20, 1651–1654. doi: 10.1021/acs.orglett.8b00408

Xiao, J., Cong, X.-W., Yang, G.-Z., Wang, Y.-W., and Peng, Y. (2018b). Stereoselective synthesis of a podophyllum lignan core by intramolecular reductive nickel-catalysis. *Chem. Commun.* 54, 2040–2043. doi: 10.1039/C8CC00001H

Xiao, J., Nan, G. M., Wang, Y. W., and Peng, Y. (2018c). Concise synthesis of (+)-β- and γ-apopicropodophyllins, and dehydrodesoxypodophyllotoxin. *Molecules* 23, 3037. doi: 10.3390/molecules231 13037

Yamamoto, Y., Mori, S., and Shibuya, M. (2015). A combined transition-metal-catalyzed and photopromoted process: synthesis of 2,3-fused 4-phenylnaphthalen-1-yl carboxylates from 1,7-diaryl-1,6-diynes. *Chem. Eur. J.* 21, 9093–9100. doi: 10.1002/chem.201500978

Yamazaki, S. (1999). Chromium(VI) oxide-catalyzed benzylic oxidation with periodic acid. *Org. Lett.* 1, 2129–2132. doi: 10.1021/ol9 91175k

Yan, K., Yang, D., Wei, W., Wang, F., Shuai, Y., Li, Q., et al. (2015). Silver-mediated radical cyclization of alkynoates and α-keto acids leading to coumarins via cascade double C–C bond formation. *J. Org. Chem.* 80, 1550–1556. doi: 10.1021/jo502474z

Yi, L., Chen, L., Guo, X., Lu, T., Wang, H., Ji, X., et al. (2018). A synthetic disaccharide derivative of diphyllin, TAARD, activates human natural killer cells to secrete interferon-gamma via toll-like receptor-mediated NF-κB and STAT3 signaling pathways. *Front. Immunol.* 9:1509. doi: 10.3389/fimmu.2018.01509

Young, A. N., Herrera, D., Huntsman, A. C., Korkmaz, M. A., Lantvit, D. D., Mazumder, S., et al. (2018). Phyllanthusmin derivatives induce apoptosis and reduce tumor burden in high-grade serous ovarian cancer by late-stage autophagy inhibition. *Mol. Cancer Ther.* 17, 2123–2135. doi: 10.1158/1535-7163.MCT-17-1195

Yu, Z., Dan, W., Jie, H., and Li, Z. (2010). Synthesis and bioevaluation of novel analogues of justicidin A. *Med. Chem. Res.* 19, 71–76. doi: 10.1007/s00044-009-9172-1

Zhang, H.-J., Rumschlag-Booms, E., Guan, Y.-F., Liu, K.-L., Wang, D.-Y., Li, W.-F., et al. (2017). Anti-HIV diphyllin glycosides from *Justicia gendarussa*. *Phytochem* 136, 94–100. doi: 10.1016/j.phytochem.2017.01.005

Zhao, C., Rakesh, K. P., Mumtaz, S., Moku, B., Asiri, A. M., Marwani, H. M., et al. (2018) Arylnaphthalene lactone analogues: synthesis and development as excellent biological candidates for future drug discovery. *RSC Adv.* 8, 9487–9502. doi: 10.1039/C7RA13754K