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FUNCTIONALIZATION OF PORPHYRINS THROUGH C-C BOND FORMATION REACTIONS WITH FUNCTIONAL GROUP-BEARING ORGANOMETALLIC REAGENTS

Toshikatsu Takanami*

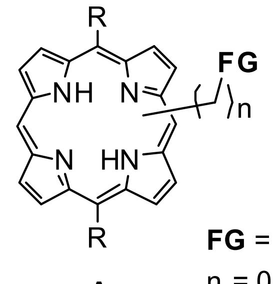
Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan, takanami@my-pharm.ac.jp

Abstract – Interest in the chemistry of porphyrins and related tetrapyrrolic macrocycles has increased greatly in recent years because of the importance of these compounds in many areas of chemistry, biology, and material sciences. Consequently, the development of efficient synthetic strategies and intermediates for the preparation of porphyrin derivatives with a variety of peripheral substituents has become an active field of research. Functionalized porphyrins, which contain chemically reactive functional groups such as esters, amides, nitriles, and formyl groups on the porphyrin core and as peripheral substituents, are potential precursors for more complicated porphyrin derivatives. However, current methods for synthesizing functionalized porphyrins generally suffer from limitations, including tedious multi-step preparation, laborious chromatographic purification, and low yields. This review describes our recent efforts to address some of these challenges using the following strategies: (1) a palladium-catalyzed Negishi cross-coupling reaction of halogenated porphyrins with functional group-bearing organozinc reagents, and (2) the silylmethylation of porphyrins with silylmethyllithium and magnesium reagents, where the silylmethyl groups can be used as protected analogs of various chemically reactive functionalities, such as formyl and hydroxymethyl groups.

CONTENTS

1. INTRODUCTION

Porphyrins are a class of chemically and biologically important heteroaromatic macrocycles that are ubiquitous in nature and have diverse applications in many areas of chemistry, biology, and material sciences.[1] For example, they are used as homogeneous catalysts,[2] photosensitizers for photodynamic therapy (PDT),[3] materials for nonlinear optics (NLO) and solar energy conversion systems,[4] and synthetic receptors for various organic and inorganic species.[5] The chemical, physical, and biological properties of porphyrins can be tuned by the electronic, steric, and conformational environments of their peripheral substituents, and by the central metal ion.[1] Therefore, a large number of synthetic strategies and intermediates for preparing porphyrin derivatives bearing a diverse variety of peripheral substituents have been investigated.[6–8]

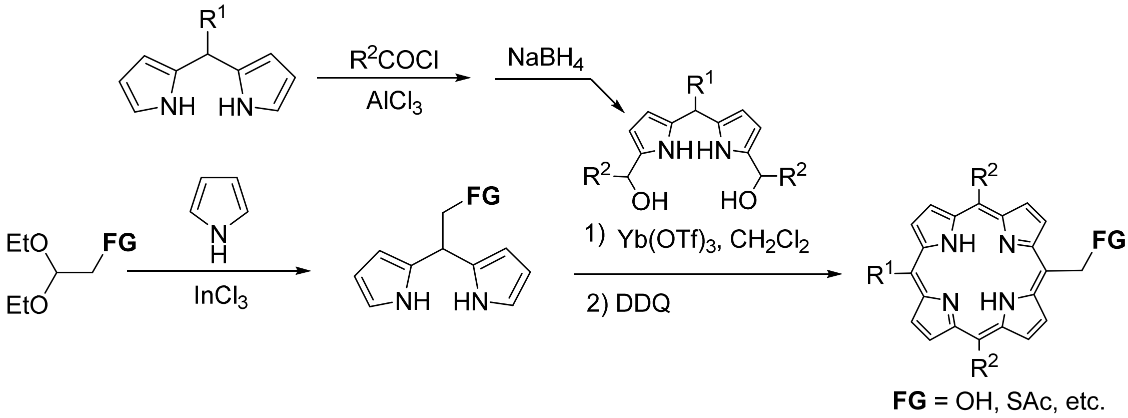


A

FG = CO_2R, Cl, CN, *etc.*
n = 0, 1, 2, 3, ---

Figure 1. Functionalized porphyrins

Functionalized porphyrin **A**, which possesses chemically reactive functional groups such as esters, amides, nitrile, and formyl groups on the porphyrin core and the peripheral substituents, is a potential precursor for more complicated porphyrin derivatives (Figure 1). However, the synthetic utility of functionalized porphyrins is limited, partly because they are difficult to synthesize. The classic approach involves multiple condensation reactions of aldehydes with various monopyrroles or substituted dipyrromethanes under acidic conditions, followed by oxidation of the resulting porphyrinogen intermediates (Scheme 1).[7] Despite the significant improvements made by Lindsay and co-workers with the introduction of new reaction conditions,[8] multiple condensation methods still suffer from low yields, significant side products, and tedious purifications. This has hindered the efficient preparation of functionalized porphyrin derivatives. Thus, developing a simple, practical, general approach for synthesizing functionalized porphyrins remains an important goal.



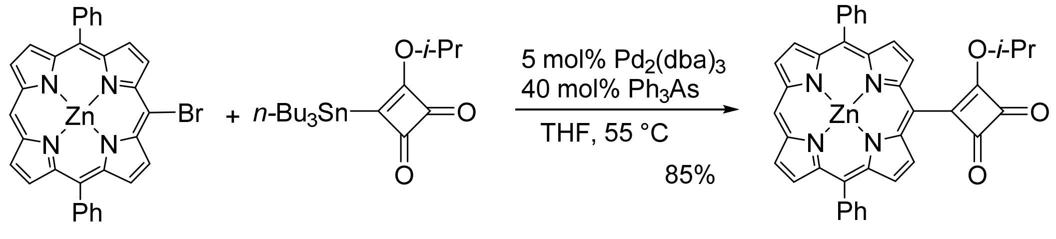
Scheme 1. An example of the preparation of functionalized porphyrins

Over the last few years, our group has pursued two different strategies to achieve this goal. The first strategy involves the direct preparation of functionalized porphyrins through the palladium-catalyzed cross-coupling of preformed halogenated porphyrins with organozinc reagents, which contain chemically reactive functional groups such as esters, halogens, and pseudohalogens. The second strategy consists of the silylmethylation of porphyrins with silylmethyllithium and magnesium reagents, followed by the conversion of the silylmethyl groups on the porphyrin core to other functional groups such as hydroxymethyl, formyl, alkoxymethyl, fluoromethyl, and alkenyl groups. We have used these simple strategies to prepare a variety of functionalized porphyrins, ranging from *meso*- and *β*-mono-functionalized porphyrins to unsymmetrical *meso,meso*-bifunctionalized porphyrins, in good yields.[9] We describe the details of these strategies in the following sections.

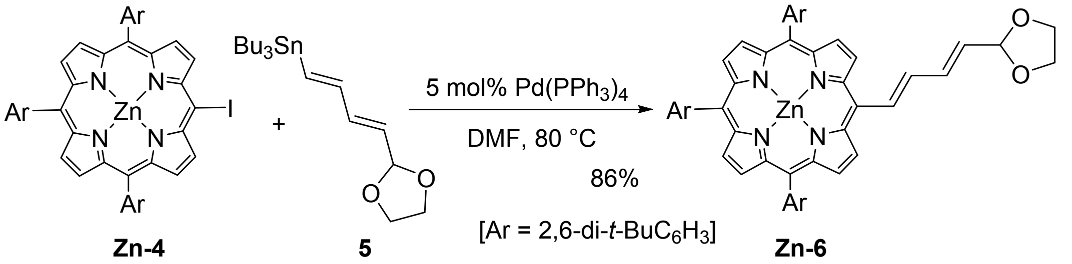
2. PALLADIUM-CATALYZED CROSS-COUPLINGS WITH FUNCTIONAL GROUP-BEARING ORGANOZINC REAGENTS

2-1. Porphyrins Bearing Functional Groups on the Peripheral Alkyl Substituents

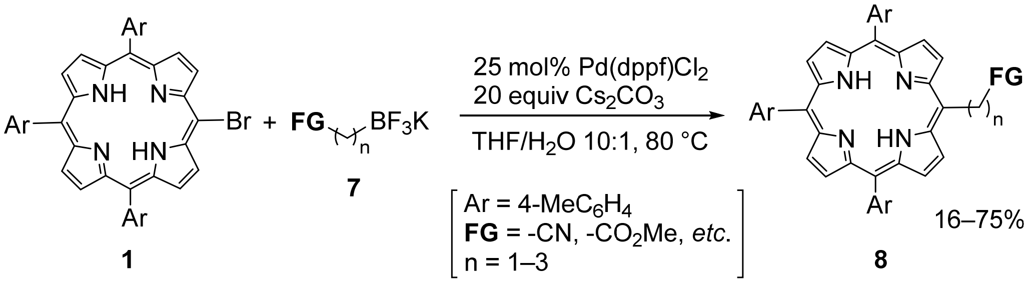
Transition metal-catalyzed cross-couplings of organic halides with organometallic reagents have become standard powerful carbon-carbon bond formation reactions in synthetic organic chemistry.[10] In recent years, a number of different porphyrin derivatives have been constructed using metal-mediated cross-coupling reactions with preformed halogenated porphyrins as the electrophilic coupling partner for the organometallic nucleophiles.[6,11–13] Most studies have focused on couplings with simple aryl and alkenyl organometallic reagents, particularly organoboron[14] and tin[15] reagents. In contrast, very few examples of transition metal-catalyzed cross-coupling reactions with reactive functional group-bearing organometallic reagents for preparing functionalized porphyrins have been reported. Liebeskind and co-workers reported the preparation of 3-cyclobutenyl-1,2-dione-substituted porphyrins **Zn-3** via the Stille reaction of the zinc complex of bromoporphyrin **Zn-1** with *n*-butylstannylcyclobutenedione **2** using a $Pd_2(dba)_3/AsPh_3$ catalyst system (Scheme 2).[16] Odobel and co-workers also reported the Stille reaction of dienyltin acetal **5** with iodoporphyrin zinc complex **Zn-4** to afford the corresponding porphyrin **Zn-6** with dienal substituents at the *meso*-positions (Scheme 3).[17] Most recently, Senge and co-workers used potassium organotrifluoroborates **7** containing ester, nitrile, and amide groups as the nucleophilic coupling partner in the palladium-catalyzed coupling reactions of bromoporphyrins **1** to afford functionalized porphyrins **8** in moderate to good yields (Scheme 4).[18] In addition to organometallic reagents, several carbon-based organic nucleophiles, such as 1,3-diketones and acrylates, can also be used as the coupling partner in transition metal-catalyzed couplings with halogenated porphyrins **9** (Scheme 5).[19]



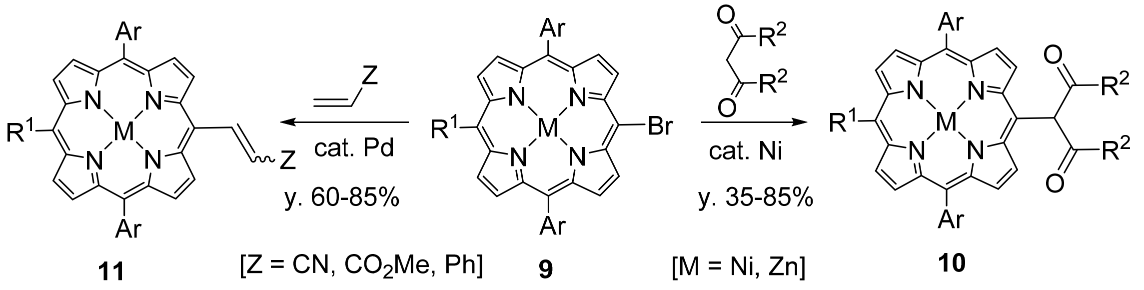
Scheme 2. Palladium-catalyzed Stille coupling of *meso*-bromoporphyrin **Zn-1** with *n*-butylstannylcyclobutenedione **2**



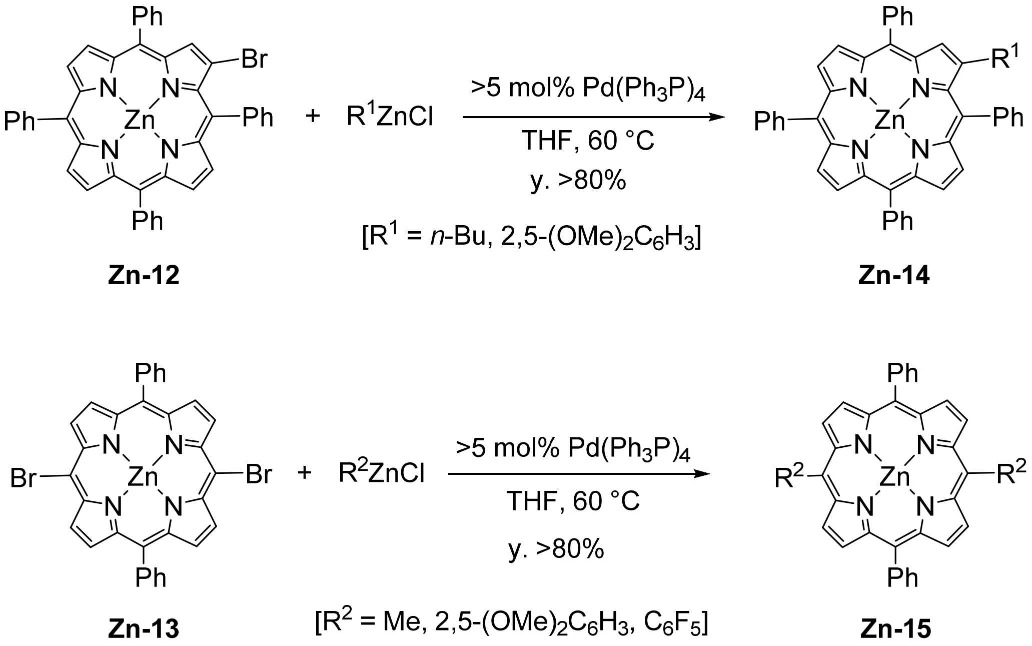
Scheme 3. Palladium-catalyzed Stille coupling of *meso*-iodoporphyrins **Zn-4** with dienyltin acetal **5**



Scheme 4. Palladium-catalyzed coupling reactions of bromoporphyrins **1** with organotrifluoroborates **7**



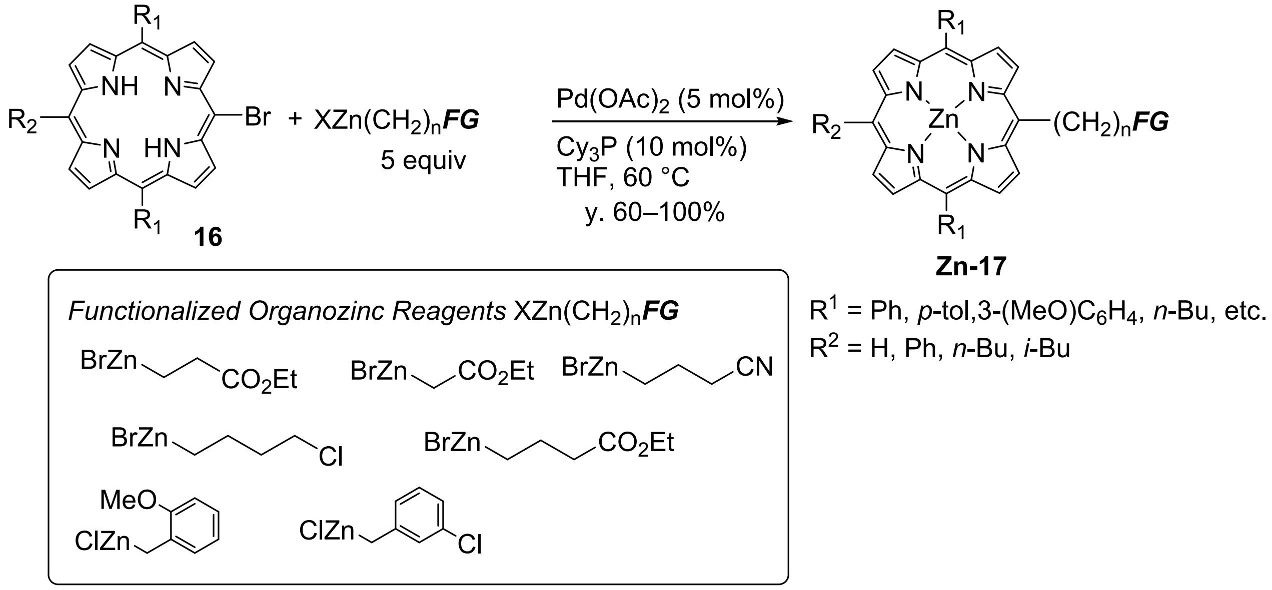
Scheme 5. Palladium and nickel-catalyzed coupling of bromoporphyrins **9** with organic nucleophiles



Scheme 6. Palladium-catalyzed Negishi cross-couplings of bromoporphyrins with simple alkyl and arylorganozinc reagents

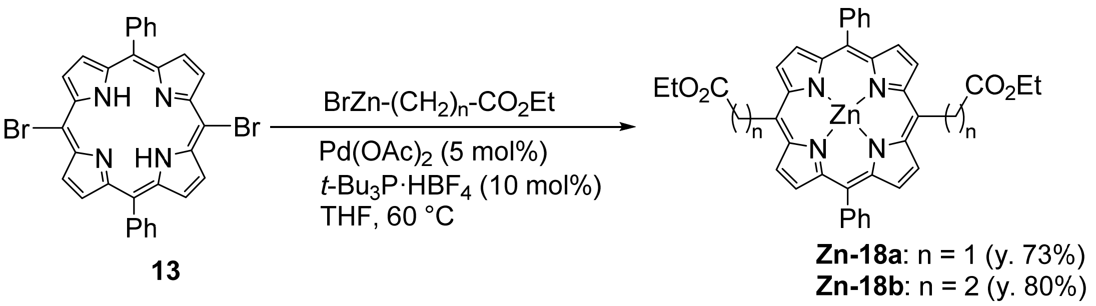
Organozinc reagents show excellent functional group tolerance, and functional group-bearing organozinc reagents allow polyfunctional molecules to be constructed without the need for protection-deprotection strategies or functional group interconversion.[20] Therefore, functionalized porphyrin **A** could be readily prepared by a cross-coupling reaction of preformed halogenated porphyrins and functional group-bearing organozinc reagents. When we began our work in this area in 2004, only Therien and co-workers had published metal-catalyzed cross-couplings of halogenated porphyrins with organozinc reagents. They used simple alkyl and arylzinc reagents, such as MeZnCl, *n*-BuZnCl, $[2,5\text{-}(OMe)_2C_6H_3]ZnCl$, and C_6F_5ZnCl, in Pd-catalyzed Negishi cross-coupling reactions of Zn complexes of β-bromoporphyrin **Zn-12** and *meso*-dibromoporphyrin **Zn-13** (Scheme 6).[21] This was the first example of a Pd-catalyzed Negishi cross-coupling reaction in porphyrin synthesis.

Recently, we developed a practical method for synthesizing functionalized porphyrins **Zn-17** where the *meso*-alkyl substituents contain chemically reactive groups such as -COOR, -Cl, and -CN. The method involves the palladium-catalyzed Negishi cross-coupling of easily available brominated precursors **16** with the corresponding functional group-bearing organozinc reagents (Scheme 7).[22] The reaction is catalyzed by $Pd(OAc)_2/Cy_3P$, and proceeds under mild conditions with a variety of bromoporphyrins, including their Zn(II), Ni(II), and Cu(II) complexes as well as the free bases. The reaction is suitable for a wide range of functional groups and affords the desired products in good yields. Similar reaction conditions with a different phosphine ligand, $t\text{-}Bu_3P{\cdot}HBF_4$, produced bifunctionalized Zn(II) complexes **Zn-18** from the corresponding free base, dibromoporphyrin **13** (Scheme 8).



R^1 = Ph, *p*-tol,3-$(MeO)C_6H_4$, *n*-Bu, etc.
R^2 = H, Ph, *n*-Bu, *i*-Bu

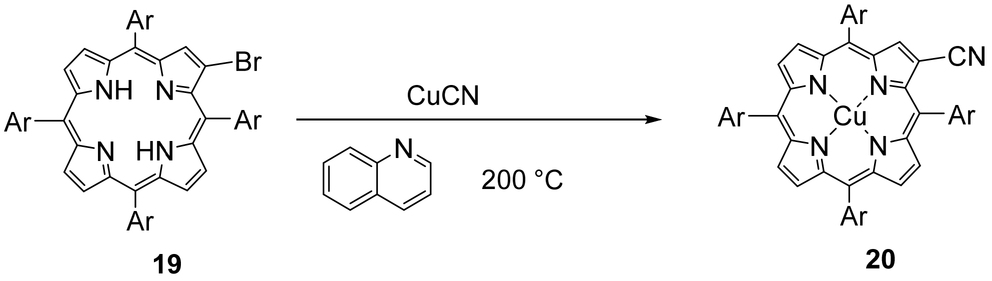
Scheme 7. Palladium-catalyzed coupling of free-base bromoporphyrins **16** with functionalized organozinc reagents



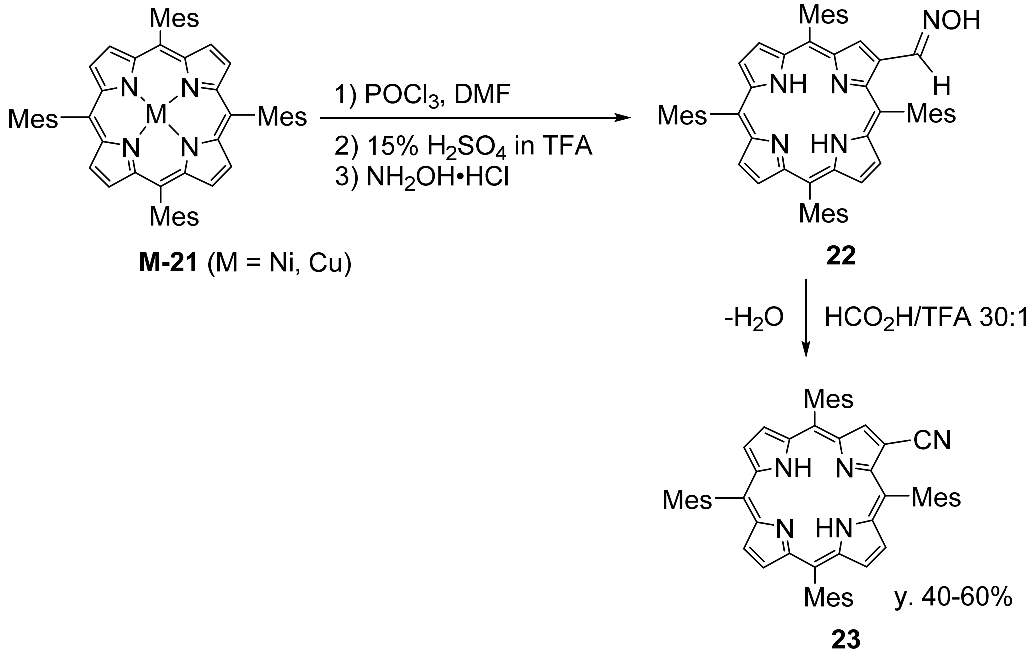
Scheme 8. Palladium-catalyzed bis-functionalization of dibromoporphyrin **13**

2-2. Cyanation of Porphyrins with Cyanoethylzinc Bromide as a Cyanating Agent

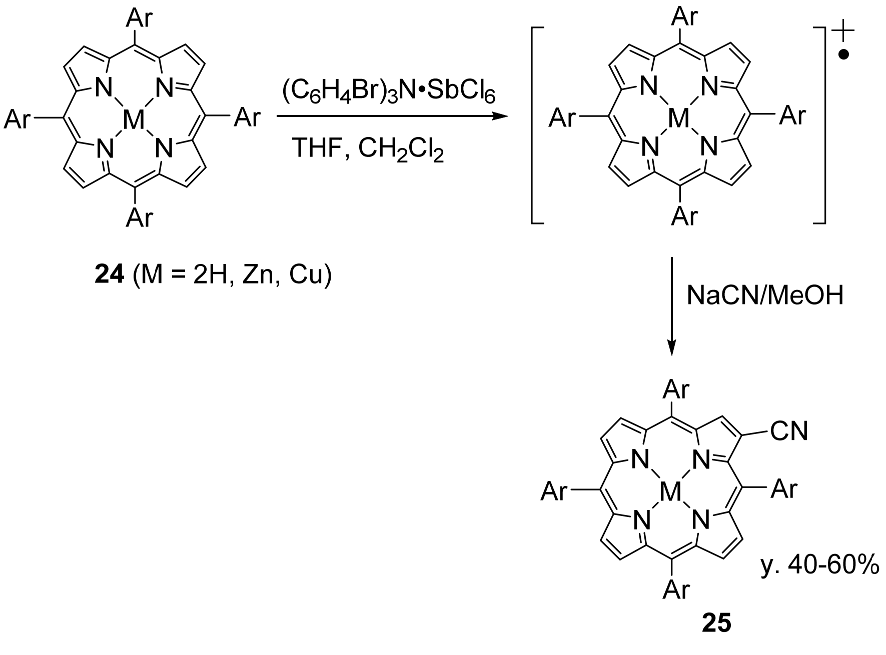
Cyano-substituted porphyrins are among the most useful precursors for porphyrin derivatives because the nitrile group is an intermediate for many important functional groups, such as aldehydes, amines, amides, and carboxylic acid derivatives.[23] The Rosenmund-von Braun cyanation reaction is usually used to access cyano-substituted porphyrins, with stoichiometric copper(I) cyanide as the cyanating agent (Scheme 9).[24] However, the Rosenmund-von Braun cyanation usually requires an elevated reaction temperature to promote the cyanation of non-metallic base porphyrins; the reactions are generally performed in a refluxing solvent such as quinoline above 200 °C. To achieve cyanation at a lower reaction temperature (~100 °C), the substrate porphyrins must be protected with metals, such as Ni(II) and Zn(II). Alternatively, the following three methods have been reported for the cyanation of porphyrins: i) a multi-step synthesis, involving Vilsmeier formylation, oxime formation, and dehydration (Scheme 10);[25] ii) nucleophilic addition of cyanide ions to the π-cation radical of porphyrins (Scheme 11);[26] and iii) Friedel–Crafts cyanation of porphyrins with cyanogen bromide and a Lewis acid (Scheme 12).[27] These reactions involve cationic porphyrin intermediates and are not suitable for the preparation of porphyrins bearing more than one nitrile group, because the introduction of a CN group deactivates the system toward further cyanation.



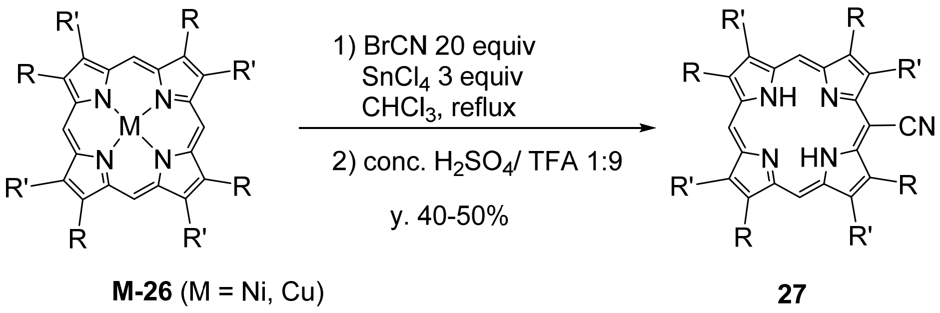
Scheme 9. The Rosenmund-von Braun cyanation of porphyrins



Scheme 10. A multi-step synthesis of cyanoporphyrins

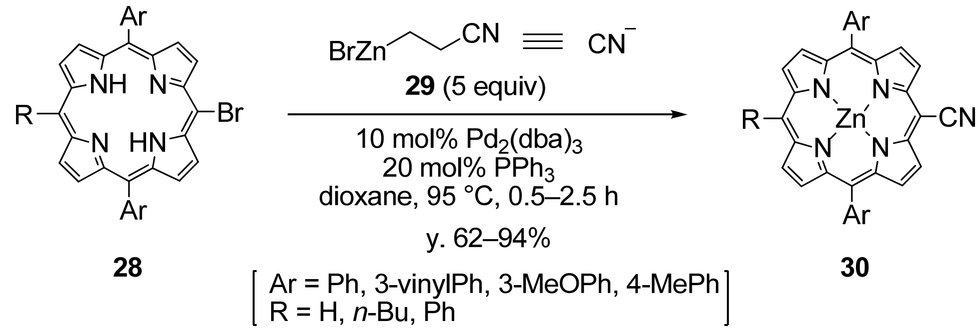


Scheme 11. Preparation of cyanoporpyrins via nucleophilic addition of cyanide ions to the π-cation radical of porphyrins

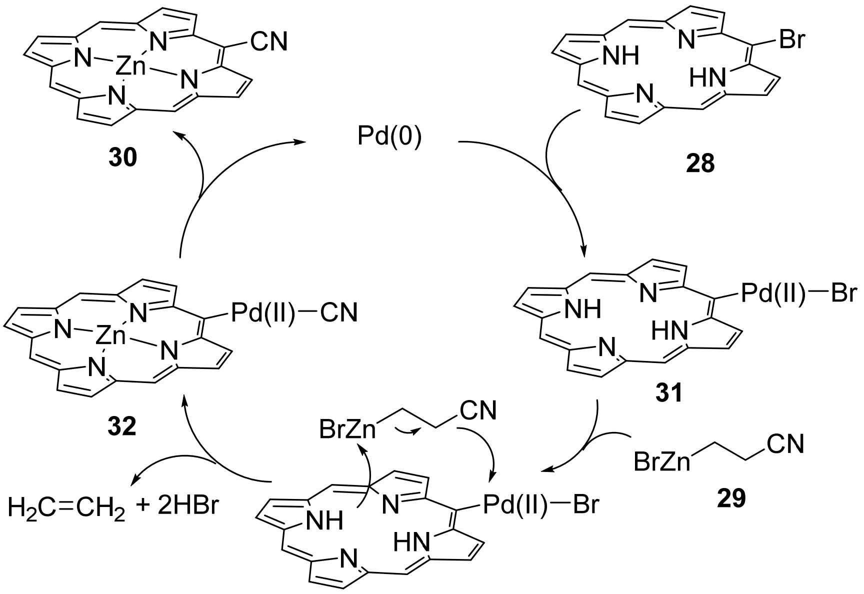


Scheme 12. Friedel–Crafts cyanation of porphyrins

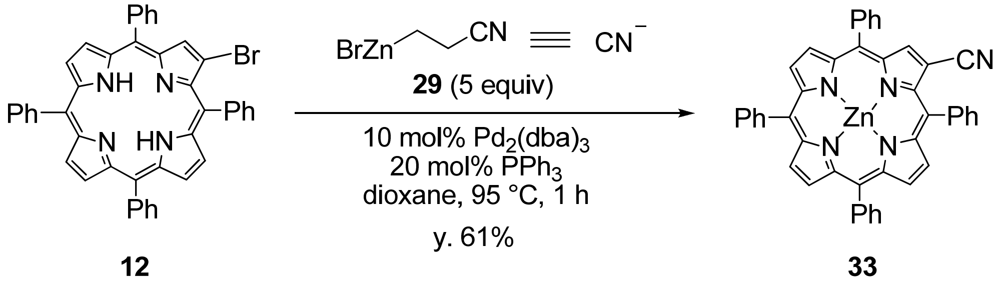
The cyanation of aryl halides catalyzed by palladium and related transition metals[28] offers an alternative route to cyanoporphyrins. Our method was the first to apply palladium-based cyanation to porphyrins. The main problem with the palladium-catalyzed cyanation of aryl halides is catalyst deactivation by an excess of cyanide ions in the reaction mixture. Therefore, new approaches to the development of catalysts and cyanating agents have been sought by numerous research groups.[28] During our work on the palladium-catalyzed Negishi cross-couplings of bromoporphyrins **28** with functional group-bearing organozinc reagents,[22] we unexpectedly found that 2-cyanoethylzinc bromide **29** functions as an effective cyanide ion source for the cyanation of porphyrins (Scheme 13).[29,30] Although details of the catalytic mechanism have not been clarified, the generation of free cyanide ions is thought to occur via a Brood-type fragmentation of zinc reagent **29** (Scheme 14). Thus, the reaction is initiated by the oxidative addition of Pd(0) to the C–Br bond of substrate **28**. Subsequent metal ion insertion from zinc reagent **29** to the porphyrin core simultaneously generates the cyanide ion and ethylene. Finally, reductive elimination of Pd(II) cyanide intermediate **32** gives product **30**. During this process, the molar ratio of the cyanide ions to the catalyst is 1:1, which prevents catalyst deactivation. The catalytic protocol can easily be applied to a variety of bromoporphyrins, such as *meso*-mono-, *meso*-di-, and β-mono-bromo-substituted porphyrins, enabling the synthesis not only of *meso*- and β-mono-cyanated porphyrins (Schemes 13 and 15) but also of *meso*-dicyano-substituted derivatives (Scheme 16).



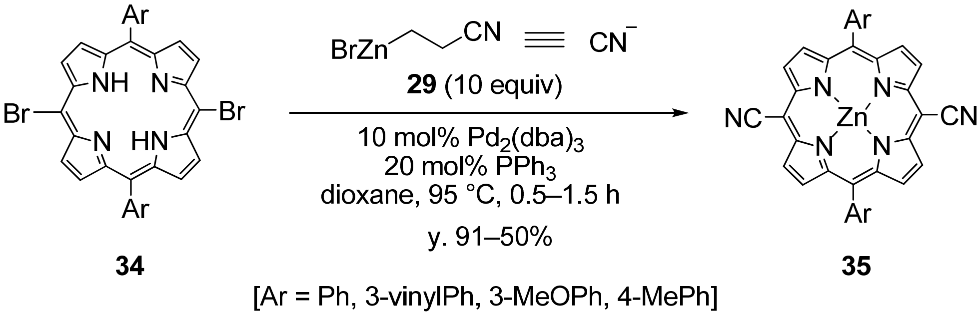
Scheme 13. Catalytic cyanation of porphyrins with cyanoethylzinc bromide



Scheme 14. Plausible reaction mechanism for the catalytic cyanation of porphyrins



Scheme 15. Catalytic preparation of β-cyanoporphyrin **33**



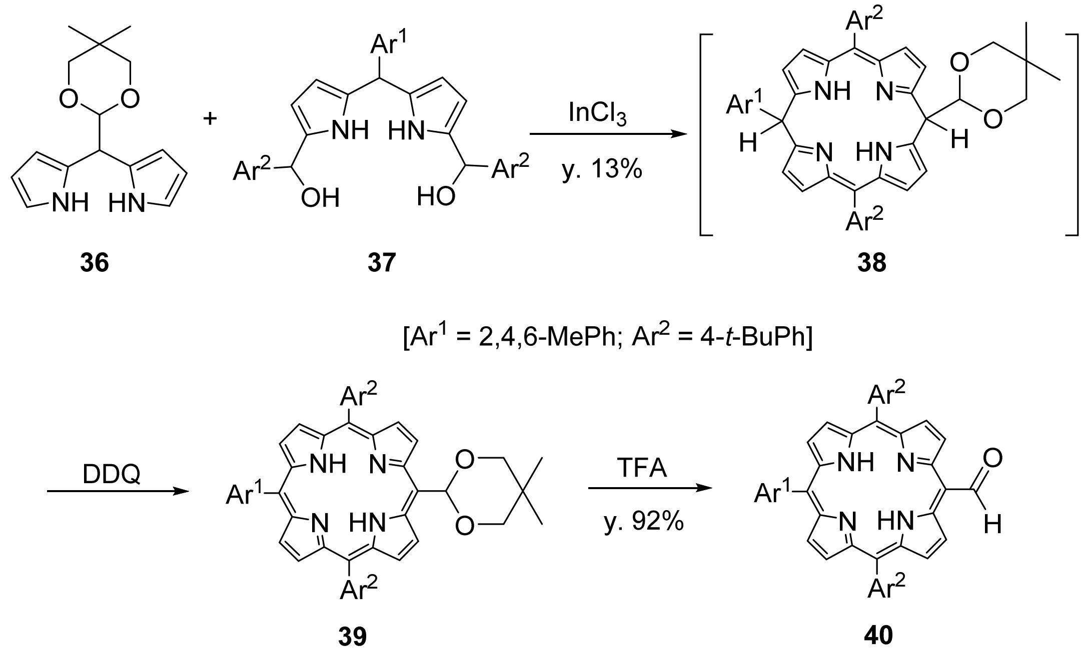
Scheme 16. Catalytic preparation of *meso*-dicyano-substituted porphyrin **35**

3. SILYLMETHYLATION OF PORPHYRINS WITH SILYLMETHYLLITHIUM AND MAGNESIUM REAGENTS

3-1. *meso*-Formyl- and Hydroxymethylporphyrins

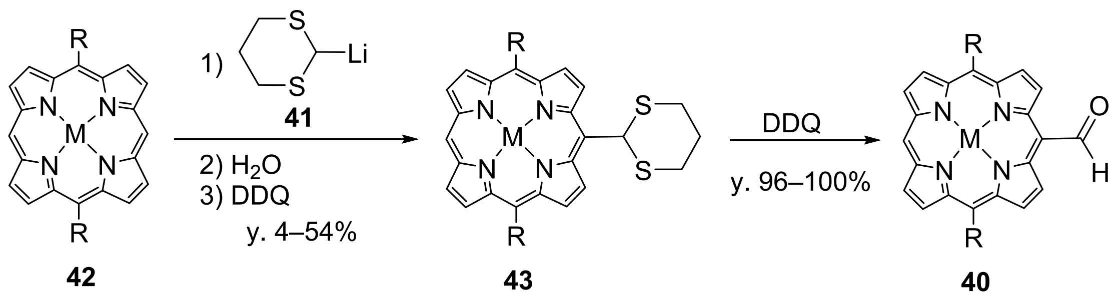
Formylporphyrins are one of the most useful precursors for more complicated porphyrin derivatives.[31,32] The conventional method for introducing a formyl group into a porphyrin core involves the Vilsmeier formylation and related reactions.[25a,33] However, this allows limited control over the site of formylation, and it works well only with Ni(II) and Cu(II) complexes which lack acid-sensitive functional groups because the formylation requires strongly acidic conditions. In addition, the demetallation of the resulting formyl-substituted metal complexes to the corresponding free bases also requires harsh acidic conditions, such as CF_3CO_2H in H_2SO_4.

In 2004, two groups reported significant advances in the preparation of formylporphyrins. Lindsey and co-workers demonstrated that dipyrromethane derivatives **36** bearing acetal substituents as masked formyl groups can be useful precursors for formyl-substituted free-base porphyrins **40**.[32a] The preparation consists of a three-step procedure that involves a Lewis acid-promoted condensation of dipyrromethane derivatives **36** and **37**, followed by oxidation of the resulting dihydroporphyrin intermediate **38** with DDQ to give acetal-substituted porphyrin **39**, and deprotection of its acetal group (Scheme 17). However, low yields of the desired formylporphyrins **40** are a major problem. Another substantial advance in the preparation of formylporphyrins was made by Senge and co-workers.[34] They achieved the preparation of *meso*-formylporphyrins **40** by using a stepwise procedure that involves an S_NAr reaction of 2-lithio-1,3-dithiane **41** with 5,15-disubstituted porphyrins **42** to generate the corresponding *meso*-(1,3-dithianyl)porphyrin **43** and the subsequent oxidative conversion of the dithianyl moiety into the CHO group (Scheme 18). This approach can be used under basic conditions to prepare *meso*-formylated Ni(II) complexes **Ni-40** in good yields. However, the S_NAr reaction of lithium reagent **41** with free-base porphyrins produced the free-base formylporphyrins **2H-40** in only low to moderate yields.



[Ar^1 = 2,4,6-MePh; Ar^2 = 4-*t*-BuPh]

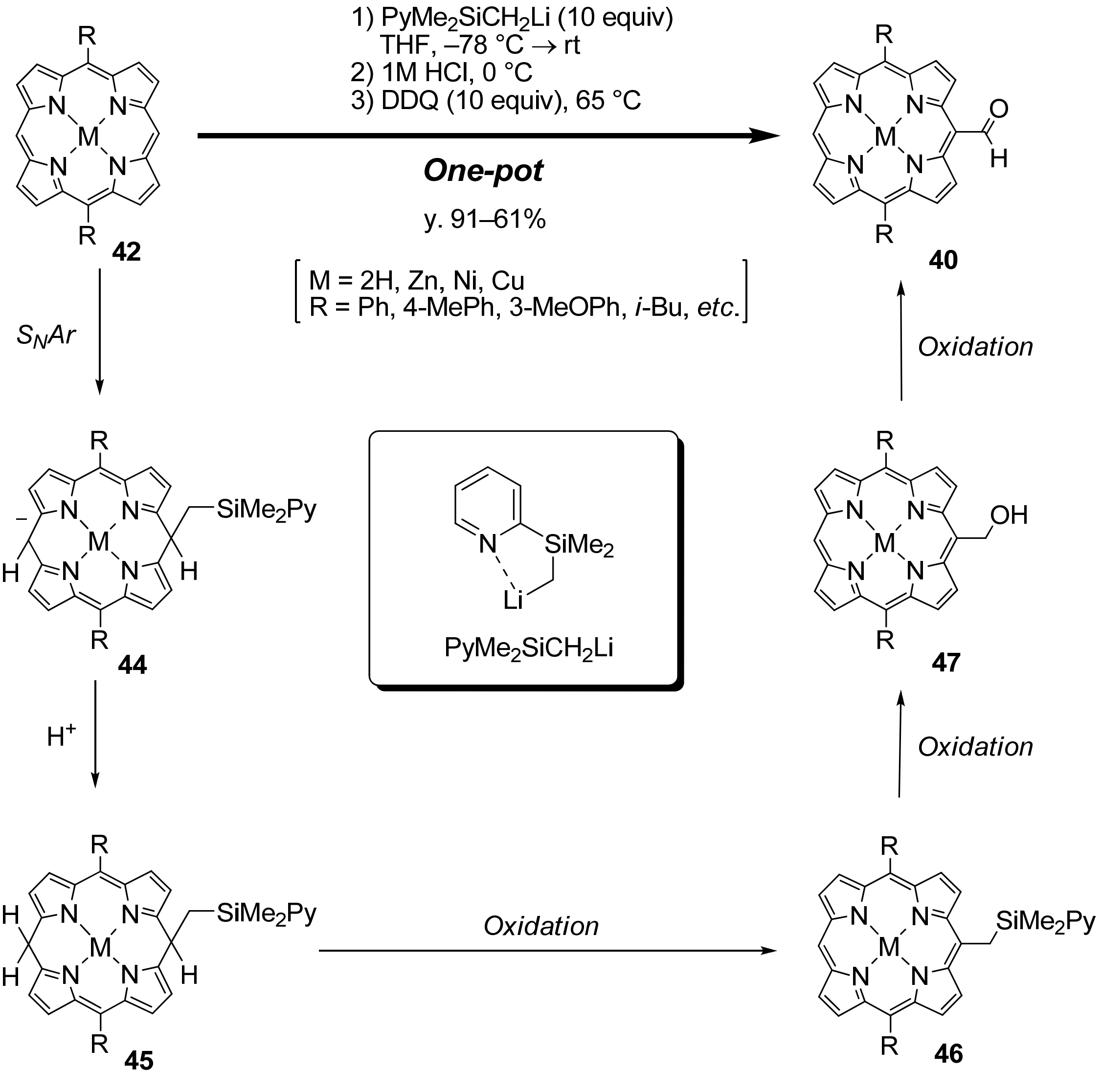
Scheme 17. Preparation of formylporphyrins via the condensation of dipyrromethane derivartives



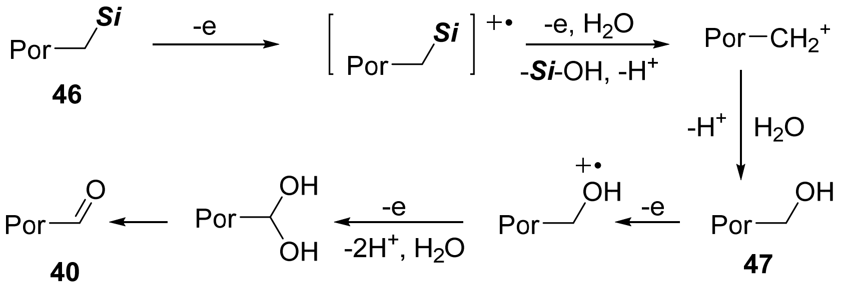
[M = 2H, Ni; R = Ph, 3-MeOPh, *i*-Bu]

Scheme 18. Synthesis of formylporphyrins **40** via an S$_N$Ar reaction with 2-lithio-1,3-dithiane **41**

We used [bis(2-pyridyldimethylsilyl)methyl]lithium (PyMe$_2$SiCH$_2$Li)[35] instead of 2-lithio-1,3-dithiane as an organolithium reagent for the *meso*-formylation of 5,15-disubstituted porphyrins **42** based on the S$_N$Ar strategy.[36–38] Scheme 19 shows the simple one-pot three-step formylation of porphyrin **42** using PyMe$_2$SiCH$_2$Li as an organolithium reagent. The formylation involves the S$_N$Ar reaction of 5,15-disubstituted porphyrin **42** with PyMe$_2$SiCH$_2$Li followed by the hydrolysis of the resulting anionic species **44** and successive oxidation reactions of dihydroporphyrin **45** and silylmethyl- and hydroxymethyl-substituted porphyrin **46** and **47**, respectively. Although the oxidation mechanism for silylmethylporphyrin **46** and hydroxymethylporphyrin **47** is not clear, we suggest the mechanism shown in Scheme 20. Each oxidation reaction is initiated by a single-electron transfer[39,40] from the respective compounds (**46** and **47**) to DDQ, which is a well-known electron acceptor.[41,42] The one-pot protocol is suitable for a range of 5,15-diaryl- and 5,15-dialkyl-substituted free-base porphyrins as well as their metal complexes, providing a new series of porphyrins with a formyl group at the *meso* position in good to high yields (Scheme 19).

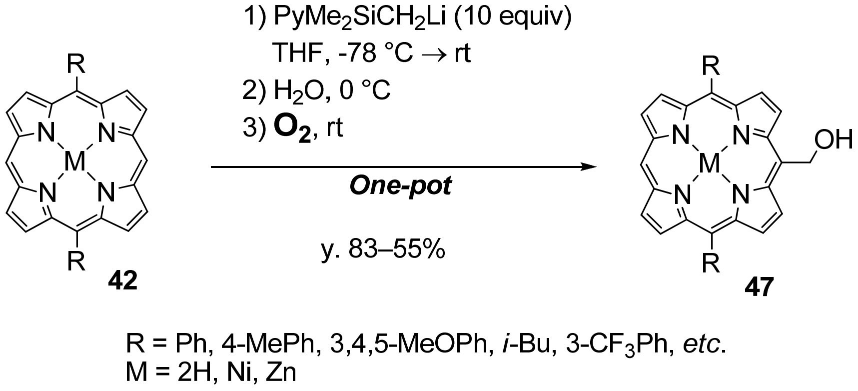


Scheme 19. Direct one-pot conversion of 5,15-disubstituted porphyrins **42** to *meso*-formylporphyrins **40** via an S_NAr reaction with $PyMe_2SiCH_2Li$

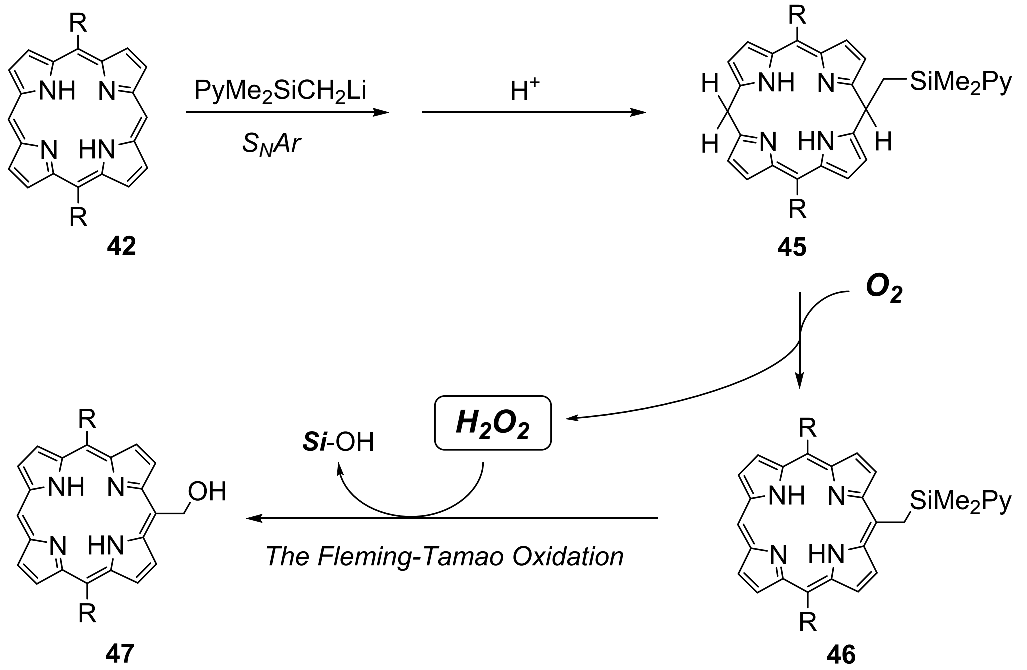


Scheme 20. Plausible oxidation mechanism for silylmethylporphyrin **46** and hydroxymethylporphyrin **47**

Furthermore, changing the oxidizing agent from DDQ to molecular oxygen produced *meso*-hydroxymethylporphyrin **47** in good to high yields, without further oxidation of the hydroxymethyl functionality to an aldehyde (Scheme 21).[43] Using molecular oxygen as an oxidizing agent allows a wide variety of substrates to be used, including 5,15-dialkyl- and 5,15-diaryl-substituted free-base porphyrins and their metal complexes, to afford the corresponding *meso*-hydroxymethyl-porphyrins in good yields. A plausible mechanism for the hydroxymethylation is shown in Scheme 22. The oxidative conversion of intermediate **45** to *meso*-hydroxymethylporphyrin **47** proceeds by a Fleming-Tamao oxidation mechanism,[44] in which hydrogen peroxide, generated in situ from the aerobic oxidation of dihydroporphyrin **45**, oxidizes the silyl group to a hydroxyl group.



Scheme 21. Direct *meso*-hydroxymethylation of 5,15-diphenylporphyrin **42** by an S_NAr reaction with $PyMe_2SiCH_2Li$, followed by hydrolysis and aerobic oxidation

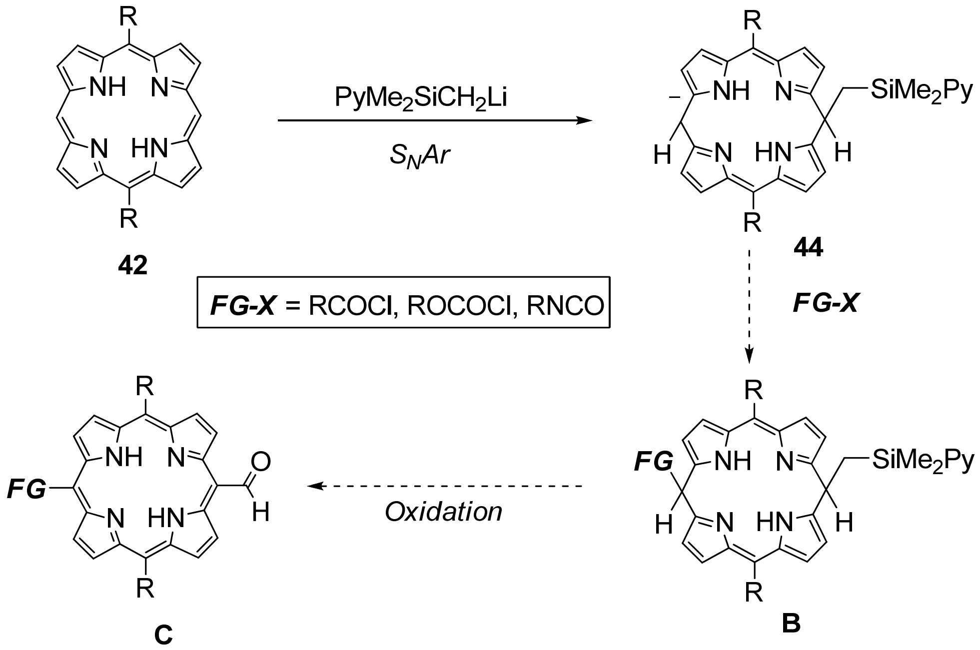


Scheme 22. Plausible reaction pathway for the one-pot *meso*-hydroxymethylation of 5,15-disubstituted porphyrins

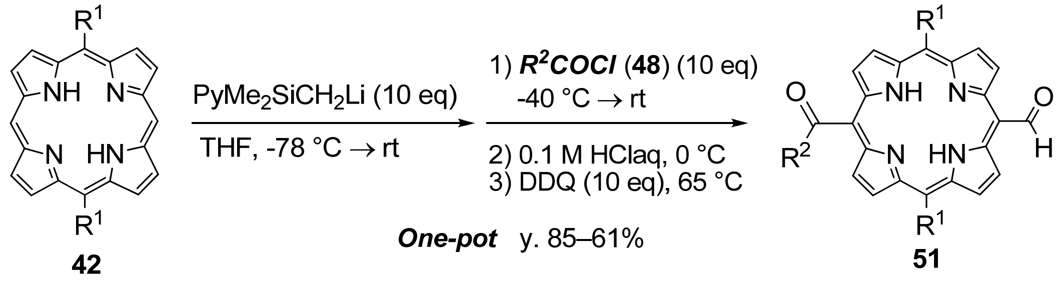
3-2. Unsymmetrical Bifunctionalization of 5,15-Disubstituted Porphyrins

Unsymmetrical porphyrins bearing two distinct reactive functional groups at the *meso* positions are valuable building blocks for more complex porphyrin systems. Each functional group directly attached to the porphyrin core can be replaced with other functionalities. We published the first direct preparation of unsymmetrical porphyrins with two different reactive functional groups at the *meso* positions.[45] The formylation of porphyrins with $PyMe_2SiCH_2Li$ proceeds through the generation of anionic species **44** (Scheme 19).[36,43] Thus, we envisaged that anionic intermediate **44** could be trapped by an electrophile (FG-X), such as an acyl chloride, to form unsymmetrical porphyrin **C** with a formyl group and other chemically reactive functionalities (Scheme 23).

Thus, we examined the unsymmetrical bifunctionalization of 5,15-disubstituted porphyrins **42** with a one-pot procedure, involving an S_NAr reaction with $PyMe_2SiCH_2Li$ followed by trapping the resulting anion with several electrophiles, such as acyl chlorides **48**, chloroformates **49**, and isocyanates **50**, and then oxidation with DDQ.[46] The one-pot sequential reaction using acyl chlorides as an electrophile proceeded smoothly, enabling the direct conversion of **42** into the desired *meso*-acyl-substituted formylporphyrins **51** in good to high yields (Scheme 24). Similarly, chloroformates produced *meso*-alkoxycarbonyl-substituted formylporphyrins **52** (Scheme 25), and isocyanates produced *meso*-carbamoyl-substituted formylporphyrins **53** (Scheme 26).

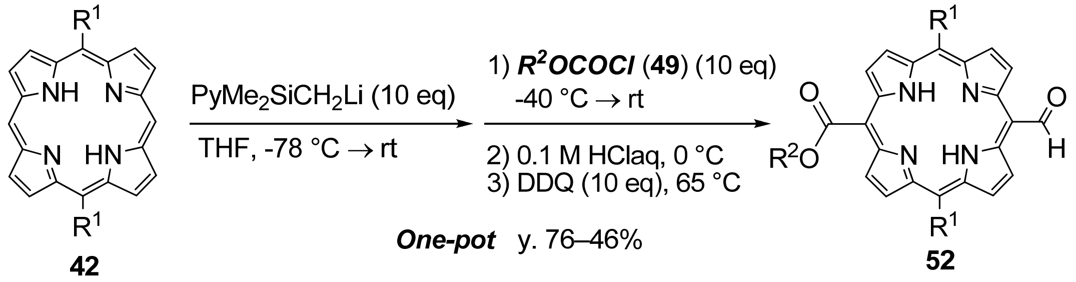


Scheme 23. Our proposed direct method for the unsymmetrical bifunctionalization of porphyrins



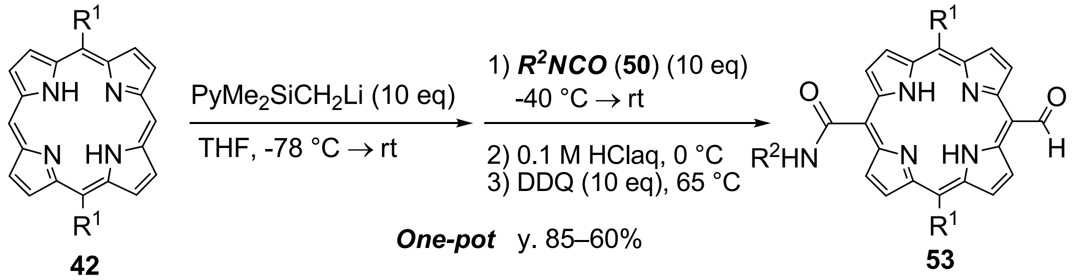
R^1 = Ph, 4-MePh, 3-MeOPh, 3-CF_3Ph, *i*-Bu
R^2 = Ph, 4-MeOPh, 4-CF_3Ph, Me, *i*-Pr

Scheme 24. One-pot preparation of *meso*-acyl-substituted formylporphyrins **51** using acyl chloride **48** as the electrophile



R^1 = Ph, 4-MePh, 3-MeOPh, 3-CF_3Ph, *i*-Bu
R^2 = Me, *i*-Pr, CH_2Ph

Scheme 25. One-pot preparation of *meso*-alkoxycarbonyl-substituted formylporphyrins **52** using chloroformates **49** as the electrophile

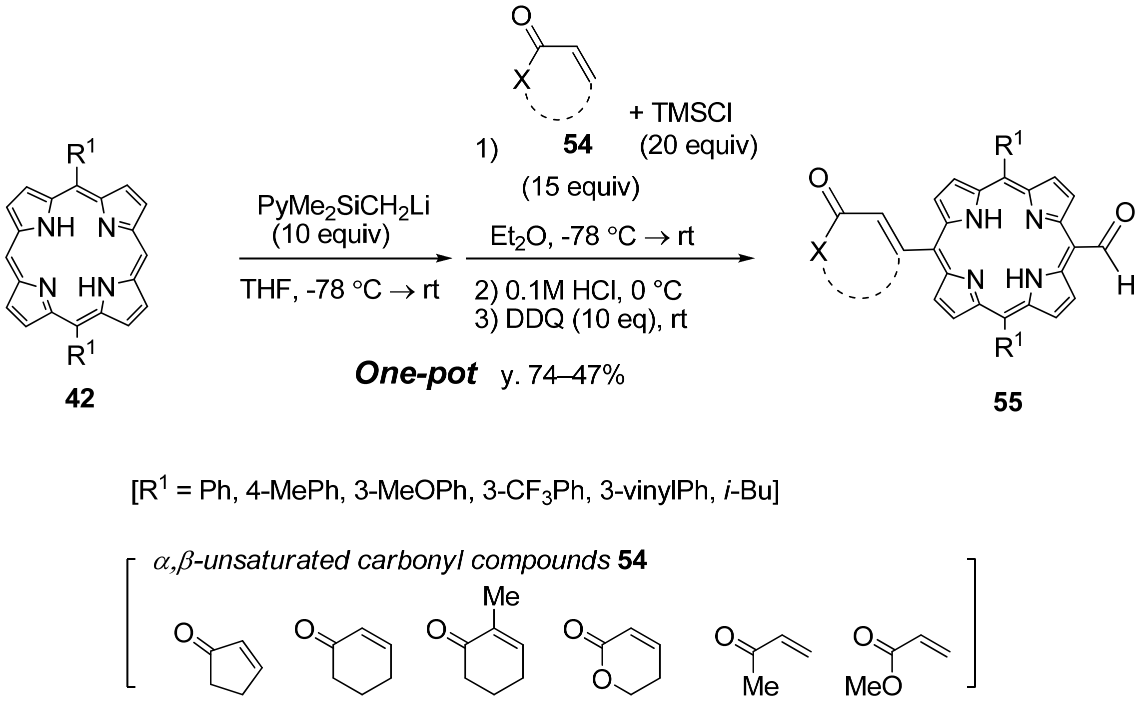


R^1 = Ph, 4-MePh, 3-MeOPh, 3-CF_3Ph, *i*-Bu
R^2 = Ph, 4-MeOPh, 4-BrPh, Et, *i*-Pr, *c*-C_6H_{11}

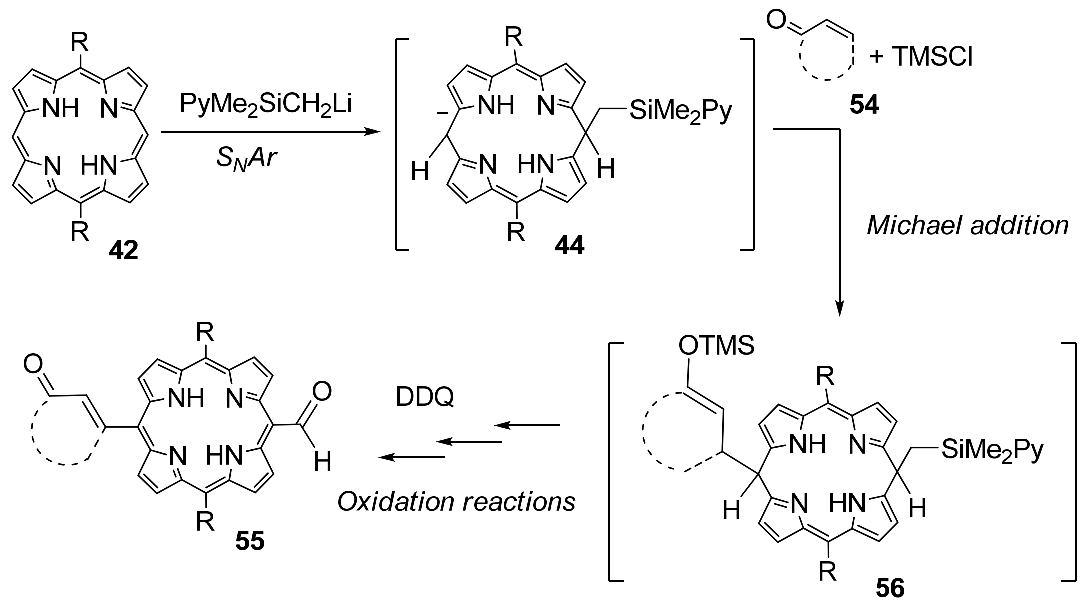
Scheme 26. One-pot preparation of *meso*-carbamoyl-substituted formylporphyrins **53** using isocyanates **50** as the electrophile

We used α,β-unsaturated carbonyl compounds **54** as an electrophile to introduce an activated alkenyl substituent and formyl group directly onto the *meso* carbons of free-base 5,15-disubstituted porphyrins **42** (Scheme 27).[47] The process involves a sequential S_NAr reaction of free-base 5,15-disubstituted porphyrins with $PyMe_2SiCH_2Li$, followed by a conjugate addition to an enone or alkenoate in the presence of TMSCl, and then oxidation with DDQ. Crucially, formal direct couplings between enones or alkenoates and porphyrins at the *meso* positions take place during the reaction and provide *meso*-activated alkenyl-substituted *meso*-formylporphyrins **55**, which has never been achieved by previous porphyrin functionalization methods. This simple one-pot procedure requires mild conditions, is suitable for a wide range of 5,15-diaryl- and 5,15-dialkyl-substituted porphyrins, and works for cyclic and acyclic alkenoates and enones. It allows the direct conversion of free-base 5,15-disubstituted porphyrins to the corresponding *meso*-activated alkenyl-substituted *meso*-formylporphyrins **55** in good yields.

We suggest that the reaction proceeds via porphodimethene derivative **56**, which bears a $PyMe_2SiCH_2$ group and an enol silyl ether moiety on the sp^3 carbons of the ring (Scheme 28). Thus, anionic intermediate **44**, generated from the S_NAr reaction of porphyrin **42** with $PyMe_2SiCH_2Li$, undergoes conjugate addition to α,β-unsaturated carbonyl compound **54** in the presence of TMSCl to give porphodimethene derivative **56**. The silylmethyl group, enol silyl ether moiety, and porphodimethene ring on **56** are oxidized with DDQ to a formyl group, an enone or alkenoate moiety, and the porphyrin core, respectively, resulting in final product **55**. However, the precise order of these oxidation reactions is not yet clear.[48]



Scheme 27. One-pot direct conversion of 5,15-disubstituted porphyrins **42** to *meso* activated alkenyl-substituted *meso*-formylporphyrins **55** using α,β-unsaturated carbonyl compounds **54** as electrophiles



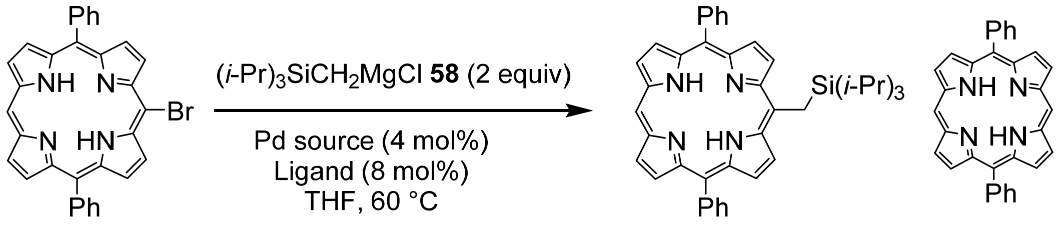
Scheme 28. Plausible reaction mechanism for the one-pot direct conversion of 5,15-disubstituted porphyrins to the corresponding *meso*-activated alkenyl-substituted *meso*-formylporphyrins

3-3. Silylmethylporphyrins: a Multipurpose Synthon for Fabrication of Porphyrins

Silylmethyl-substituted porphyrin, which is proposed as a reaction intermediate **46** in the formylation of porphyrins via the S_NAr reaction with silylmethylithium reagents (Scheme 19),[36] could be used as a multipurpose synthon for fabricating porphyrin derivatives by converting the silylmethyl groups. Silylmethyl groups are very versatile and undergo many transformations to a wide variety of functional groups, including hydroxymethyl, formyl, and alkenyl groups.[49] However, the intermediate silylmethylporphyrins **46** could not be isolated owing to their instability under oxidation conditions. Even using molecular oxygen instead of DDQ did not suppress the overoxidation of the silylmethylporphyrins **46**, and hydroxymethyl-substituted porphyrins **47** were obtained as the sole isolable products (Schemes 21 and 22).[36,43]

Recently, we have developed a facile, efficient method for preparing silylmethyl-substituted porphyrins using the palladium-catalyzed Kumada cross-coupling reaction of bromoporphyrins with silylmethyl Grignard reagents.[50,51] Table 1 shows that the success of this reaction relies on the use of $Pd_2(dba)_3$ as the catalyst and that $Ph_2P(O)H$ was the only effective ligand (entry 11).[52] The use of well-defined palladium tertiary phosphine complexes, either generated in situ or preformed, was ineffective in the coupling reaction, and afforded low yields of the silylmethyl-substituted diphenylporphyrin **59** and the dehalogenated product **60**. The palladium *N*-heterocyclic carbene complex, PEPPSI, which is often an effective catalyst in the Kumada reaction,[53] also produced low yields (entry 3). The Kumada coupling reaction with a $Pd_2(dba)_3/Ph_2P(O)H$ catalyst is compatible with many *meso*-mono-, *meso*-di-, and β-bromo-substituted porphyrins and a variety of silylmethyl magnesium reagents, and generally achieves good yields (Schemes 29–31).

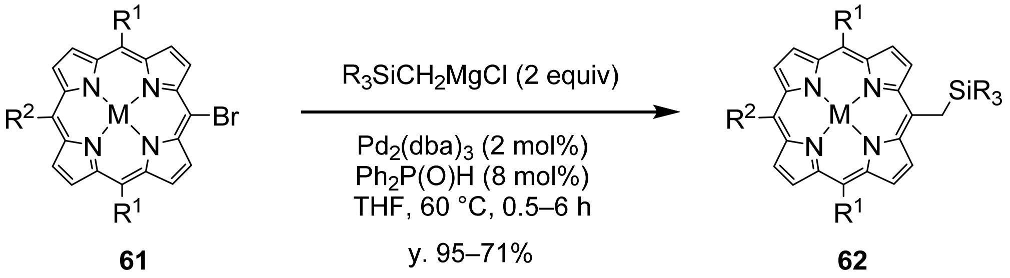
Table 1. Palladium-catalyzed screening for Kumada cross-coupling of bromoporphyrin **57** with silylmethylmagnesium reagent **58**



57 **59** **60**

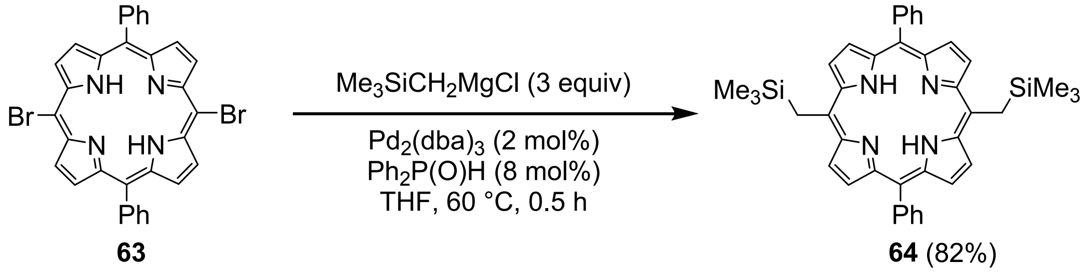
Entry	Pd source	Ligand	*t* (h)	Yield (%)[a] of **59**	Yield (%)[a] of **60**
1	$Pd(PCy_3)_2Cl_2$	-	8	26	70
2	$Pd(P(t\text{-}Bu)_3)_2$	-	8	18	73
3	PEPPSI[b]	-	4	22	76
4	$Pd(OAc)_2$	*rac*-BINAP[d]	12	0	>99
5		SPhos[e]	12	0	98
6		$BPPCy_2$[f]	12	trace	94
7		$Ph_2P(O)H$	10	43	53
8	$Pd_2(dba)_3$[c]	*rac*-BINAP	12	0	>99
9		SPhos	12	0	>99
10		$BPPCy_2$	10	16	79
11		$Ph_2P(O)H$	6	87	8

[a] Isolated yield. [b] PEPPSI: [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride. [c] 2 mol % $Pd_2(dba)_3$ was used. [d] BINAP: 2,2'-bis(diphenyl-phosphino)-1,1'-binaptharene. [e] SPhos: 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl. [f] $BPPCy_2$: 2-(di-cyclohexylphosphino)biphenyl

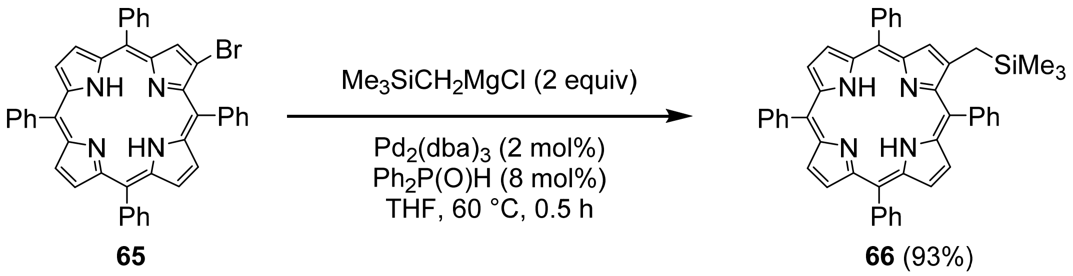


[R_3Si = (i-Pr)$_3$Si, Me_3Si, Et_3Si, $PhMe_2Si$, Ph_3Si, ($PhCH_2$)Me_2Si, (i-PrO)Me_2Si, (Me_3Si)$_2$CHSi; R^1 = Ph, 4-MePh, 3-(CH_2=CH)Ph, 4-(i-$Pr_3SiC{\equiv}C$)Ph, 2,4,6-Me_3Ph, 3-MeOPh, n-Bu; R^2 = H, Ph; M = 2H, Mg, Zn, Ni]

Scheme 29. Palladium-catalyzed cross-coupling of *meso*-bromoporrhyn **62** with silylmethyl Grignard reagents

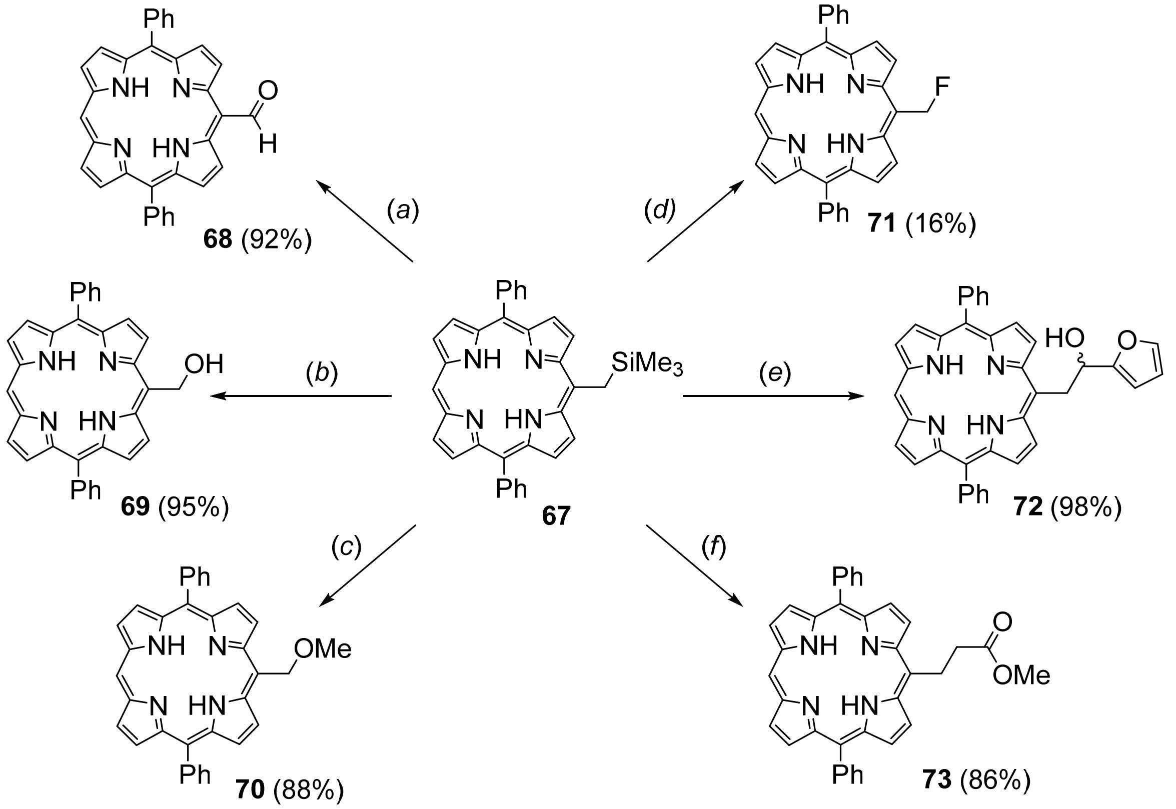


Scheme 30. Preparation of bis(trimethylsilylmethyl)porphyrin **64**



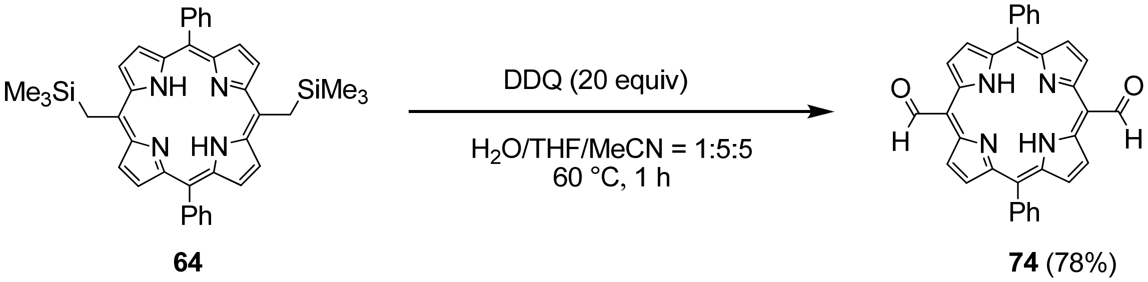
Scheme 31. Preparation of β-silylmethyl-substituted porphyrin **66**

The resulting silylmethyl-substituted porphyrin **67** could be used as a multipurpose synthon for fabricating porphyrin derivatives through a variety of transformations of the silylmethyl groups, including the DDQ-promoted oxidative conversion to CHO, CH_2OH, CH_2OMe, and CH_2F functionalities,[54] and the fluoride ion-mediated desilylative introduction of carbon-carbon single bonds[55] (Scheme 32). The DDQ-mediated formylation could also be used for the conversion of the *meso*-di- and β-silylmethylporphyrins **64** and **66** to the corresponding formyl derivatives **74** and **75** (Schemes 33 and 34). To our knowledge, these results are the first examples of direct, regioselective preparation of *meso*-di- and β-formyl-substituted free-base porphyrins under mild conditions. The installation of a carbon-carbon double bond at the carbon α to the porphyrin core via the Peterson olefination, which is one of the most valuable transformations in organosilicon chemistry, was achieved using bis(trimethylsilyl)methyl-substituted porphyrin **76** as the substrate. The reaction of porphyrin **76** with aldehyde **77** proceeded smoothly in the presence of TBAF to furnish Peterson olefination product **78** (Scheme 35).[56]

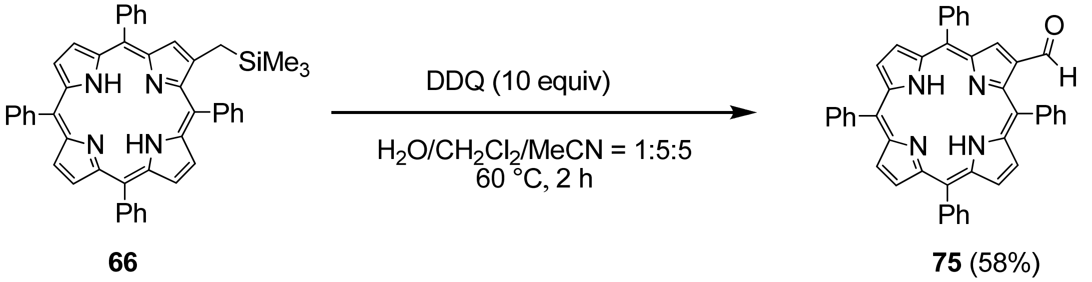


Reagents and conditions: (a) **DDQ** (10 equiv), $H_2O/THF/CH_3CN$ = 1:5:5, 60 °C, 1 h; (b) **DDQ** (3 equiv), H_2O/THF = 1:10, 25 °C, 0.5 h; (c) **DDQ** (3 equiv), MeOH/dioxane = 1:10, 25 °C, 12 h; (d) **DDQ** (5 equiv), DAST (1.5 equiv), CH_2Cl_2, 25 °C, 3 h; (e) **TBAF** (1 equiv), furfural (10 equiv), THF, 4ÅMS, 25 °C, 5 min; (f) **TBAF** (1 equiv), $BrCH_2CO_2Me$ (10 equiv), THF, 4ÅMS, 25 °C, 5 min.

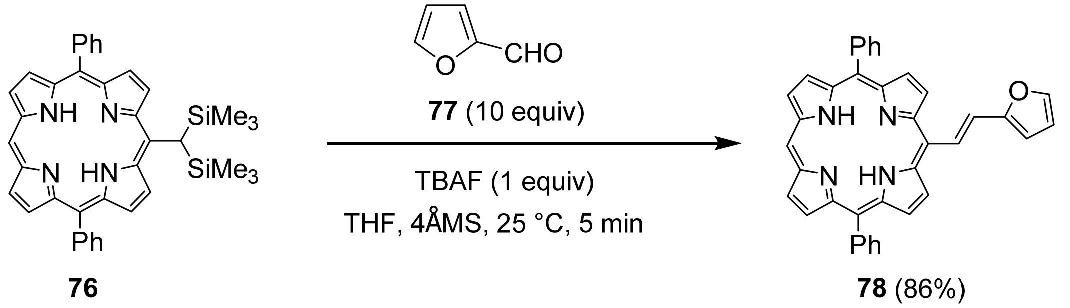
Scheme 32. Transformations of the silylmethyl group on porphyrin **67**



Scheme 33. Preparation of *meso*-diformylporphyrin **74**



Scheme 34. Preparation of β-formylporphyrin **75**



Scheme 35. Desilylative Peterson olefination of bis(trimethylsilyl)methyl-substituted porphyrin **76**

4. CONCLUSION

In this review, we have described our recent efforts toward developing concise, straightforward routes to functionalized porphyrins with chemically reactive functional groups such as esters, amides, nitriles, and formyl groups on the porphyrin core and the peripheral substituents. We have directly introduced functional groups to the porphyrin core via palladium-catalyzed cross-coupling reactions with organozinc reagents. Furthermore, we developed a stepwise approach involving the silylmethylation of porphyrins with silylmethyllithium and magnesium reagents, followed by converting the silylmethyl groups to other functional groups. We expect these functionalized porphyrins will be useful building blocks for the total synthesis of more complex porphyrin compounds, which will allow the step economy of the routes to be optimized. Furthermore, we hope the results described here will aid the design and construction of new porphyrin systems for potential applications in areas such as catalysis, medicine, and molecular recognition and sensing. We are currently conducting further studies, the results of which will be reported in due course.

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Toshikatsu Takanami was born in Miyagi, Japan, in 1957. He received his Ph.D. degree from Osaka University in 1990. He started his academic carrier at Meiji Pharmaceutical University as a research asssociate in 1986, and was promoted to associate professor in 2004. He has been a professor at Meiji Pharmaceutical University since 2009. His research interest is in the area of porphyrin chemistry toward synthetic organic chemistry, organoheteroatom chemistry, and electroorganic synthesis.