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SYNTHESIS OF MULTISUBSTITUTED BENZOFURANS/INDOLES USING MULTICHLORINATED PHENOLS/ANILINES VIA PALLADIUM-CATALYZED SITE-SELECTIVE SONOGASHIRA COUPLING

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Abstract – Multisubstituted benzofurans/indoles are a critical class of compounds in the fields of pharmaceuticals and natural products. A useful method of preparing 2-substituted benzofurans/indoles is the Pd-catalyzed Sonogashira coupling of 2-halophenols/2-haloanilines and terminal alkynes, followed by cyclization. For the syntheses of multisubstituted benzofurans/indoles, the use of multichlorinated phenols/anilines as coupling partners is powerful because the synthetic steps required are reduced and all dichlorophenol and dichloroaniline positional isomers are commercially available and inexpensive. However, their use in benzofuran/indole synthesis is limited because of their low reactivity compared with those of the corresponding iodo or bromo compounds. Furthermore, site-selective Sonogashira coupling at the 2-position of the multihalogenated phenols/anilines is sterically and electronically challenging. To overcome these problems, dihydroxyterphenylphosphine (DHTP) has been developed as a ligand that enables the highly *ortho*-selective Sonogashira coupling of 2-chlorophenols/2-chloroanilines with terminal alkynes. Using the Pd–DHTP catalyst, chlorinated benzofurans/indoles are successfully obtained, which are easily converted to other derivatives by substitution of the chloro group. In this review, we summarize this and related studies to demonstrate the utility of this method.

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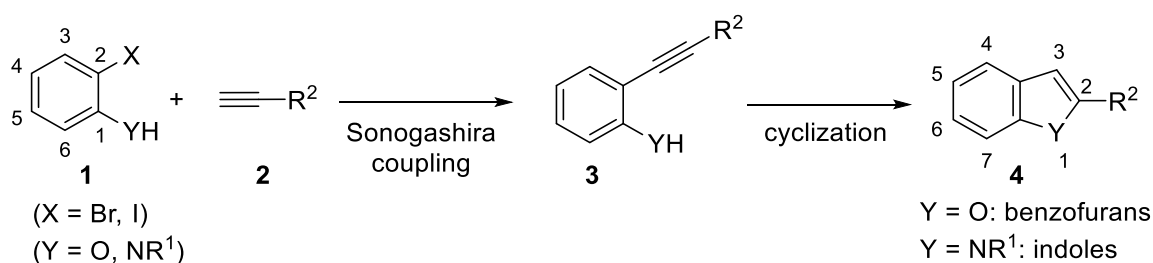
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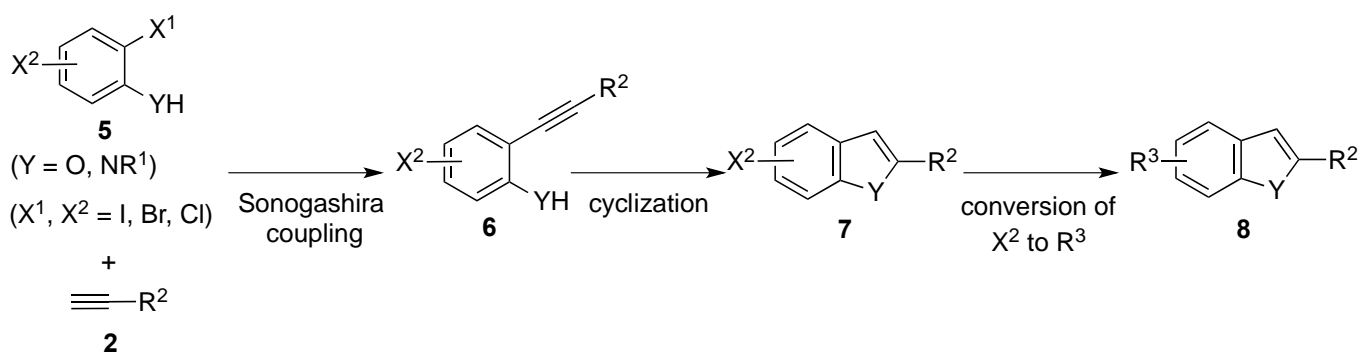
1. INTRODUCTION

Benzofuran and indole are critical frameworks often occurring in biologically active natural and therapeutic products.¹ Therefore, numerous syntheses, including Pd-catalyzed cross-coupling, have been attempted to obtain the desired structures.² A powerful method for the synthesis of 2-substituted benzofurans/indoles (**4**) is the Sonogashira coupling³ of 2-halophenols/2-haloanilines (**1**) with terminal alkynes (**2**), followed by the cyclization of the corresponding alkynylated compound (**3**) (Scheme 1).⁴ This convenient method is often conducted in one-pot, with iodo or bromo compounds commonly employed as substrates. However, reactions with chloro compounds, which are often less expensive and more readily available than the corresponding iodo or bromo compounds, are limited because of their low reactivity. Therefore, more efficient methods, which include novel catalyst systems, are desirable for chloro substrates.



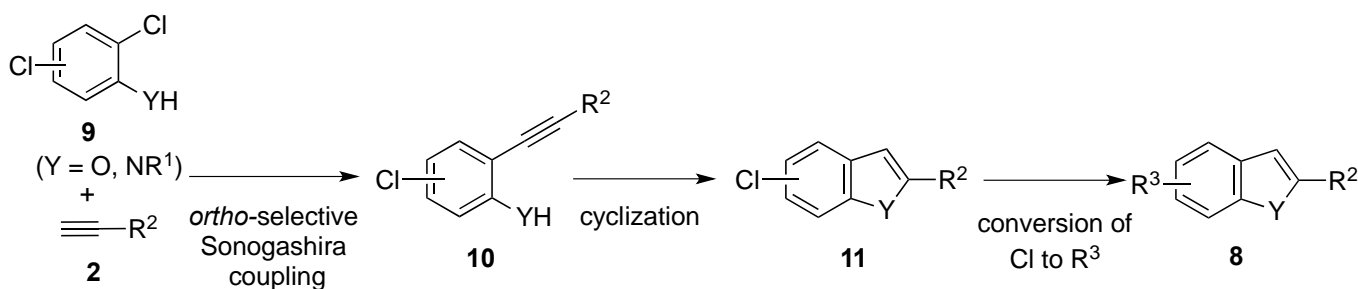
Scheme 1. Conventional synthesis of 2-substituted benzofurans/indoles **4** from 2-halophenols/2-haloanilines **1** via Sonogashira coupling and cyclization

To obtain multisubstituted benzofurans/indoles (**8**), halogenated benzofurans/indoles (**7**) are versatile intermediates that are further converted to the desired compounds using various methods, such as cross coupling.⁵ Sonogashira coupling using dihalophenols/dihaloanilines (**5**) and subsequent cyclization is a straightforward synthesis of the desired compound **7** (Scheme 2).^{5a,6} However, substrates are limited to those bearing different halogens ($X^1 \neq X^2$) for site-selective Sonogashira cross-coupling at the 2-position. In addition, a bromo or an iodo group at the 2-position is required for high reactivity. These substrates often require multistep preparations, and therefore, a synthesis using more easily available substrates, such as dichlorophenols/dichloroanilines ($X^1 = X^2 = \text{Cl}$), is required. Moreover, all dichlorophenol and dichloroaniline positional isomers are commercially available and inexpensive. Various trichlorinated isomers are also available. Thus, a synthesis using these multichlorinated substrates would be a powerful tool for the synthesis of multisubstituted benzofurans/indoles.



Scheme 2. Synthesis of multisubstituted benzofurans/indoles **8** from dihalophenols/dihaloanilines **5**

In this review, we summarize the synthesis of multisubstituted benzofurans/indoles from dichlorophenols/dichloroanilines (**9**) via Pd-catalyzed *ortho*-selective Sonogashira coupling, followed by cyclization (Scheme 3). Examples of trichloroaniline derivatives as substrates are also included.



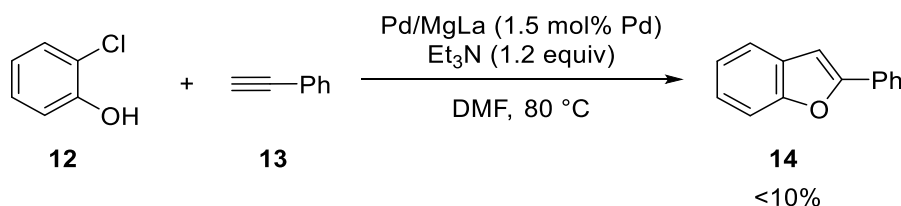
Scheme 3. Synthesis of multisubstituted benzofurans/indoles **8** via *ortho*-selective Sonogashira coupling and cyclization of dichlorophenols/dichloroanilines **9**

2. SYNTHESIS OF DISUBSTITUTED BENZOFURANS FROM DICHLOROPHENOLS

2-1. Synthesis of Monochlorobenzofurans from Dichlorophenols via *ortho*-Selective Sonogashira Coupling/Cyclization

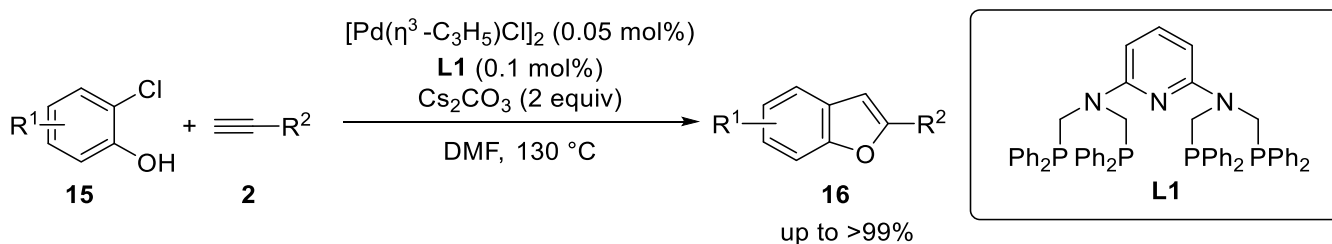
The use of dichlorophenols is a powerful tool for monochlorobenzofuran synthesis. However, Sonogashira coupling of even monochlorophenol is challenging because of its low reactivity compared with 2-iodo- and 2-bromophenol. For 2-chlorophenol, the catalytic systems must induce reaction at the chloro position, which is electronically deactivated and often sterically hindered by the adjacent hydroxy group. However, several catalytic systems have successfully synthesized benzofurans from 2-chlorophenol. Thus, before discussing dichlorophenol reactions, examples of monochlorophenol reactions are presented.

In 2006, Hell *et al.* reported the preparation of 2-phenylbenzofuran (**14**) via Sonogashira coupling of 2-chlorophenol (**12**) with ethynylbenzene (**13**), followed by cyclization using a Pd/MgLa mixed oxide catalyst (Scheme 4).⁷ However, the yield of **14** was less than 10%.



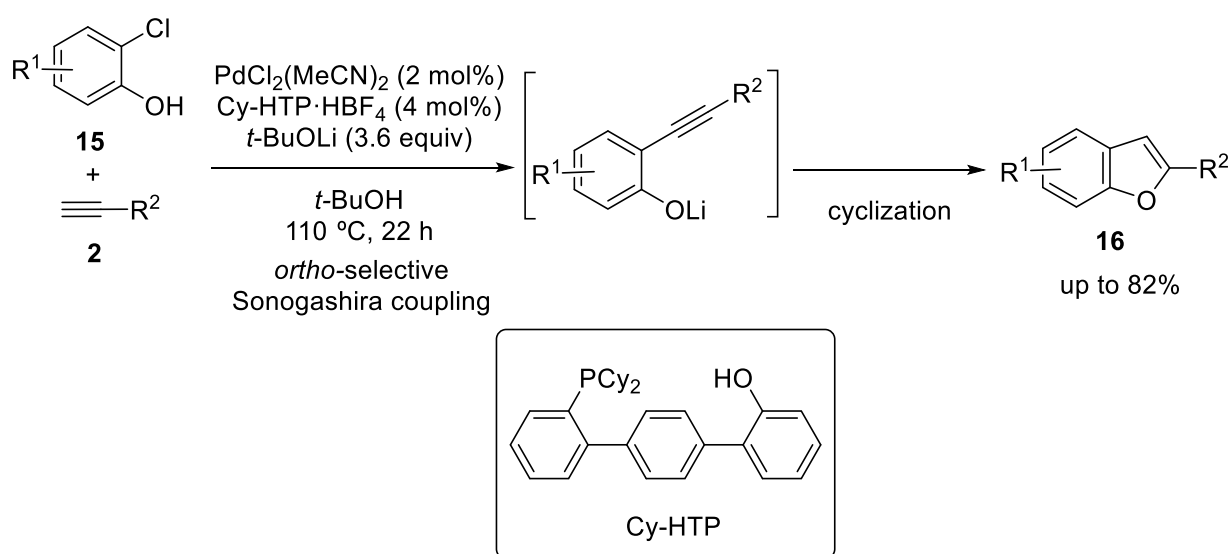
Scheme 4. Synthesis of 2-phenylbenzofuran (**14**) using a Pd/MgLa mixed oxide catalyst

A more efficient synthesis, using a catalyst derived from Pd and the *N,N,N',N'*-tetra(diphenylphosphinomethyl)pyridine-2,6-diamine ligand (**L1**), was reported by Li *et al.* (Scheme 5).⁸ Various 2-substituted benzofurans (**16**) were prepared from 2-chlorophenols (**15**) in moderate-to-excellent yields. However, although the use of this catalyst system selectively yielded bromobenzofurans from the corresponding dibromophenols, chlorobenzofuran synthesis from dichlorophenols has not been reported.



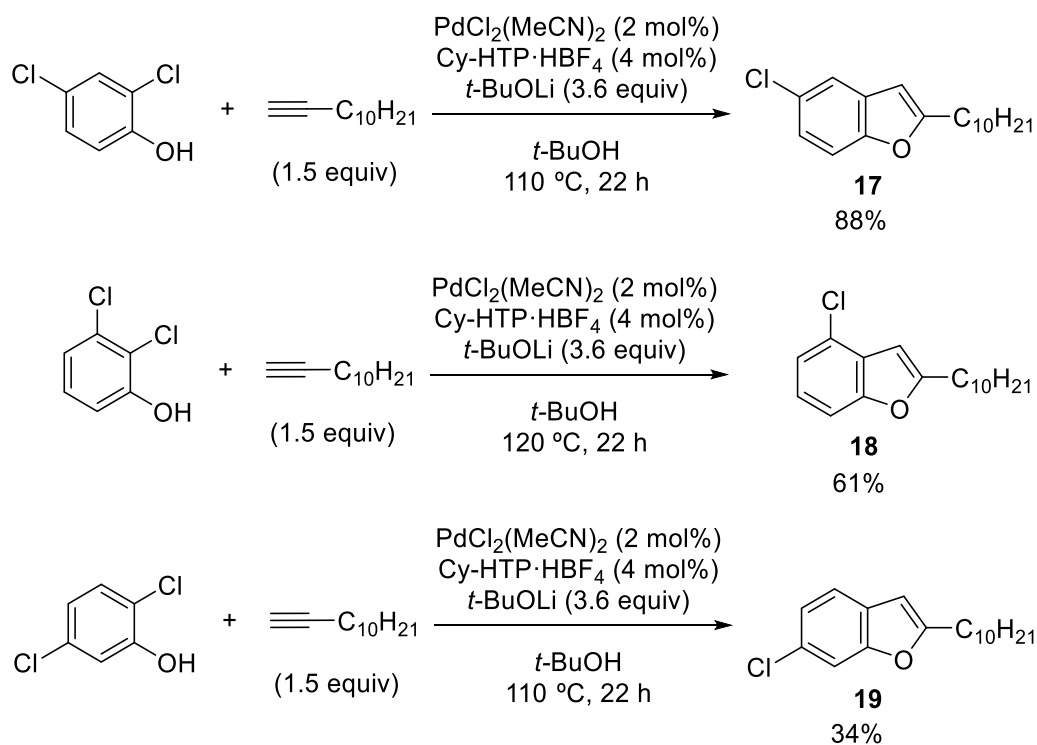
Scheme 5. Synthesis of benzofurans **16** using a Pd-*N,N,N',N'*-tetra(diphenylphosphinomethyl)pyridine-2,6-diamine (Pd-**L1**) catalyst

Our group has developed hydroxyterphenylphosphine (HTP) ligands and used them in Pd-catalyzed cross-couplings.^{9,10} The dicyclohexylphosphino version of HTP, Cy-HTP, was an effective ligand for 2-substituted benzofuran synthesis via Sonogashira coupling/cyclization using various 2-chlorophenols (**15**) and terminal alkynes (**2**) (Scheme 6).¹⁰ The ligand was purified as an HBF₄ salt, which was directly used in the reaction. Employing lithium *tert*-butoxide as the base and *tert*-butanol as the solvent, the reaction proceeded smoothly, yielding the desired **16**. However, other phosphine ligands, such as *t*-Bu₃P, 2-dicyclohexylphosphinobiphenyl (Cy-JohnPhos), and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), resulted in poor yields of the desired **16**.



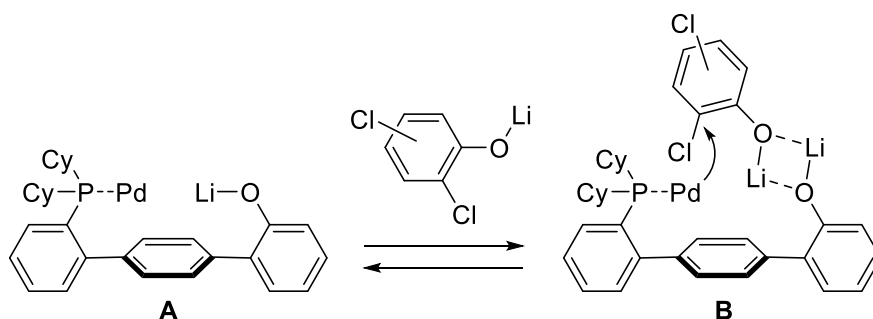
Scheme 6. Synthesis of benzofurans **16** using the Pd-Cy-HTP catalyst

The Pd-Cy-HTP catalyst was also applicable to the *ortho*-selective Sonogashira coupling of dichlorophenols. Thus, the selective synthesis of monochlorobenzofurans from dichlorophenols was achieved using this catalyst. Notably, chlorobenzofurans **17–19** were obtained from three dichlorophenol isomers in moderate-to-high yields (Scheme 7). Only small amounts (<10%) of di-coupled alkynylbenzofurans were formed, showing the high *ortho*-selectivity of the Sonogashira coupling. While there are numerous site-selective cross-couplings in the literature,¹¹ this is the first, still rare, example of *ortho*-selective Sonogashira coupling of dichlorophenols.



Scheme 7. Syntheses of chlorobenzofurans (**17–19**) from dichlorophenols using the Pd–Cy-HTP catalyst

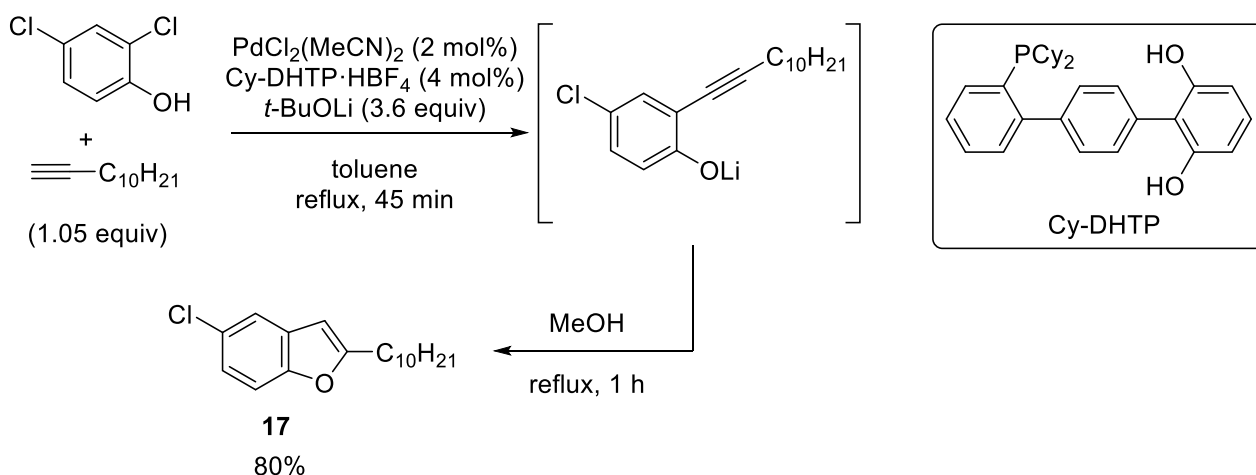
As lithium phenoxides form aggregates,¹² the high reactivity and excellent *ortho*-selectivity of the Pd–Cy-HTP catalyst is due to complex formation between the lithium salts derived from the catalyst and dichlorophenols (Scheme 8). The hydroxy groups of Cy-HTP and dichlorophenol are deprotonated by lithium *tert*-butoxide. These lithium phenoxides, **A** and lithium dichlorophenoxide, are in equilibrium with heteroaggregate **B**, wherein the 2-chloro group of the substrate is close to the Pd atom of **A**. This accelerates the oxidative addition of the 2-chloro group.



Scheme 8. Complex formation between lithium salts of Pd–Cy-HTP and dichlorophenols

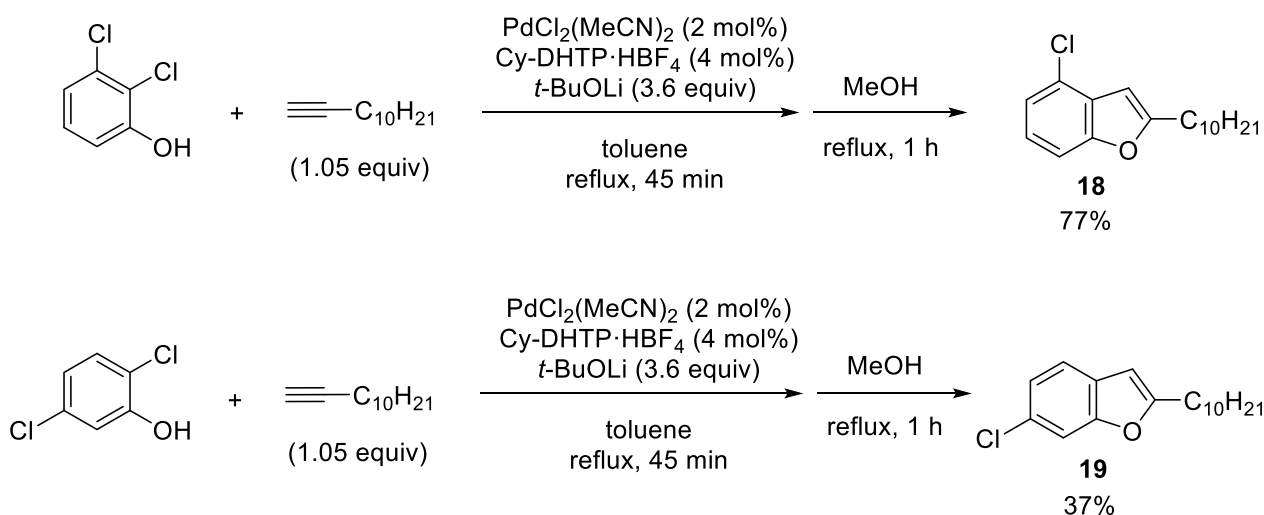
We improved the method by replacing HTP with dihydroxyterphenylphosphine (DHTP), which has two hydroxy groups and shows higher reactivity and *ortho*-selectivity than those of HTP in Kumada–Tamao–

Corriu coupling.¹³ Sonogashira coupling of 2,4-dichlorophenol and dodec-1-yne was conducted using the ligand Cy-DHTP, and the reaction proceeded smoothly at the 2-chloro position within 45 min, followed by cyclization, which was accelerated by the addition of methanol and was complete in 1 h, generating the 5-chlorobenzofuran (**17**) in a good yield (Scheme 9).¹⁴ The formation of di-coupled 5-alkynylbenzofuran was not observed.



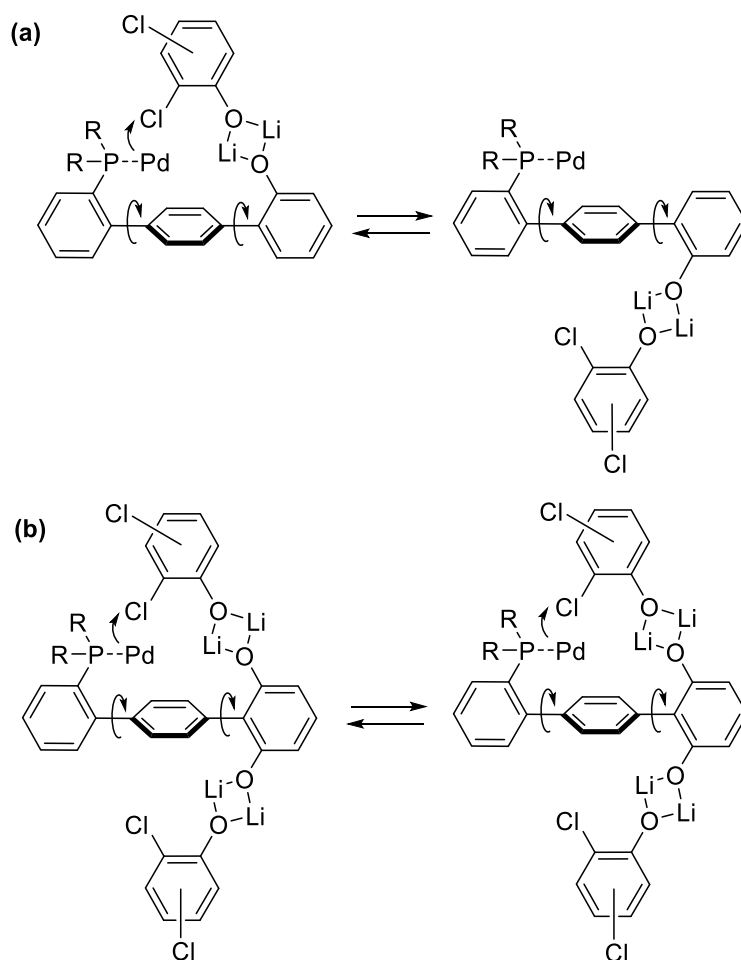
Scheme 9. One-pot synthesis of chlorobenzofuran **17** using the Pd–Cy-DHTP catalyst

Benzofuran products with 4-chloro or 6-chloro group were also synthesized from 2,3- and 2,5-dichlorophenol, respectively, using the Pd–Cy-DHTP catalyst (Scheme 10). Using 2,3-dichlorophenol, the reaction proceeded smoothly, generating the desired product (**18**) in a good yield. Conversely, the reaction employing 2,5-dichlorophenol resulted in a lower yield of the product (**19**).



Scheme 10. Syntheses of chlorobenzofurans **18** and **19** from 2,3- and 2,5-dichlorophenols using the Pd–Cy-DHTP catalyst

The improved reactivity of DHTP compared with that of HTP is due to the flexibility in C–C bond rotation for the proposed intermediates, as shown in Scheme 11. For the Pd–Cy-HTP catalyst, the conformation with the lithium phenoxide moiety close to Pd is in equilibrium with the conformation with these groups on opposite sides of the terphenyl structure (Scheme 11a). Conversely, for the Pd–Cy-DHTP catalyst, Pd is always located on the same side of the terphenyl group as a lithium phenoxide moiety (Scheme 11b). This results in further acceleration of the oxidative addition of the 2-chloro group to Pd, inducing higher reactivity and selectivity in the Sonogashira coupling.

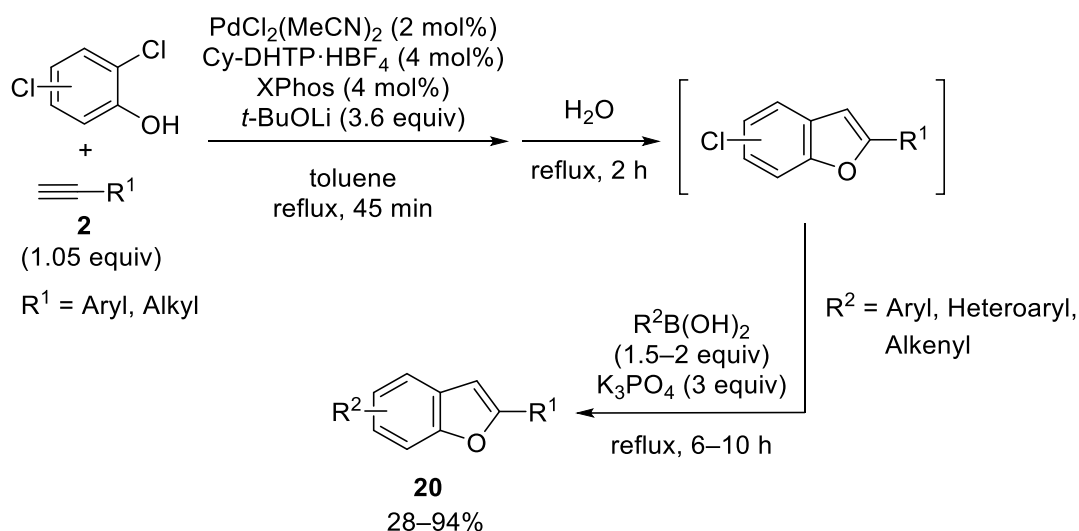


Scheme 11. C–C Bond rotation within the proposed intermediates of (a) Cy-HTP and (b) Cy-DHTP

2-2. One-Pot Synthesis of Disubstituted Benzofurans via *ortho*-Selective Sonogashira Coupling/Cyclization/Suzuki–Miyaura Coupling

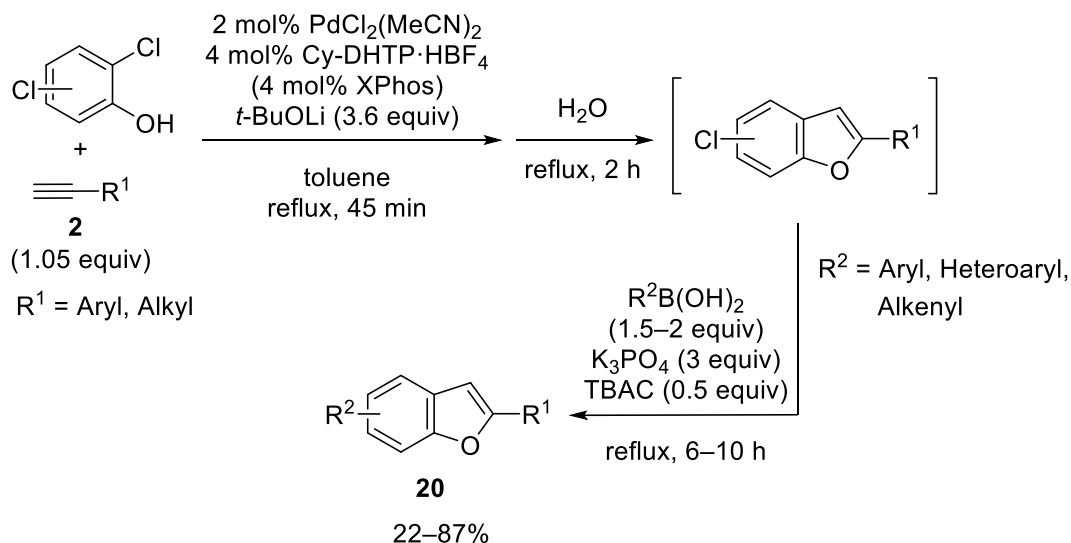
The Pd–Cy-DHTP catalyst was used in sequential one-pot syntheses of disubstituted benzofurans (**20**) from dichlorophenols, terminal alkynes, and boronic acids (Scheme 12).¹⁴ The use of two ligands, Cy-DHTP and XPhos, was effective in the one-pot synthesis. Water was selected as the cosolvent to promote cyclization

and Suzuki–Miyaura coupling.¹⁵ After chlorobenzofuran formation via *ortho*-selective Sonogashira coupling followed by cyclization, boronic acid was added to the reaction vessel along with K_3PO_4 . Mechanistic studies showed that the Pd–Cy–DHTP catalyst promoted *ortho*-selective Sonogashira coupling, while the Pd–XPhos catalyst accelerated Suzuki–Miyaura coupling.



Scheme 12. One-pot synthesis of disubstituted benzofurans **20**

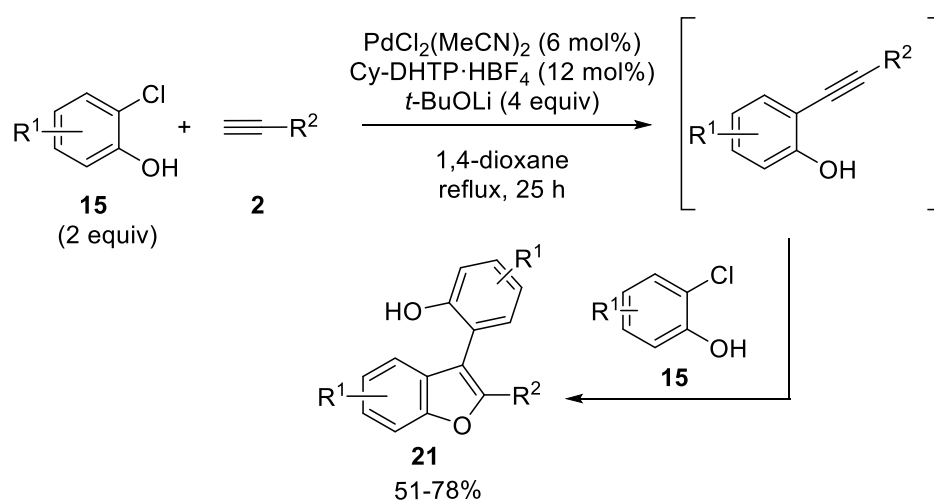
We further examined the reaction conditions and found that the addition of a substoichiometric amount of tetrabutylammonium chloride (TBAC) during the Suzuki–Miyaura coupling step accelerated the reaction without using XPhos (Scheme 13).¹⁶ Four isomers of dichlorophenol, 2,3-, 2,4-, 2,5-, and 2,6-dichlorophenols, were used as substrates, yielding the corresponding **20**. For the less reactive boronic acids, such as 3-pyridylboronic acid, the addition of both XPhos and TBAC was effective in yielding the desired **20**.



Scheme 13. One-pot synthesis of disubstituted benzofurans **20** using TBAC as an additive

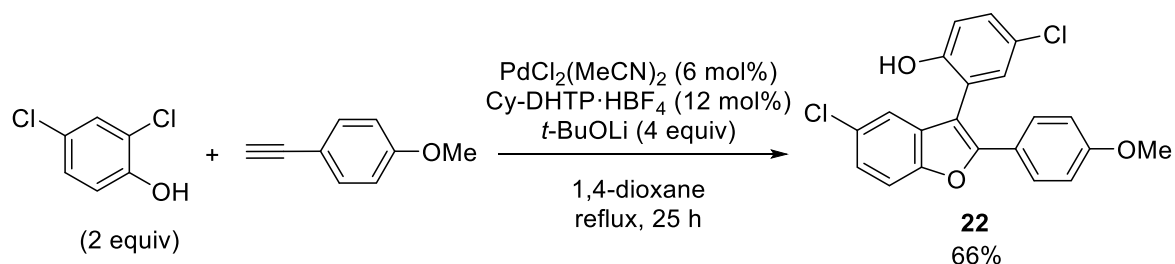
3. SYNTHESIS OF MULTISUBSTITUTED BENZOFURANS FROM DICHLOROPHENOLS VIA *ORTHO*-SELECTIVE SONOGASHIRA COUPLING/CACCHI CYCLIZATION

During the investigation of 2-substituted benzofuran synthesis,¹⁴ the formation of a small amount of 3-arylated benzofuran **21** was observed, representing the incorporation of two molecules of **15**. This revealed the possibility of the one-pot synthesis of **21** using 2 equivalents of the 2-chlorophenol (**15**) and 1 equivalent of terminal alkyne (**2**). The Pd–Cy–DHTP catalyst was used in this synthesis. After reaction condition optimization, *ortho*-selective Sonogashira coupling and subsequent oxypalladation/reductive elimination (Cacchi cyclization)¹⁷ proceeded smoothly, generating the desired product **21** in moderate-to-good yields (Scheme 14).¹⁸



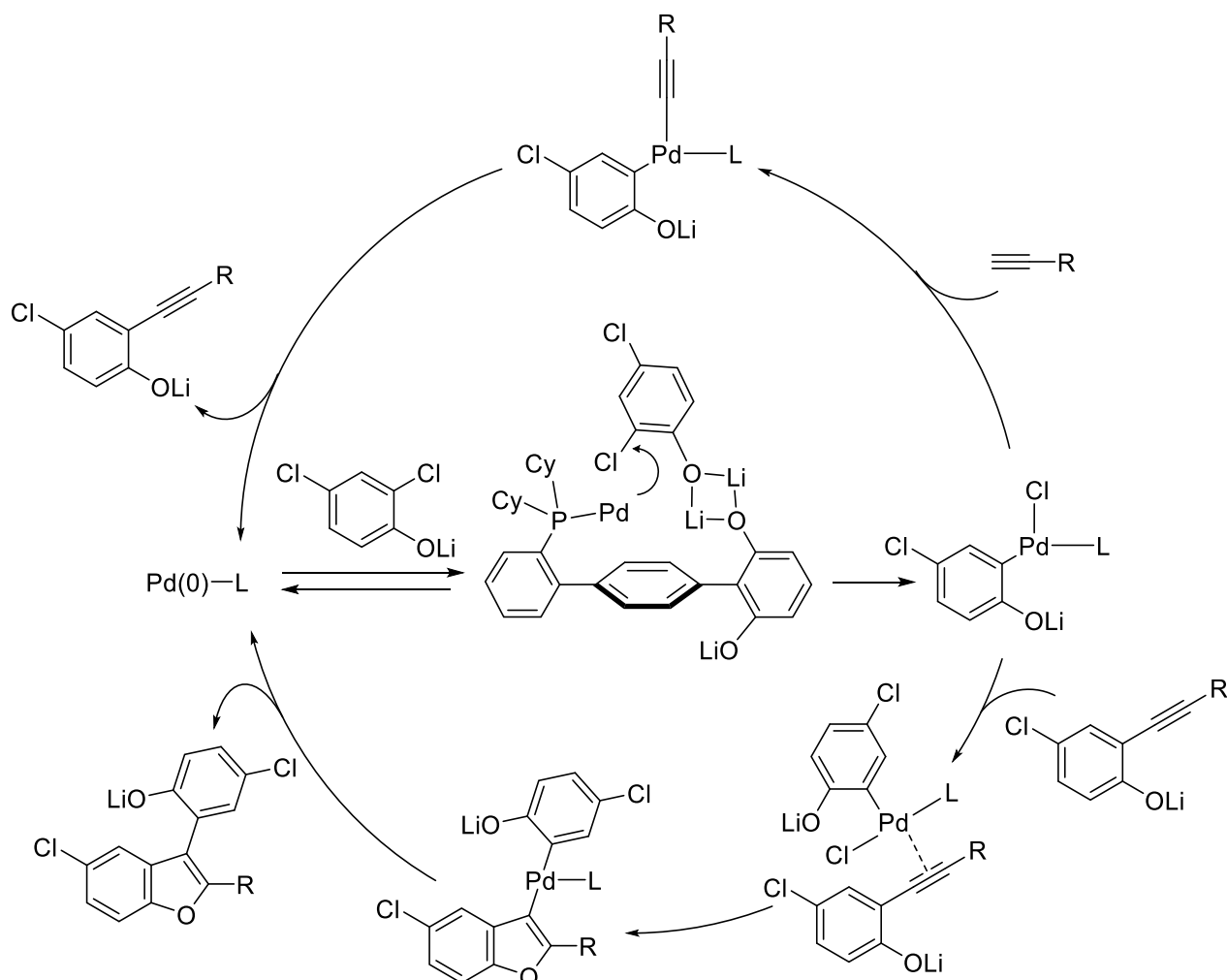
Scheme 14. One-pot synthesis of benzofurans **21** via Sonogashira coupling/Cacchi cyclization

Notably, the reaction with 2,4-dichlorophenol yielded the desired 3-arylated product **22** in a 66% yield (Scheme 15), indicating that the oxidative addition of 2,4-dichlorophenol to Pd(0) selectively occurred at the 2-chloro group. Conversely, the reaction using 2,3-dichlorophenol did not yield the 3-arylated product, instead generating only 3-protonated benzofuran. We propose that oxypalladation after Sonogashira coupling did not proceed because of the bulkiness of the remaining 3-chloro group of 2-alkynyl-3-chlorophenol.



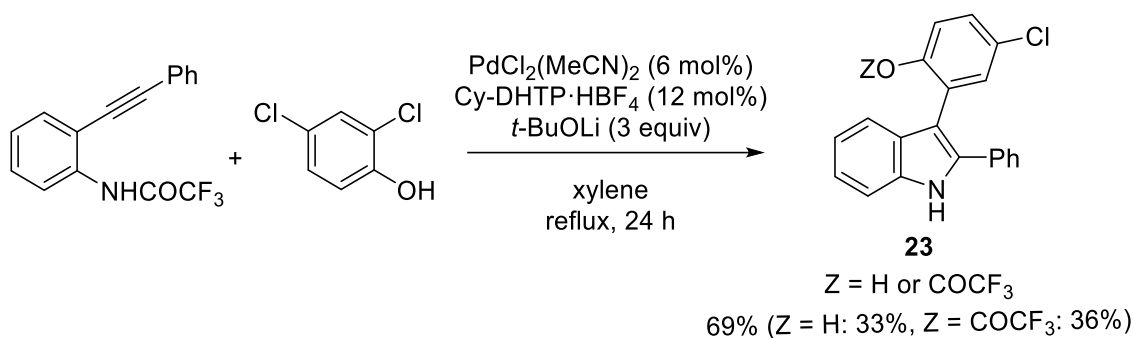
Scheme 15. Synthesis of benzofuran **22** from 2,4-dichlorophenol via Sonogashira coupling/Cacchi cyclization

The proposed reaction pathway is illustrated in Scheme 16. In the upper catalytic cycle, the *ortho*-selective Sonogashira coupling produces 2-alkynyl-4-chlorophenolate. This intermediate is then involved in the lower catalytic cycle, wherein the Cacchi cyclization generates the final product.



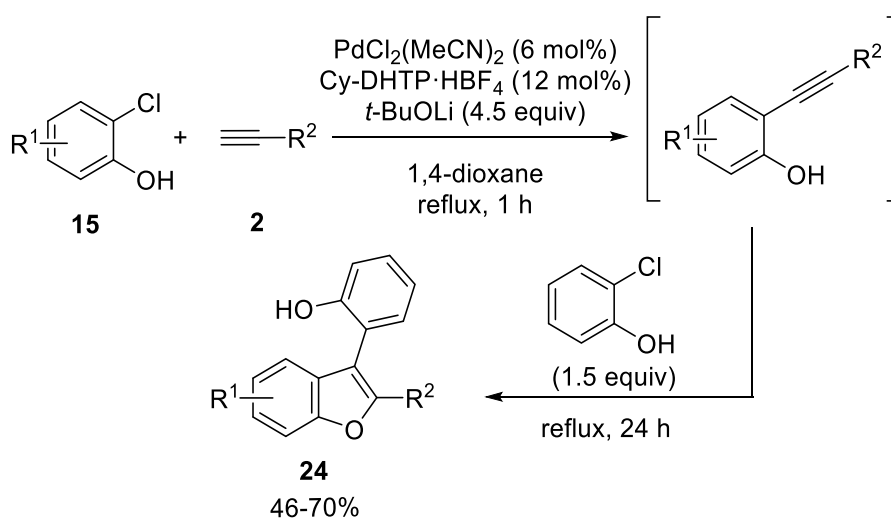
Scheme 16. Proposed reaction pathway in the synthesis of the 3-arylated benzofuran via Sonogashira coupling followed by Cacchi cyclization

Based on the proposed pathway, the reaction of 2,4-dichlorophenol with a 2-alkynylaniline derivative was evaluated. The reaction proceeded selectively at the 2-chloro group, producing the desired indole **23** in a 69% yield (Scheme 17).¹⁹ This supports our hypothesis that DHTP accelerates oxidative addition at the 2-chloro position.



Scheme 17. Synthesis of 2,3-disubstituted indole **23** using 2,4-dichlorophenol

As an extension of the above method, the reaction using two different 2-chlorophenols has also been reported (Scheme 18).¹⁸ After Sonogashira coupling of **15** and **2** for 1 h, additional 2-chlorophenol was added to the reaction vessel, and the mixture was refluxed for 24 h, producing the desired benzofurans (**24**) in moderate-to-good yields. When 4-chlorotoluene was used instead of the second 2-chlorophenol, the Cacchi cyclization did not proceed smoothly, and the yield of the desired 2,3-substituted benzofuran was only 9%. Considering that 4-chlorotoluene undergoes oxidative addition to the Pd–Cy-DHTP catalyst under these conditions, the hydroxy group of the second 2-chlorophenol is critical for promoting the oxypalladation and/or reductive elimination, although the precise mechanism of this is unclear.

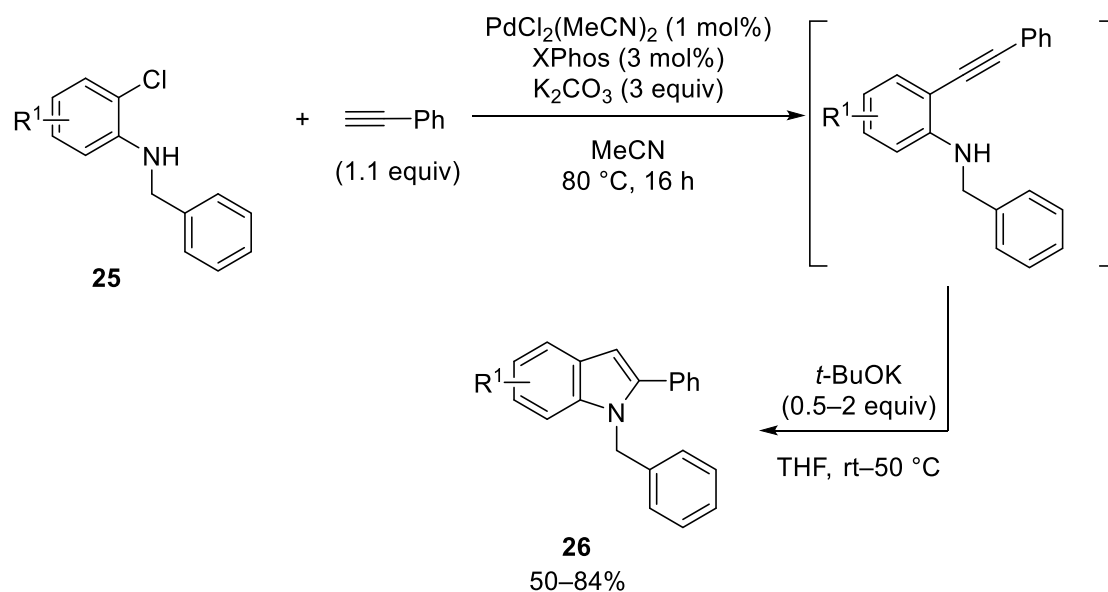


Scheme 18. One-pot synthesis of benzofurans **24** using two different 2-chlorophenols

4. SYNTHESIS OF MULTISUBSTITUTED INDOLES FROM MULTICHLORINATED ANILINES

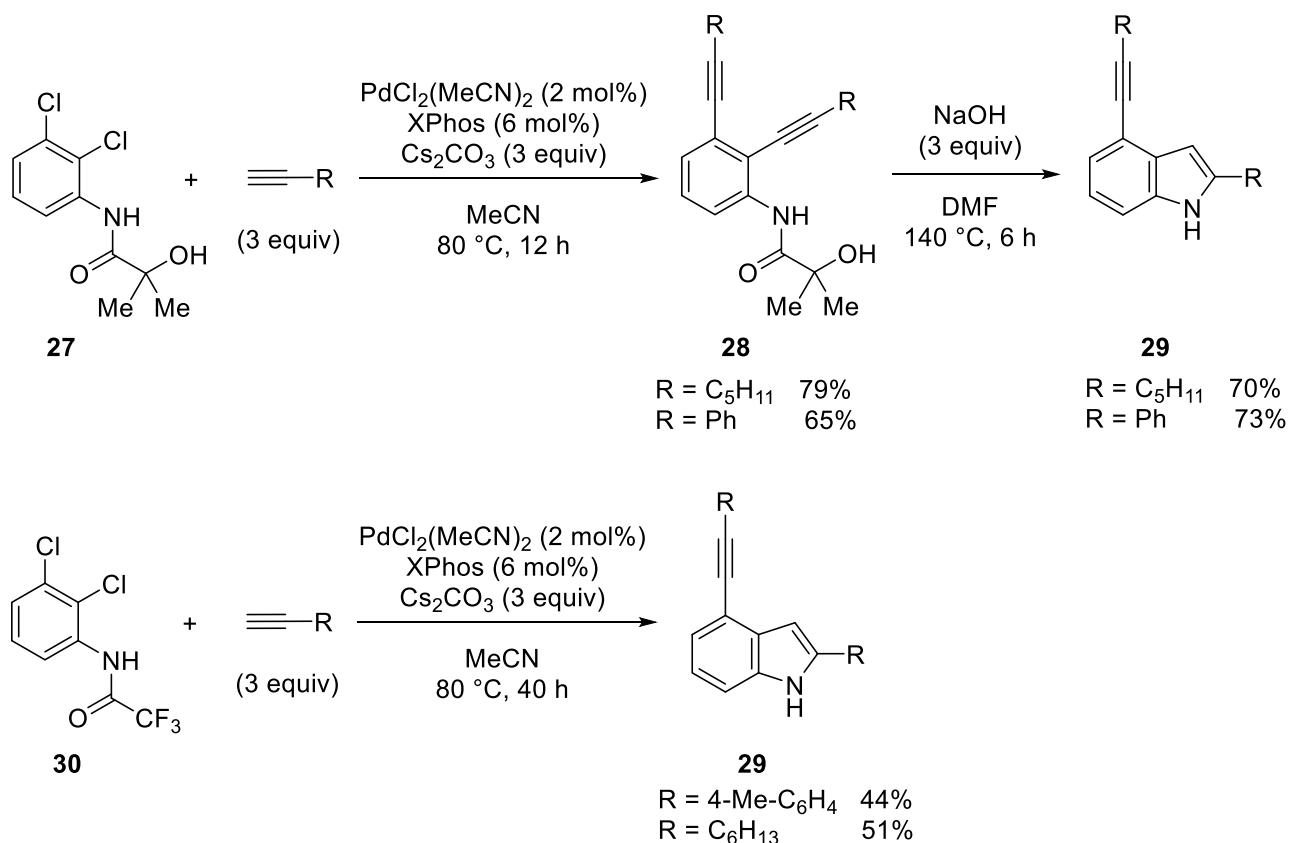
4-1. Synthesis of Multisubstituted Indoles from Dichloroanilines via *ortho*-Selective Sonogashira Coupling/Cyclization

Before describing examples of the reactions using dichloroanilines, an example using monochloroaniline is shown. In 2006, McLaughlin *et al.* reported the one-pot synthesis of 1-benzyl-2-phenylindoles (**26**) from *N*-benzylated 2-chloroanilines (**25**) and ethynylbenzene (Scheme 19).²⁰ One-pot Sonogashira coupling using the Pd–XPhos catalyst followed by cyclization promoted with potassium *tert*-butoxide generated the desired indoles **26** in moderate-to-good yields.



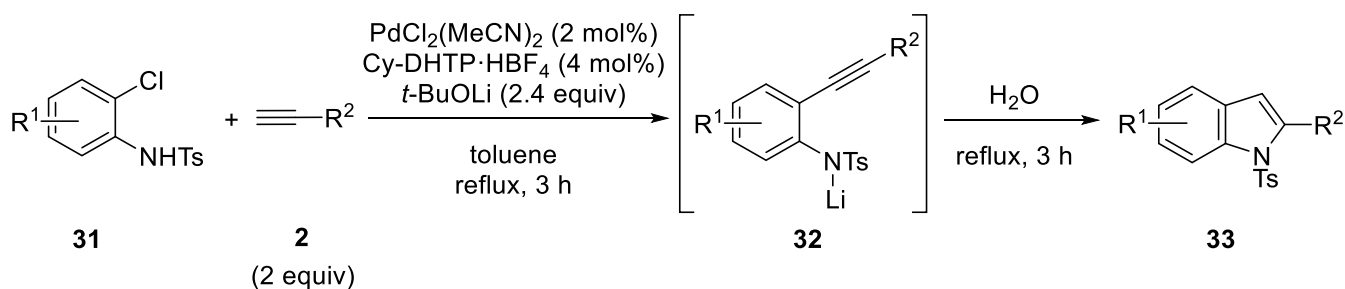
Scheme 19. One-pot synthesis of 1-benzyl-2-phenylindoles **26**

In 2011, Sanz *et al.* reported the syntheses of 4-alkynylindoles **29** from 2,3-dichloroaniline derivatives (**27**) (Scheme 20).²¹ Sonogashira coupling proceeded smoothly at the chloro positions using the Pd–XPhos catalyst; however, the reaction was not site-selective, yielding 2,3-dialkynylated anilines (**28**), which were subjected to base-promoted cyclization, yielding **29**. The use of *N*-trifluoroacetyl-protected substrates (**30**) generated **31** directly in one pot.



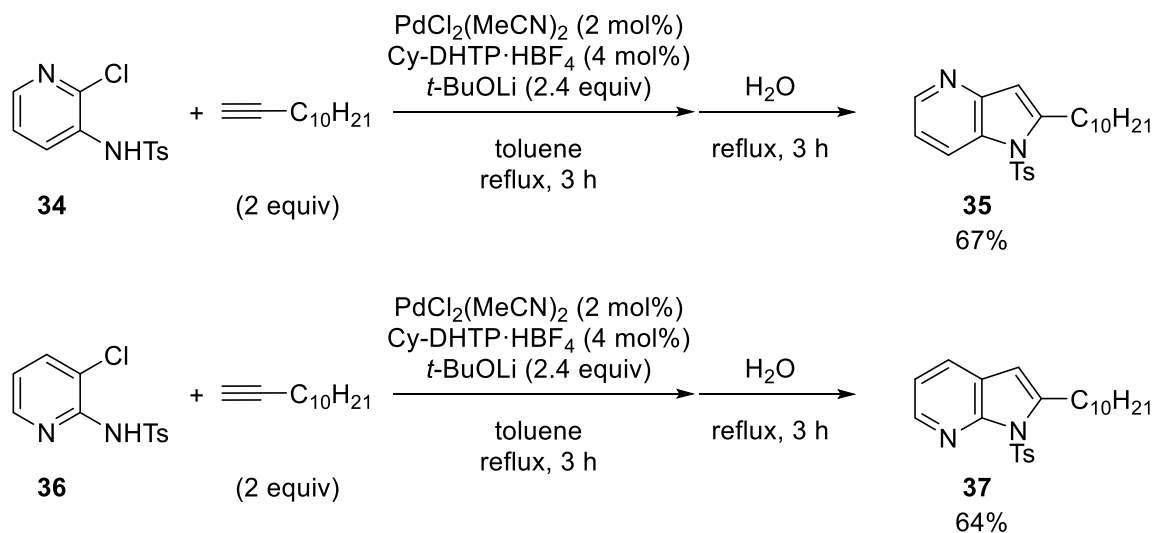
Scheme 20. Syntheses of 4-alkynyloindoles **29** from 2,3-dichloroaniline derivatives **27** and **30** using the Pd-XPhos catalyst

Conversely, the Pd-Cy-DHTP catalyst showed high reactivity and site-selectivity, similar to that observed in chlorobenzofuran synthesis. Sonogashira coupling of *N*-tosylated 2-chloroanilines (**31**) and terminal alkynes (**2**) using the Pd-Cy-DHTP catalyst proceeded smoothly at the 2-chloro position, yielding *N*-tosylated 2-alkynylanilines (**32**) (Scheme 21).²² After Sonogashira coupling, water was added as a cosolvent to promote cyclization, and the desired 2-substituted indoles (**33**) were obtained in one pot in good-to-high yields.



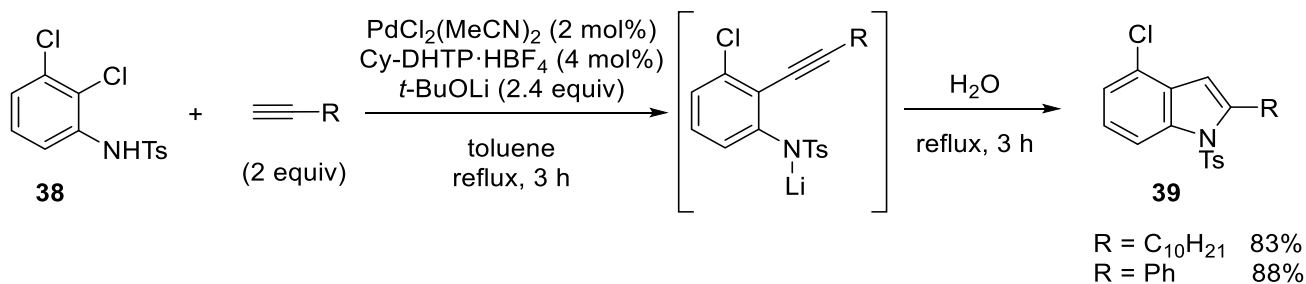
Scheme 21. One-pot synthesis of indoles **33** from 2-chloroaniline derivatives **31** using the Pd-Cy-DHTP catalyst

Aminochloropyridine derivatives (**34**, **36**) were also used as substrates (Scheme 22).¹⁶ The corresponding pyrrolopyridine derivatives (**35**, **37**) were obtained.



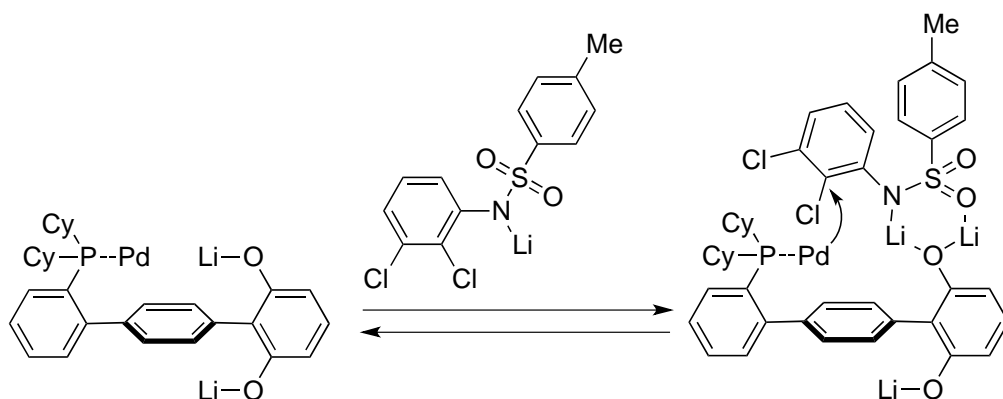
Scheme 22. One-pot syntheses of pyrrolopyridine derivatives **35** and **37** using the Pd–Cy-DHTP catalyst

The catalytic system was also used for the reactions of dichloroaniline derivatives. Using *N*-tosylated 2,3-dichloroaniline (**38**), the reaction proceeded selectively at the 2-chloro position, producing the desired 2-substituted 4-chloroindoles (**39**) in high yields, and neither 3-alkynylated anilines nor 4-alkynylated indole products were observed (Scheme 23).²²



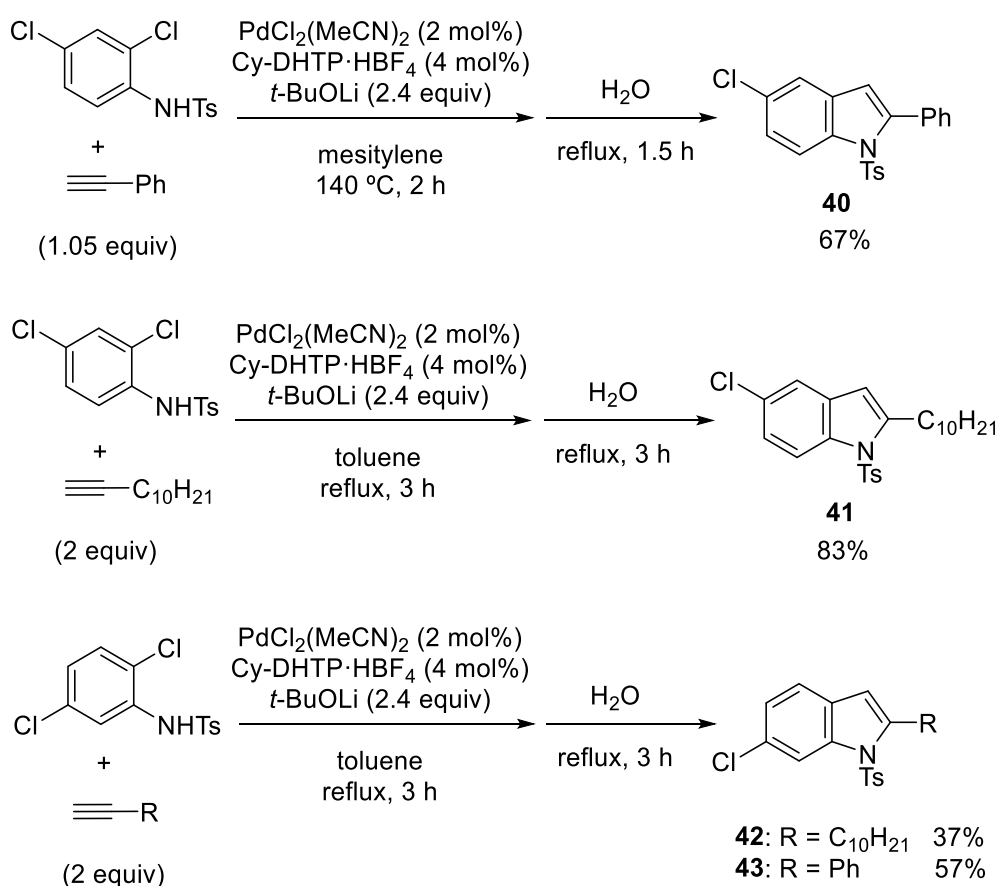
Scheme 23. One-pot synthesis of 2-substituted 4-chloroindoles **39** using the Pd–Cy-DHTP catalyst

We presume that a key to high *ortho*-selectivity is heteroaggregate formation between the lithium salts of *N*-tosylated 2,3-dichloroaniline and Pd–Cy-DHTP (Scheme 24), similar to that proposed for chlorobenzofuran synthesis (Scheme 11b).



Scheme 24. Complex formation between lithium salts of Pd–Cy–DHTP and a dichloroaniline derivative

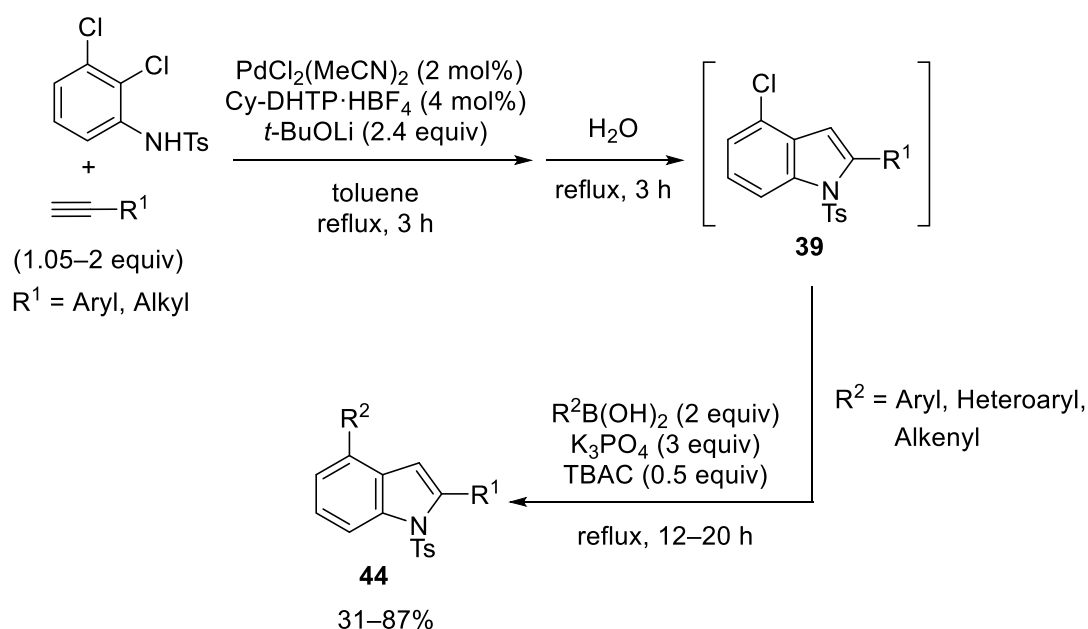
Chloroindoles with 5- (**40**, **41**) or 6-chloro group (**42**, **43**) have also been prepared from the corresponding *N*-tosylated 2,4- or 2,5-dichloroanilines, respectively, using this catalyst system (Scheme 25).



Scheme 25. One-pot syntheses of 5- and 6-chloroindole derivatives **40–43**

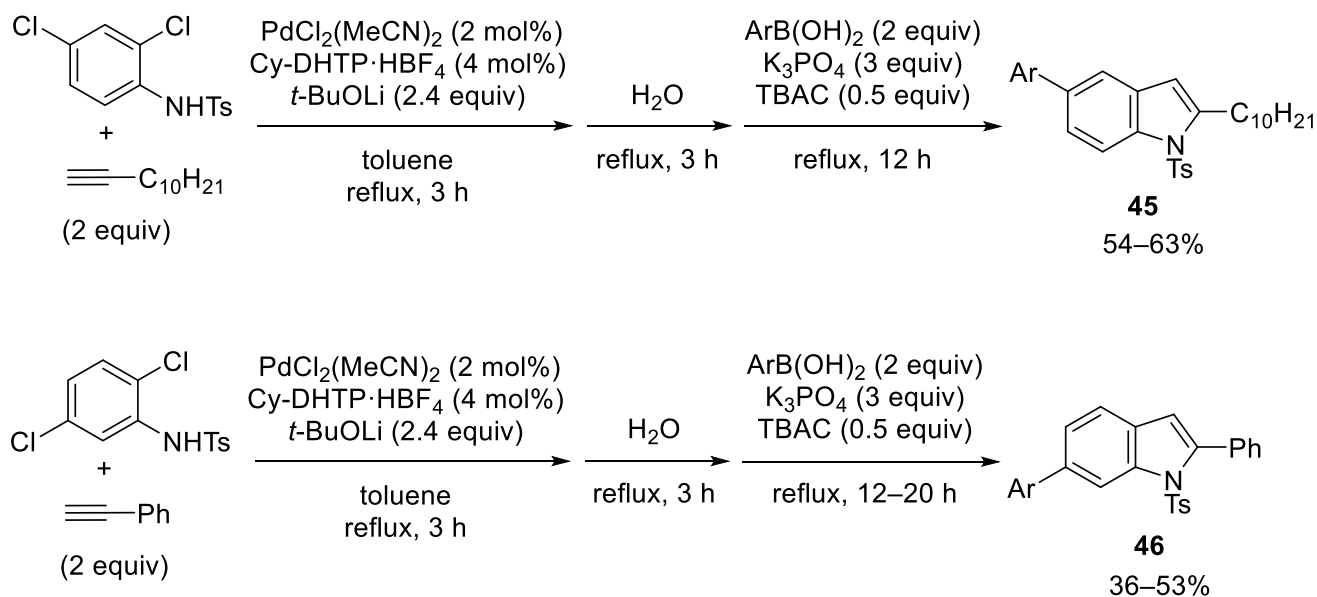
4-2. One-Pot Synthesis of Multisubstituted Indoles from Dichloroanilines via *ortho*-Selective Sonogashira Coupling/Cyclization/Suzuki–Miyaura Coupling

The Pd–Cy–DHTP catalyst was also successfully applied to the one-pot synthesis of 2,4-disubstituted indoles (**44**),²² which are challenging synthetic targets. These reactions initially produced 4-chloroindoles (**39**) via a Sonogashira coupling/cyclization sequence, followed by Suzuki–Miyaura coupling in the presence of boronic acids, generating the desired **44** in moderate-to-good yields (Scheme 26). The addition of a substoichiometric amount of a quaternary ammonium salt was key to accelerating the Suzuki–Miyaura coupling. TBAC was the most effective among the quaternary ammonium salts screened, as it may serve as a phase-transfer agent that transports the boronic acid-derived anions from the aqueous to the organic phase. Remarkably, the Pd–Cy–DHTP catalyst catalyzed both the Sonogashira and Suzuki–Miyaura coupling reactions. In contrast, a two-ligand system consisting of both Cy–DHTP and XPhos, which was effective in benzofuran synthesis,¹⁴ yielded poor results.



Scheme 26. One-pot synthesis of 2,4-disubstituted indoles **44**

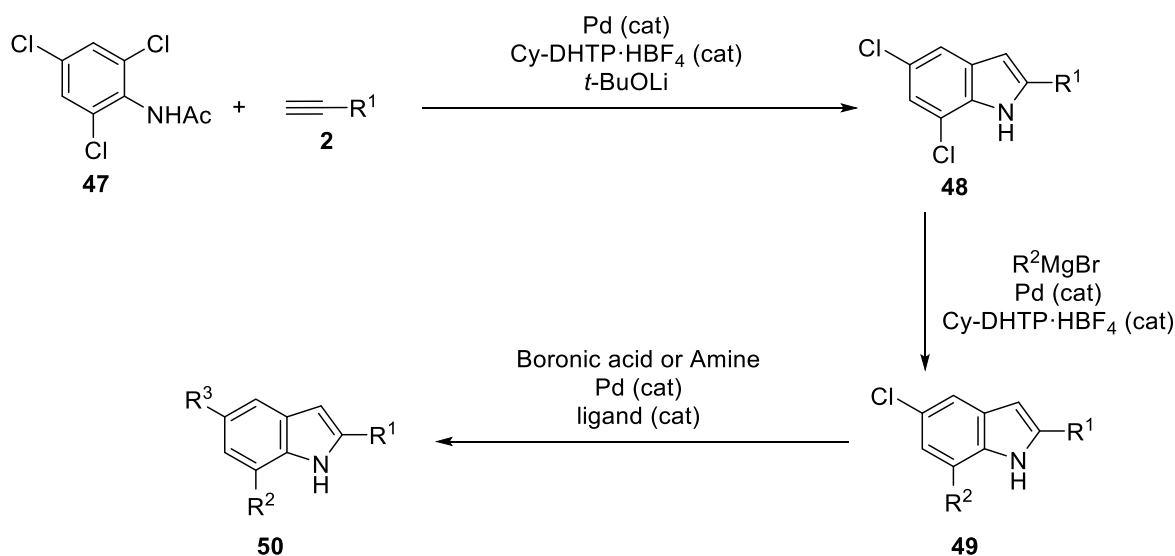
This method was also applicable to the syntheses of various indoles bearing substituents at different positions (Scheme 27).¹⁶ The use of *N*-tosylated 2,4-dichloroaniline produced indoles **45** in moderate yields. Indoles **46** were obtained using *N*-tosylated 2,5-dichloroaniline in moderate yields.



Scheme 27. One-pot syntheses of indoles **45** and **46** from 2,4- and 2,5-dichloroaniline derivatives

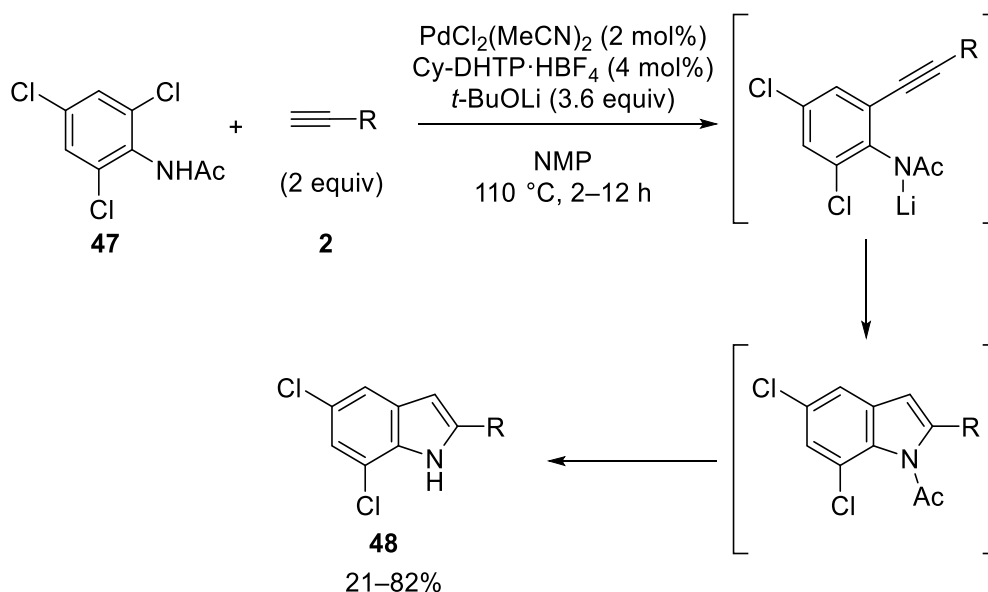
4-3. Synthesis of 2,5,7-Trisubstituted Indoles from 2,4,6-Trichloroanilines

Chloroindole synthesis using the Pd–Cy-DHTP catalyst was further extended to the three-step syntheses of 2,5,7-trisubstituted indoles from a 2,4,6-trichloroaniline derivative. In a previous study, site-selective coupling was chemoselectively achieved using an aniline bearing three different halogen groups, 2-bromo-4-chloro-6-iodoaniline, as a substrate for 2,5,7-trisubstituted indole synthesis.²³ Conversely, the Pd–Cy-DHTP catalyst enabled the syntheses of 2,5,7-trisubstituted indoles (**50**) from *N*-acetyl-2,4,6-trichloroaniline (**47**) (Scheme 28), which is readily prepared from 2,4,6-trichloroaniline.²⁴



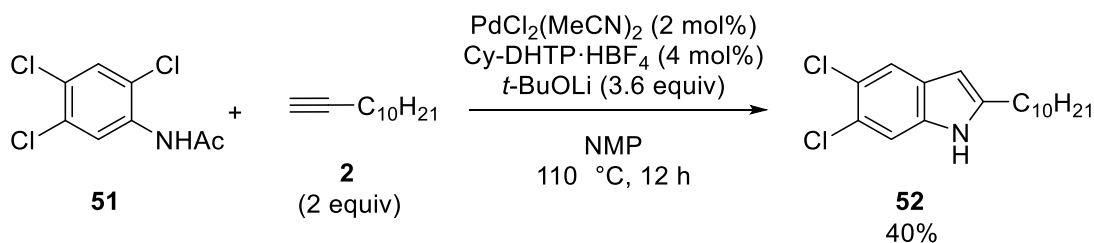
Scheme 28. Synthesis of 2,5,7-trisubstituted indoles **50**

In the first step, the Pd–Cy–DHTP catalyst promoted *ortho*-selective Sonogashira coupling of **47** with terminal alkynes (**2**) in *N*-methylpyrrolidone (NMP), and subsequent cyclization yielded 2-substituted 5,7-dichloroindoles (**48**) (Scheme 29). No acetylated indole was obtained, suggesting that cyclization of *N*-acetyl-2-alkynylaniline and subsequent deacetylation of the resulting *N*-acetylindole was rapid under the reaction conditions. Remarkably, only trace amounts of 5-alkynyl or 7-alkynyl indole were observed, indicating that further Sonogashira coupling of **48** was slow under these reaction conditions.



Scheme 29. Synthesis of 5,7-dichloroindole derivatives **48**

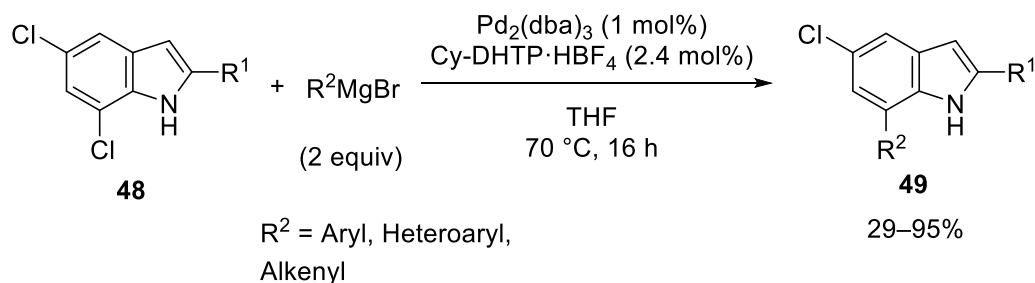
The Sonogashira coupling/cyclization conditions shown in Scheme 29 were applicable to other substrates. For example, *N*-acetyl-2,4,5-trichloroaniline (**51**) was successfully converted to the corresponding dichloroindole **52**, as shown in Scheme 30.²⁴



Scheme 30. Synthesis of 5,6-dichloroindole derivative **52**

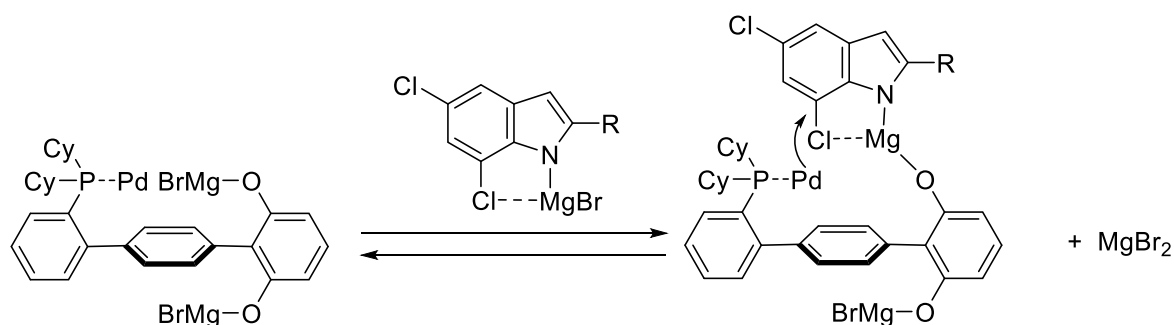
Subsequent introduction of aryl or alkenyl groups at the 7-position of **48** was conducted. The Pd–Cy–DHTP catalyst was effective for C7-selective Kumada–Tamao–Corriu coupling (Scheme 31). Various Grignard

reagents were used in the reaction, which proceeded selectively at the 7-position, successfully yielding the desired 2,7-disubstituted 5-chloroindole (**49**).



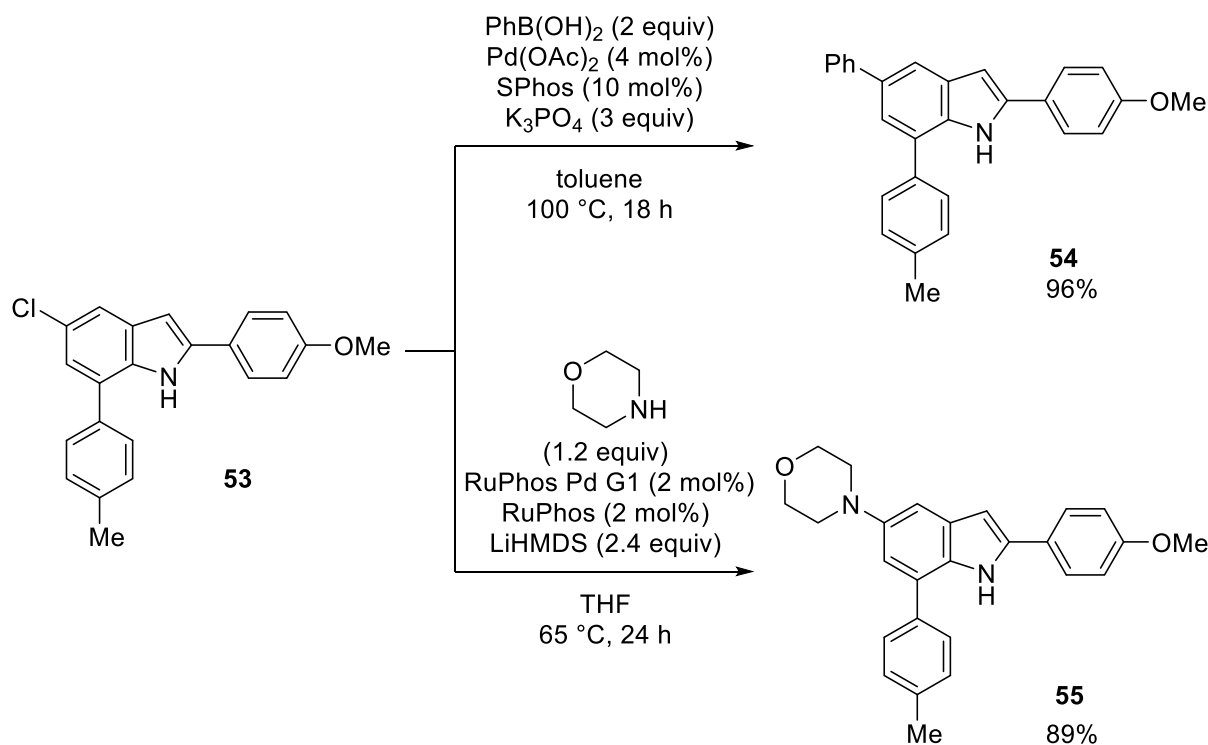
Scheme 31. C7-Selective Kumada–Tamao–Corriu coupling of 5,7-dichloroindole derivatives **48**

The proposed mechanism of the C7-selective coupling is shown in Scheme 32. The Mg salts derived from **48** and the Pd catalyst form heteroaggregates, wherein Pd is located close to the chloro group at the 7-position. Along with this proximity effect, intramolecular coordination of the chloro group to Mg also facilitates oxidative addition at this position.^{9c,25}



Scheme 32. Heteroaggregate formation between the Mg salts of Pd–Cy–DHTP and dichloroindole

Further substitution of the chlorine at the 5-position was conducted by Suzuki–Miyaura coupling²⁶ or Buchwald–Hartwig amination²⁷ according to the literature procedures (Scheme 33). Using 5-chloro-2-(4-methoxyphenyl)-7-(*p*-tolyl)indole (**53**), both reactions proceeded smoothly, generating the corresponding 2,5,7-trisubstituted indoles (**54**, **55**) in high yields.



Scheme 33. Syntheses of 2,5,7-trisubstituted indoles **54** and **55**. SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, RuPhos = 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl

5. CONCLUSION

Pd-catalyzed cross-coupling reactions are a powerful tool for the syntheses of multisubstituted benzofurans/indoles. In these reactions, the use of 2-chlorophenols/2-chloroanilines, which are readily available, is attractive, although they are generally less reactive than the corresponding iodo or bromo compounds. The use of an appropriate ligand is critical in promoting the reactions. For example, HTP and DHTP enabled *ortho*-selective cross-coupling of dichlorophenols/dichloroanilines, and chlorobenzofurans/chloroindoles were successfully obtained. These chloro groups may be further substituted with various other substituents, yielding a wide range of multisubstituted benzofurans/indoles.

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