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PALLADIUM-MEDIATED INTRAMOLECULAR BIARYL COUPLING REACTION FOR NATURAL PRODUCT SYNTHESIS

Hitoshi Abe[a]* and Takashi Harayama[b]*

a) Advanced Science Research Center, Okayama University, Okayama 700-8530, Japan, b) Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, Sanuki-shi, Kagawa 769-2193, Japan

abe@pharm.okayama-u.ac.jp; harayama@kph.bunri-u.ac.jp

Abstract – An intramoleculer biaryl coupling reaction is a useful technique for the synthesis of certain types of heterocyclic compounds. This short review describes recent advances in the Pd-mediated intramolecular C-C bond formation reaction between two aromatic rings, and several examples of natural product synthesis using this reaction. The mechanistic aspect of this reaction is also explained.

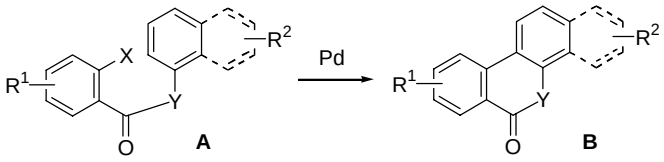
INTRODUCTION

Biaryl compounds are important building blocks for naturally occurring materials, and the methods for forming a carbon-carbon bond between two aromatic rings have been developed over the past 100 years.[1] As a classical method, the Ullmann coupling has been a standard transformation to prepare biaryl molecules although this method often requires vigorous reaction conditions. Additionally, in the Ullmann coupling, there are some difficulties regarding the synthesis of unsymmetrical biaryl molecules. As a more convenient procedure, the Suzuki-Miyaura coupling reaction[2] has been widely utilized for the biaryl synthesis, as well as the Stille coupling reaction.[3] For these transformations, functionalization on both of the aromatic rings are necessary, *i.e.*, halogenation on one aromatic ring, and the introduction of a boron or tin atom on the other one. However, two aromatic rings, if they are linked by an ester or amide group to each other, can be coupled using a Pd reagent without the introduction of the functional group on one aromatic ring.

Based on such a concept, the intramolecular Pd-mediated biaryl coupling reactions have been used to synthesize many polycyclic aromatic compounds.[4] A recent report showed that the intramolecular biaryl

coupling reaction of 2-halo-*N*-arylbenzamides (**A**; Scheme 1) to (benzo[*c*])phenanthridones (**B**) using palladium reagents was a convenient and versatile method of synthesizing condensed aromatic lactams, some of which could be transformed into polycyclic aromatic alkaloids such as (benzo[*c*])phenanthridines.[5] Moreover, benzonaphthazepine, which is a new skeletal compound, and pyrrolophenanthridine (Amaryllidaceae) alkaloids were successfully synthesized utilizing a Pd-mediated biaryl coupling reaction with regioselective C–H activation *via* the intramolecular coordination of an amine to Pd.[6]

Subsequently, the biaryl coupling reaction using Pd was applied to the synthesis of quinazoline alkaloids [luotonins A (**1**) and B (**2**) and rutaecarpine (**3**)],[7] arnottin I (**8**) (an oxa analog of benzo[*c*]phenanthridine alkaloid),[8] and graphislactones A–C (**19**-**21**) and D (**22**),[9] which possess 6*H*-dibenzo[*b*,*d*]pyran-6-one and 5*H*-dibenzo[*c*,*e*]oxepin-7-one skeletons, respectively. In this review, we present the results of applying this methodology.

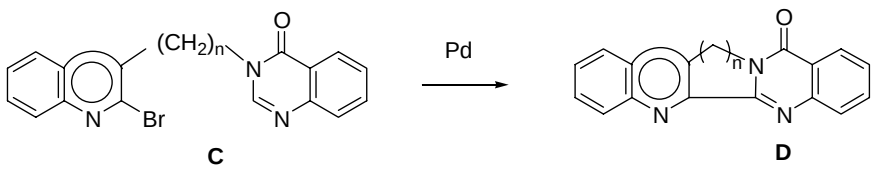


X = Br, I or OTf, Y = NMe or N-MOM

Scheme 1 Intramolecular biaryl coupling for the synthesis of phenanthridone

SYNTHESIS OF QUINAZOLINE ALKALOIDS

Recently, aryl–aryl coupling reactions using Pd reagents have been reported to be a very versatile way to synthesize polycyclic heteroaromatic compounds.[5,6] In order to examine the utility of this methodology, we subsequently designed a concise plan for synthesizing luotonins A (**1**) and B (**2**) and rutaecarpine (**3**), as shown in Scheme 2; this plan involves the aryl–aryl coupling reaction of 2-bromoaromatic heterocycles–quinazolinone (**C**) to an alkaloid (**D**) using a Pd reagent as the key reaction.



Scheme 2 Synthesis of quinazoline

Luotonins A (**1**) and B (**2**), which were isolated from *Peganum nigellastrum* Bunge,[10] are novel quinolinoquinazoline alkaloids that are cytotoxic against mouse leukemia P-388 cells *in vitro* and inhibit DNA topoisomerases I and II.[10-12] *Peganum nigellastrum* is a Chinese traditional medicine used to treat

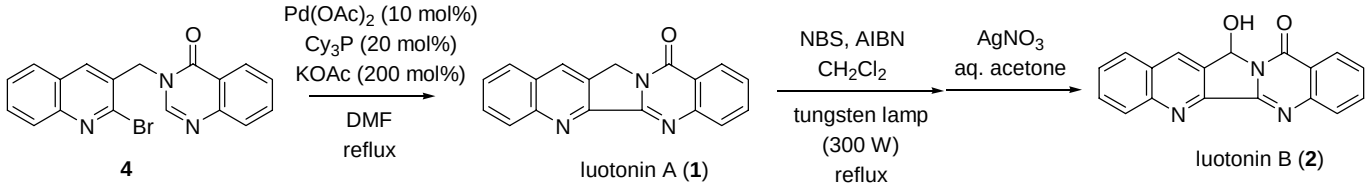
rheumatism, abscesses, and inflammation.[13]

Rutaecarpine (**3**), which is obtained from rutaceous plants such as *Evodia rutaecarpa*,[14] is an indolopyridoquinazoline alkaloid that has long been used to treat inflammation-related disorders in traditional oriental medicine.[15] In addition to its anti-inflammatory activity,[16] reports have indicated cytotoxic,[17] antiplatelet aggregation,[18] vasorelaxation,[19] and anti-anoxic activities by **3**.[20]

Due to their pharmaceutical activities, attention is still focused on the development of new synthetic methods for these alkaloids.[21,22]

Synthesis of luotonins A (**1**) and B (**2**)

The key intermediate (**4**) for the synthesis of **1** was prepared from 4(3*H*)-quinazolinone and 2-bromo-3-(bromomethyl)quinoline. The biaryl coupling reaction of **4** was examined using the Pd reagent. The conditions using our novel method ($Pd(OAc)_2$ (10 mol%), n-Bu_3P (100 mol%), DPPP (100 mol%)),[5d] and using silver carbonate as the base were not fruitful. However, using tricyclohexylphosphine (Cy_3P) as the ligand and potassium acetate (KOAc) as the base, the coupling reaction smoothly proceeded to give luotonin A (**1**) (Scheme 3). Subsequently, **1** was converted to luotonin B (**2**) by the bromination of **1** with *N*-bromosuccinimide (NBS) in the presence of 2,2'-azobisisobutyronitrile (AIBN) under irradiation from a tungsten lamp, followed by solvolysis with silver nitrate in aqueous acetone.

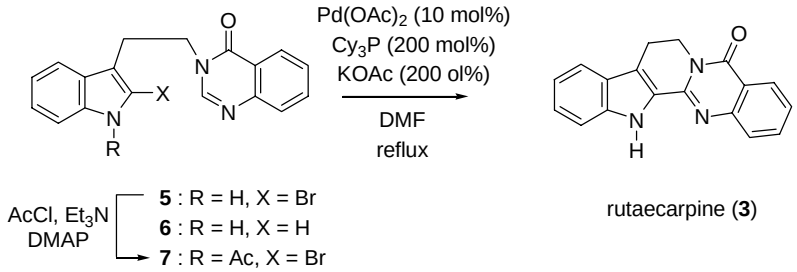


Scheme 3 Synthesis of luotonins A (**1**) and B (**2**)

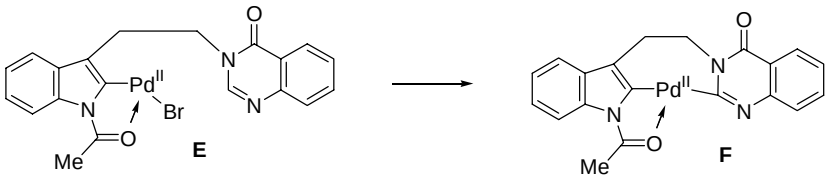
Synthesis of rutaecarpine (**3**)

3-[2-(2-Bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (**5**), the key intermediate in the synthesis of **3**, was synthesized by the bromination of 3-(2-bromoethyl)indole with NBS, followed by the reaction with 4(3*H*)-quinazolinone in the presence of K_2CO_3. First, the Pd-mediated coupling reaction of **5** was investigated (Scheme 4). Using equimolar $Pd(OAc)_2$ in the presence of Cy_3P and KOAc, the coupling reaction gave **3** in poor yield accompanied by the debromo compound (**6**). We then envisioned that the formation of the intermediate (**E**) *via* the oxidative addition of the *N*-acetyl compound (**7**) to Pd (0) and coordination of the carbonyl group to Pd (II) would help the biaryl coupling reaction or the bulkiness of the *N*-acetyl group might facilitate access to the reaction site (Scheme 5). Based on this concept, the

coupling reaction of **7**, which was prepared by the acetylation of **5**, was examined. The coupling reaction using Cy_3P and K_2CO_3 or using $PdCl_2(PPh_3)_2$ directly gave **3** in moderate yield. The reaction using Cy_3P and KOAc smoothly proceeded to yield **3** in high yields, indicating that the coupling reaction occurred first and then hydrolysis took place, or that the *N*-acetyl group of the palladacycle intermediate (**F**) might be susceptible to hydrolysis by coordination of the carbonyl group to Pd(II), followed by the coupling reaction. The use of KOAc as a base generally gave **3** in good to excellent yields, while the reaction using Ag_2CO_3 as the base caused the decomposition of **5** and **7**.



Scheme 4 Synthesis of rutaecarpine (**3**)



Scheme 5 Plausible paladacycle intermediate

SYNTHESIS OF BENZOPYRANONES

Aryl benzoates are also good precursors for the intramolecular biaryl coupling reaction to form lactone-type cyclic compounds, such as 6*H*-benzo[*d*]naphtha-[1,2-*b*]pyran-6-one, 6*H*-dibenzo[*b*,*d*]pyran-6-one, etc.

Synthesis of arnottin I (**8**)

Arnottin I (**8**) isolated from *Zanthoxylum arnottianum* Maxim.[23] involves the 6*H*-benzo[*d*]naphtha-[1,2-*b*]pyran-6-one skeleton, which is the same as in gilvocarcins (Figure 1).[24] Since these compounds have biologically important properties, such as antitumor, antibacterial, or antivirus activity,[25] interest has focused on the concise construction of the 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton.[26]

Ames and Opalko have already reported that for the biaryl coupling reaction of phenyl 2-bromobenzoate (**9**) and 2-bromophenyl benzoate (**10**), **9** produced 6*H*-dibenzo[*b*,*d*]pyran-6-one (**11**) using $Pd(OAc)_2$,

PPh_3, and NaOAc in a 41% yield, whereas **10** afforded no cyclized product **11** under the same reaction conditions.[27] In order to improve this unique biaryl coupling reaction, we investigated the reactivities of the corresponding iodo analogs **12** and **13**, which are thought to be more highly reactive than the bromo compounds.

It was found that the combination of a phosphine ligand and base was crucial for the coupling reaction of **12**. When PPh_3 was used as the ligand, NaOAc gave a better result than silver carbonate. A bidentate phosphine ligand, 1,3-bis(diphenylphosphino)propane (DPPP) gave **11** in good yield when it was used with NaOAc as the base. Interestingly, the best result was observed when no phosphine ligand was used. Other catalysts, such as bis(triphenylphosphine)palladium(II) chloride [$PdCl_2(PPh_3)_2$], palladium(II) acetylacetonate [$Pd(acac)_2$], and tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], afforded **11** in moderate yields. Conversely, the reaction of **13** under the reaction conditions that produced a good result for the reaction of **12** was extremely poor. In this case, the hydrolysis of the ester bond was predominant.

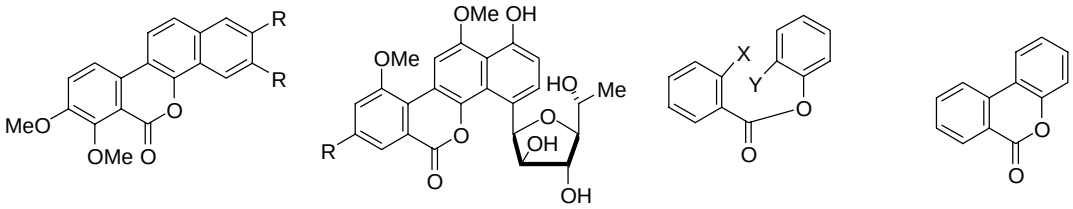
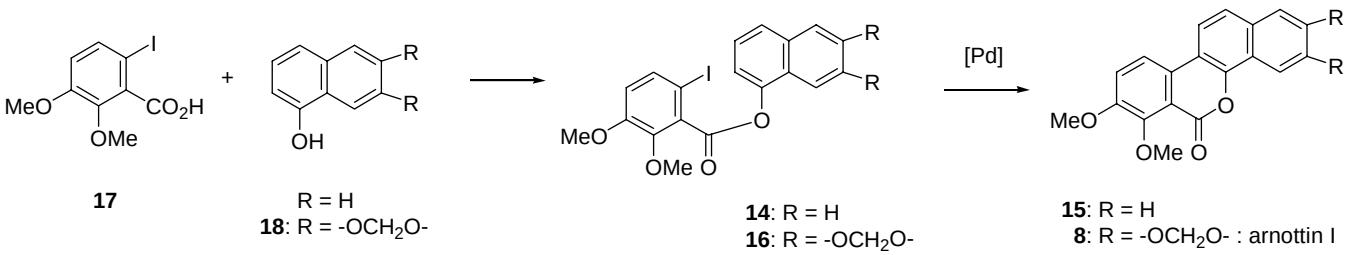


Figure 1

As a preliminary experiment for the synthesis of arnottin I, the coupling reaction of the naphthyl ester (**14**), which was prepared from 2,3-dimethoxy-6-iodobenzoic acid (**17**) and 1-naphthol, was examined (Scheme 6). While the use of $Pd(OAc)_2$ gave **15** in moderate yield, slightly higher yields were obtained when $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ was used. In this case, $Pd(acac)_2$ worked the most effectively to give **15** in up to a 79% yield.

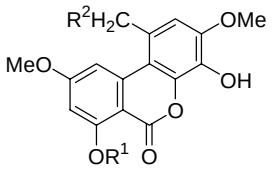


Scheme 6 Synthesis of arnottin I (**8**)

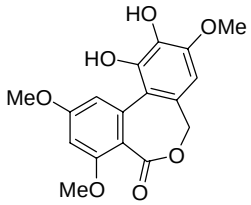
Since the Pd-mediated coupling reaction of **14** was successful, we planned the total synthesis of arnottin I (**8**) using this method. The preparation of the key compound **16** should be realized by condensation between the carboxylic acid (**17**) and naphthol (**18**), which was easily derived from the commercially available 6,7-dimethoxy-*α*-tetralone *via* several steps. The coupling reaction of **16** in the presence of the Pd reagent successfully afforded arnottin I (**8**) in satisfactory yield (Scheme 6).

Synthesis of graphislactones A–D (**19**-**22**)

Lichen substances are known as antibiotics, UV absorbers, antioxidants, and dyes.[28] In 1997, Tanahashi *et al*. isolated four phenolics from the cultured lichen mycobiont of *Graphis scripta* var. *pulverulenta*, which they called graphislactones A–D (Figure 2).[29]



graphislactone A (**19**): R^1 = H, R^2 = H
graphislactone B (**20**): R^1 = Me, R^2 = H
graphislactone C (**21**): R^1 = H, R^2 = OH



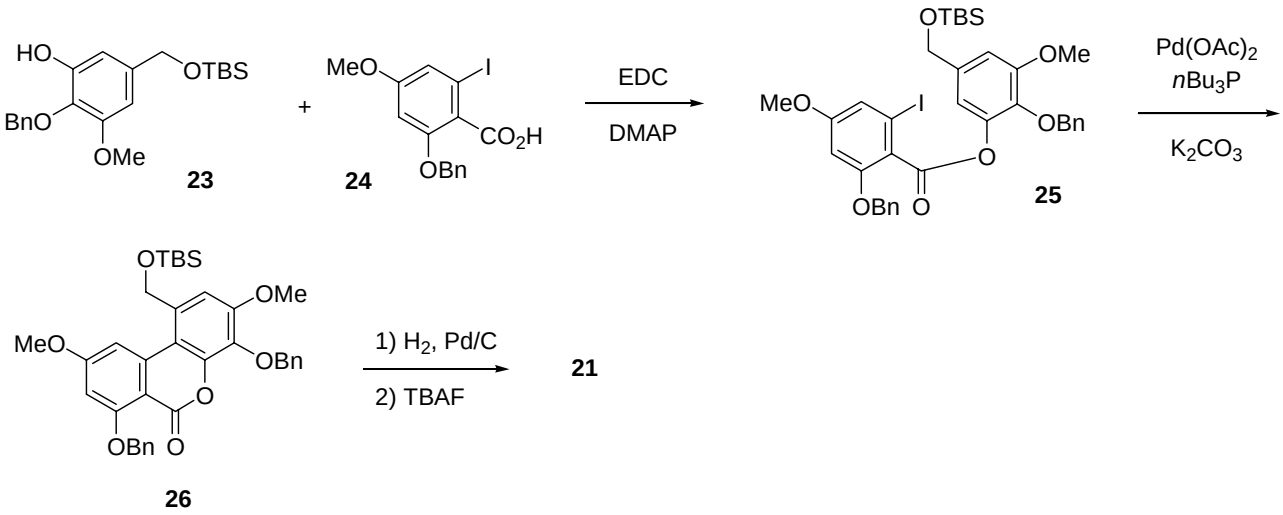
graphislactone D (**22**)

Figure 2

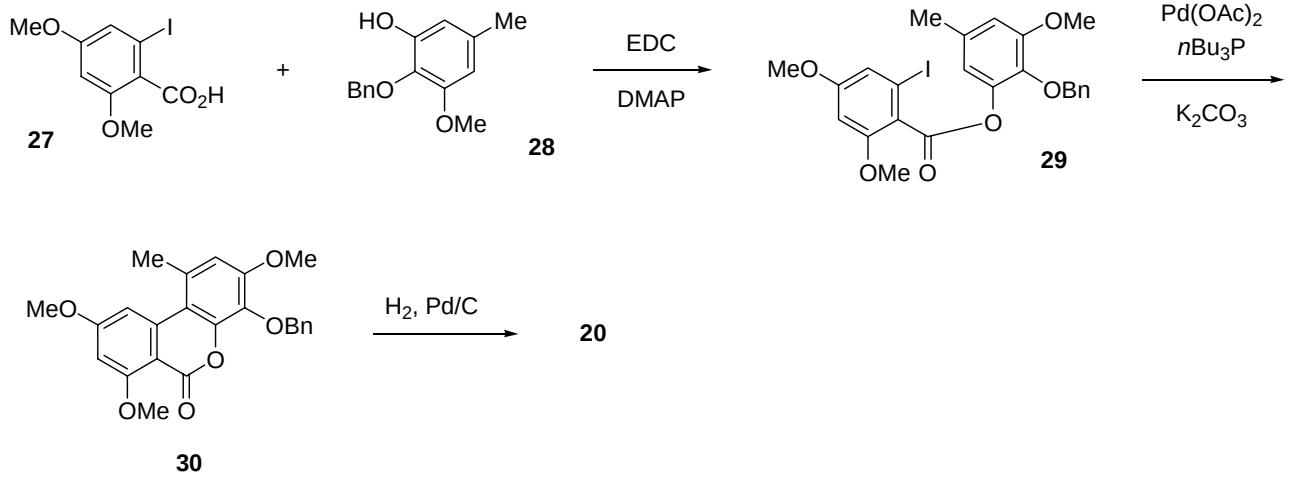
Since graphislactones A–C (**19**–**21**) have highly oxygenated 6*H*-dibenzo[*b*,*d*]pyran-6-one skeletons, we postulated that the appropriate phenyl benzoates prepared by a simple esterification between the corresponding phenols and benzoic acids would be good precursors for the synthesis of these compounds. Phenol (**23**) and acid (**24**), which are the starting materials for the synthesis of graphislactone C (**21**), were prepared from methyl 3,4-dihydroxy-5-methoxybenzoate and 3,5-dimethoxyaniline, respectively. The esterification of **24** with **23** successfully afforded the key intermediate (**25**). The Pd-mediated coupling reaction of **25** using $Pd(OAc)_2$, *n*-Bu_3P, and K_2CO_3 in DMA gave the lactone (**26**) in high yield.[30] Finally, the debenzylation of **26** followed by desilylation with TBAF produced graphislactone C (**21**) (Scheme 7).

To synthesize graphislactone B (**20**), the phenyl benzoate (**29**) was prepared from 2,4-dimethoxy-6-iodobenzoic acid (**27**) and 2-benzyloxy-3-methoxy-5-methylphenol (**28**). The Pd-mediated reaction of **29** under conditions similar to the above case also smoothly proceeded to give the lactone (**30**), which was converted to graphislactone B (**20**) in high yield (Scheme 8).

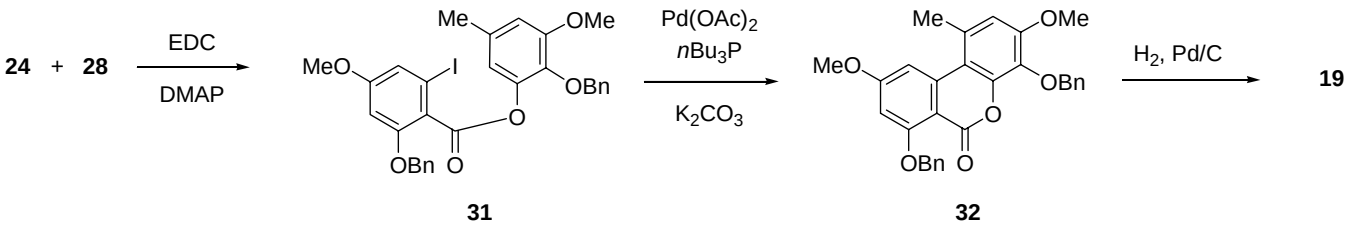
A similar strategy was attempted for the synthesis of graphislactone A (**19**). The preparation of the ester (**31**) by the condensation between **24** and **28**, followed by the Pd-mediated biaryl coupling reaction produced the lactone (**32**). Hydrogenolysis of **32** gave graphislactone A (**19**) in good yield (Scheme 9).



Scheme 7 Synthesis of graphislactone C (**21**)



Scheme 8 Synthesis of graphislactone B (**20**)

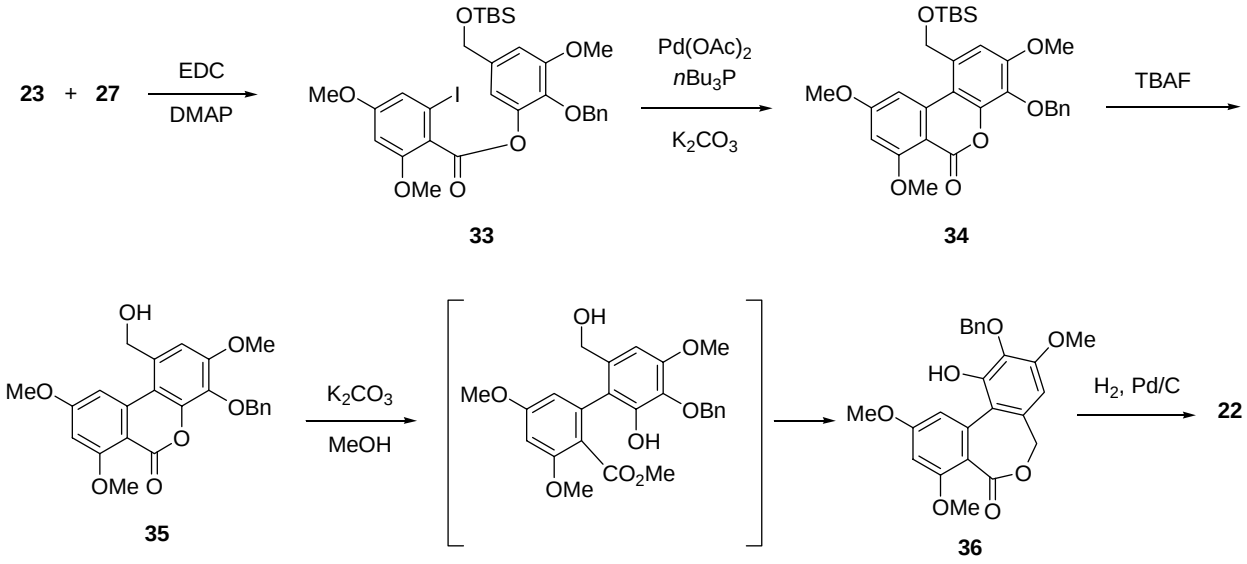


Scheme 9 Synthesis of graphislactone A (**19**)

Unlike graphislactones A–C, graphislactone D (**22**) has a different ring system, *i. e.*, 5*H*-dibenzo[*c*,*e*]oxepin-7-one. We postulated that this skeleton could be synthesized by reconstruction of the lactone ring from the 6*H*-dibenzo[*b*,*d*]pyran-6-one. Therefore, the lactone (**35**) was envisioned as a key intermediate for graphislactone (**22**). The transformation of **33** into **35** was achieved by a route

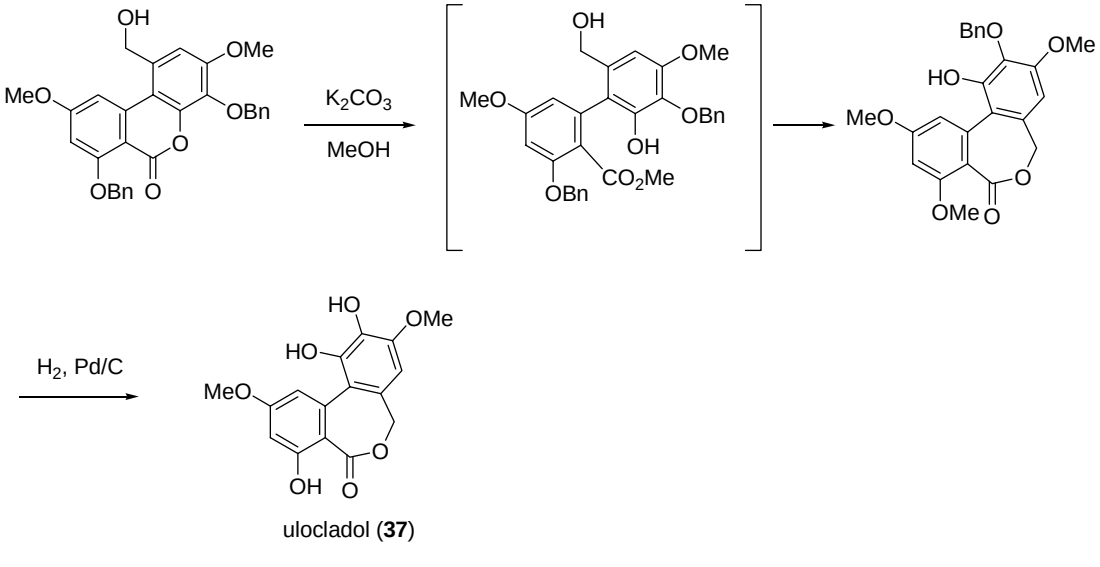
similar to that for graphislactone C. The ester (**33**) derived from **23** and **27** was subjected to the Pd-mediated biaryl coupling reaction, and then desilylated with TBAF. The treatment of the resulting **35** with an excess of K_2CO_3 in MeOH was very effective for the direct formation of the seven-membered ring lactone (**36**). Final deprotection of the benzyl group of **36** yielded graphislactone D (**22**) (Scheme 10).

The facile reconstruction of the lactone ring would be due to the thermodynamic stability of this type of ring system.



Scheme 10 Synthesis of graphislactone D (**22**)

Recently, as a related compound, the synthesis of ulocladol (**37**) was successfully performed using a similar methodology (Scheme 11).[31]



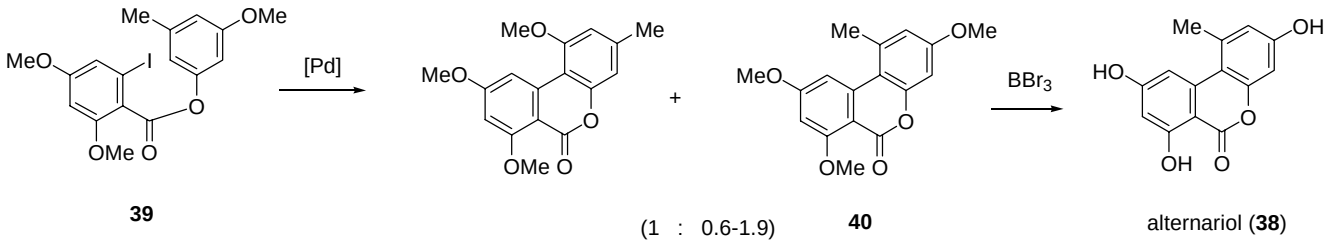
Scheme 11 Synthesis of ulocladol (**37**)

Synthesis of alternariol (**38**)

Alternariol is produced by *Alternaria* fungi, and exhibits a mycotoxicity.[32] Because of such biological activity and some other interests such as its biosynthesis and metabolism, several synthetic methods for **38** have been reported.[33] Recently, our research group attempted the synthesis of this compound using the Pd-mediated coupling reaction of the phenyl benzoate derivative.

Initially, we prepared the ester (**39**) as the precursor for the coupling reaction. In this case, however, there is an issue of regioselectivity in the Pd-mediated reaction. Actually, two regioisomers were produced with a low selectivity (0.6-1.9:1) during the reaction. After isolation of the desired **40**, demethylation was carried out with BBr_3 to afford alternariol (**38**) (Scheme 12).[34]

Further investigation about the regioselectivity should be progressed in the near future.



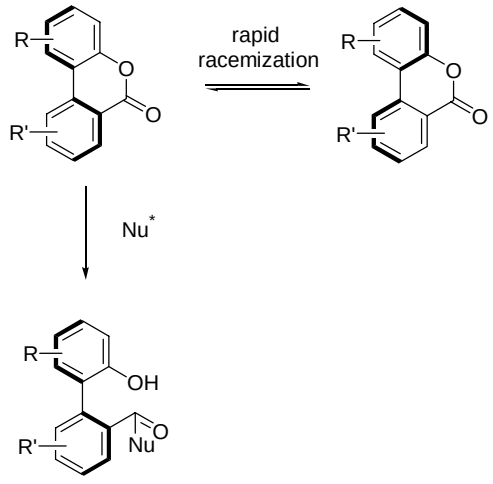
39 (1 : 0.6-1.9) **40** alternariol (**38**)

Scheme 12 Synthesis of alternariol (**38**)

BRINGMANN'S LACTONE CONCEPT

The 6*H*-dibenzo[*b*,*d*]pyran-6-one can be transformed into biphenyl derivatives by the attack of a nucleophile involving lactone ring opening. When using an optically active nucleophile, the produced biphenyl compound often possesses an axial chirality. This unique process is well known as the 'lactone concept,' proposed by Bringmann and co-workers.[35] The appearance of stereoselectivity by the 'lactone concept' can be rationalized by the dynamic kinetic optical resolution.

In solution, rapid racemization between two atropisomers is possible for the lactone compound, and thus the chiral nucleophile can attack toward only one enantiomeric isomer. The enantioselective (or diastereoselective) lactone-ring opening totally takes place (Scheme 13).

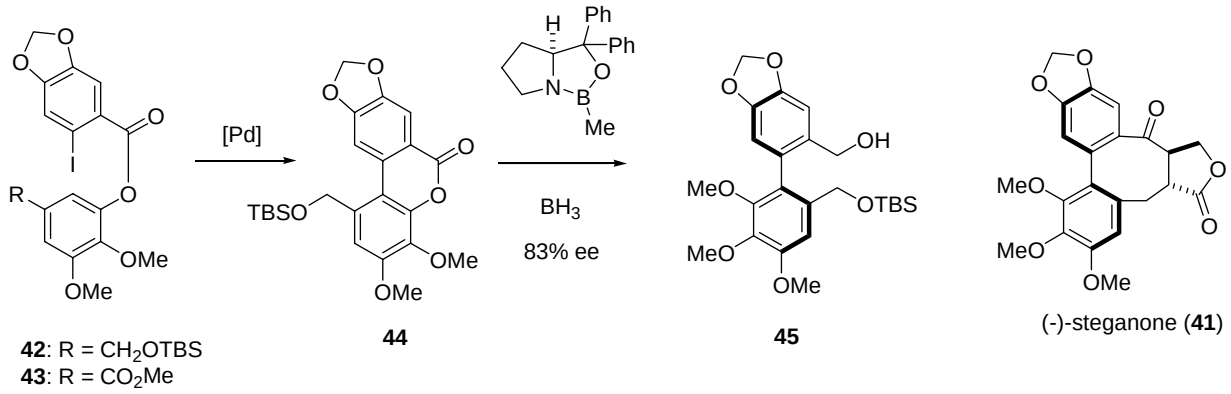


Scheme 13 Asymmetric lactone-ring opening

Based on the above 'lactone concept,' there have been many reports on the asymmetric synthesis of natural products.[35] In this review, we summarize our recent approach for the synthesis of (-)-steganone and the valoneic acid derivative using the 'lactone concept.'

Formal synthesis of (-)-steganone (**41**)

Since steganone (**41**)[36] is a structurally unique substrate, many synthetic studies have been reported.[37] Among them, the 'lactone concept' is one of the most appropriate approaches for the construction of the atropisomeric biaryl part. The phenyl benzoates (**42** and **43**) were easily prepared from the corresponding phenol and benzoic acid. The intramolecular coupling of **42** using Pd reagent was successfully produced the lactone **44**, while the other ester in which R is COOMe did not afford the desired product. Successive asymmetric reduction with oxaborolidine[38]-BH_3 would also be effective for generation of the axially chiral biphenyl (**45**), which was the important intermediate of (-)-steganone (**41**) (Scheme 14).[30,39]



42: R = CH_2OTBS
43: R = CO_2Me

44

45

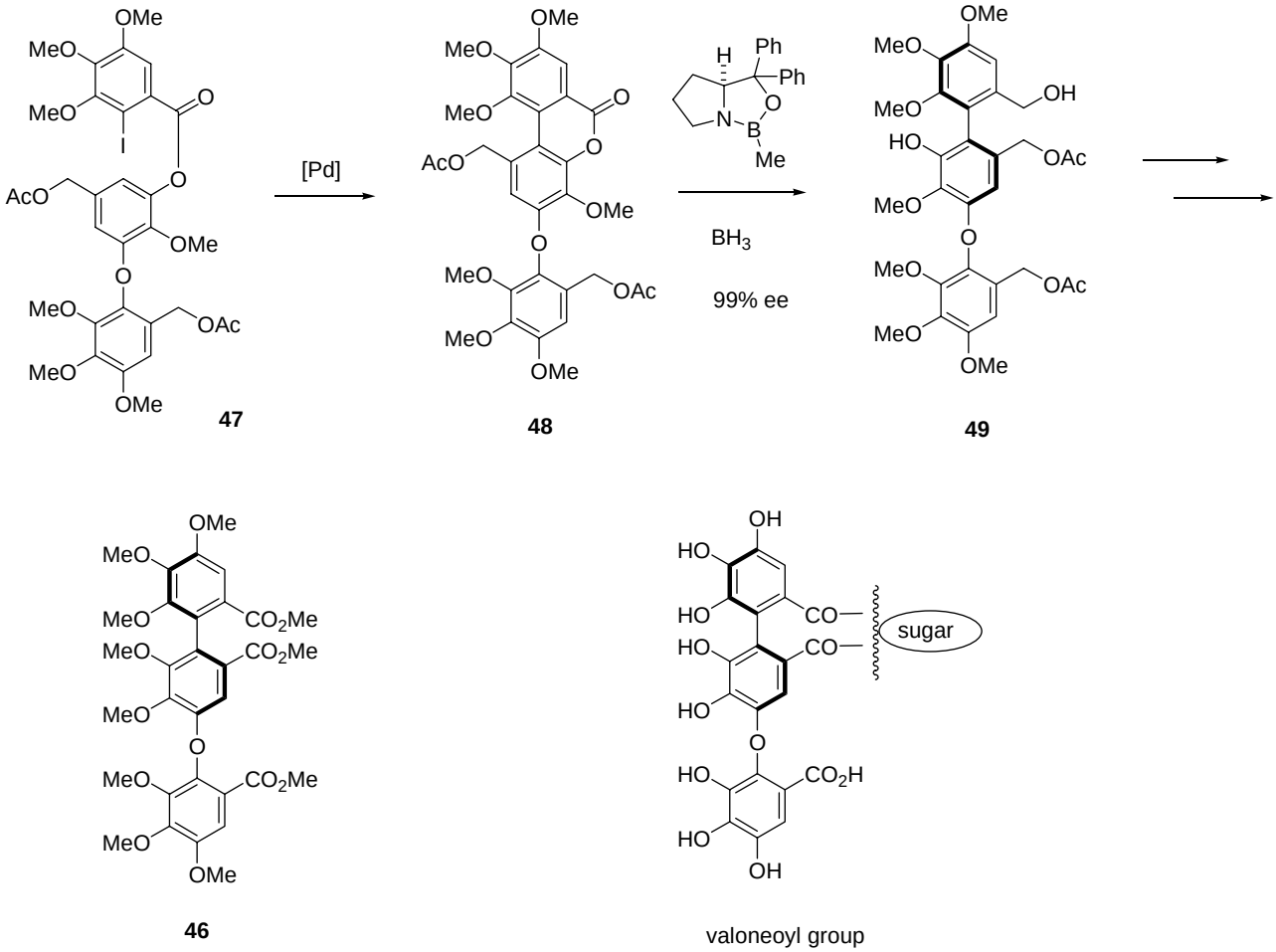
(-)-steganone (**41**)

Scheme 14 Formal synthesis of (-)-steganone (**41**)

Asymmetric synthesis of valoneic acid derivative (**46**)

Ellagitannins are polyphenolic compounds, and a certain class is expected for medicinal use because of its antioxidant property.[40] Oligomeric ellagitannnins often involve a valoneoyl group in their structures, which possess an axial chirality on the biphenyl moiety. Although several total syntheses of ellagitanninns have been demonstrated,[41] there is no report about the synthesis of a valoneoyl group-containing substrate. Recently, we succeeded in the enantioselective synthesis of the valoneic acid derivative (**46**) using the 'lactone concept.'

In this case, the ester (**47**) was a good precursor for the intramolecular biaryl coupling reaction. The coupled product, the lactone (**48**), was successfully transformed into the optically active biphenyl (**49**) in a similar way as the above method. A further transformation was carried out for completion of the synthesis of **46** in an enantioselective manner (Scheme 15).[42]



Scheme 15 Asymmetric synthesis of valoneic acid derivative (**46**)

MECHANISTIC STUDY

The mechanistic aspect of the Pd-mediated intramolecular aryl-aryl coupling reaction has been investigated.[43] At least three different mechanisms have been proposed as shown in Figure 3, in which the key intermediates (**50**-**52**) are depicted.[43a] Among them, the intermediate (**52**) seems more likely than the Heck-type (**50**) and the electrophilic aromatic substitution (S_EAr) (**51**) intermediates.

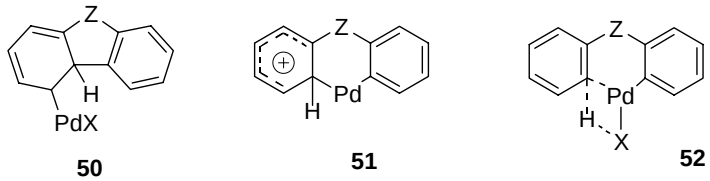


Figure 3

Since the Heck-type reaction should usually proceed *via cis* addition and *syn* elimination steps, the intermediate **50** would be excluded.[43a] In the investigation of the reactivity,[43d] the reaction rate was not

influenced by the electronic character of the substituents, whereas in the classical S_EAr mechanism, electron donating groups should increase the rate of the reaction. This indicates that the Pd-mediated biaryl coupling reaction would not take place *via* the classical S_EAr process. Consequently, the σ-bond metathesis pathway *via* (**52**) is plausible at this stage.

CONCLUSIONS

The intramolecular biaryl coupling reaction provides an efficient route to the polycyclic aromatic system, which is a versatile tool for the synthesis of various types of heterocyclic natural products. This methodology is important not only for the synthesis of heterocyclic compounds, but also for the preparation of the axially chiral biaryl molecules. In addition, the mechanistic aspect has been intensively investigated so that the detailed mechanism of this coupling reaction can be revealed.

ACKNOWLEDGEMENTS

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Dr. Hitoshi Abe was born in 1962, and graduated from Kyoto University where he obtained his Ph. D under the supervision of Prof. K. Fuji. He was appointed as Research Assistant at Okayama University in 1992, and was promoted to Associate Professor in 2003. His research interests are in natural product synthesis and heteroatom chemistry.

Dr. Takashi Harayama was born in Hyogo prefecture in 1941, and received his B.S. in 1963 from Osaka University and Ph. D. in 1970 from Kyoto University. He was appointed as Research Assistant at Kyoto University in 1970, and moved to Chiba Universityy as Associate Professor in 1988. He became Professor at Okayama University in 1992 and retired in 2006. He is now Professor at Tokushima Bunri University from 2006. His research interests are in natural product synthesis and heterocyclic chemistry.