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Directed Magnesiation of Polyhaloaromatics using the Tetramethylpiperidylmagnesium Reagents $TMP_2Mg\cdot 2LiCl$ and $TMPMgCl\cdot LiCl$

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Abstract: A convenient and efficient functionalization of polyhaloaromatics *via* regioselective magnesiation has been developed. Starting from simple, inexpensive but structurally challenging arenes, metallation by magnesium amide bases was achieved under mild conditions. The desired Grignard reagents were stable towards aryne formation, were obtained in good yields within short reaction times and could be reacted with a variety of typical electrophiles, providing attractive, functionalized building blocks in good to excellent yields. As an application we have prepared the antimicrobial natural product 2,6-dichloro-3-phenethylphenol isolated from the New Zealand liverwort *Riccardia marginata*. This synthesis involves a mixed bimetallic compound prepared *via* metallation of a phenylboronic acid pinacol ester derivative and subsequent selective cross-coupling.

Keywords: acylation; cross-coupling; Grignard reactions; metallation; natural products; synthetic methods

Introduction

The metallation of aromatics is a convenient approach to the functionalization of these unsaturated scaffolds.[1] Besides the conventional lithium bases, such as LDA,[2] TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl),[2] BuLi,[2] the Schlosser base (LIC-KOR = BuLi·*t*-BuOK)[3] or the Fort base (BuLi–LiDMAE; LiDMAE = lithium 2-*N*,*N*-dimethylaminoethoxide),[4] a range of bimetallic ate-bases has been introduced by Kondo, Mulvey, Mongin and Uchiyama.[5] Although the lithiation of polyhalogenated benzenes **1** has been well studied,[6] the practicability of this method is very limited by the stability of the resulting *ortho*-halophenyllithium of type **2a**. These compounds decompose usually between −90 °C and −40 °C depending on the nature of the halogen leading to the corresponding arynes[7] **3**, which undergo further reactions. The corresponding magnesium derivatives of type **2b** display a much better stability and undergo aryne formation only at higher temperatures (50–80 °C). Actually, they have to be heated for the extensive formation of arynes[8] (Figure 1).

Especially polyfunctional aryl halides are of high importance as agrochemicals, pharmaceuticals and building blocks,[9] for example, diclofenac or propanil. Also these halogenated aromatics are found in many natural products. Thus, for example, the chlorinated bibenzylphenol **4** isolated from the New Zealand liverwort *Riccardia marginata*[10] displays antimicrobial activity against *Bacillus subtilus, Candida albicans* and *Trichophyton mentagrophytes.*

Recently, we have reported the preparation of highly reactive magnesium TMP amides such as $TMP_2Mg\cdot 2LiCl$ (**5**)[11] and $TMPMgCl\cdot LiCl$ (**6**)[12] which proved able to magnesiate various aromatics under mild conditions.

Herein, we wish to report the use of magnesium amides **5** and **6** for the magnesiation of various polyhaloaromatics and subsequent reactions with electrophiles leading to polyfunctional halogenated arenes. Furthermore, we demonstrate the utilility of our procedure by preparing the antimicrobial natural product **4** in 4 steps and 59% overall yield.

Results and Discussion

We have first examined the magnesiation of all three isomers of dichlorobenzene[13] (**7**–**9**). With these sub-

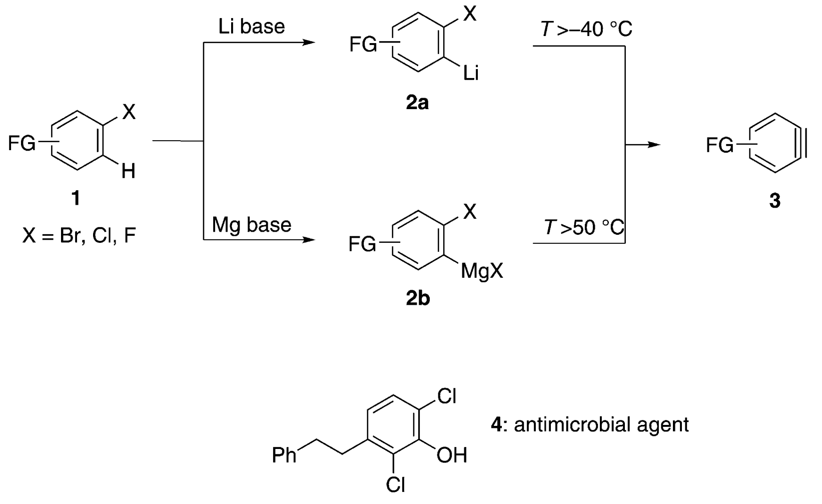
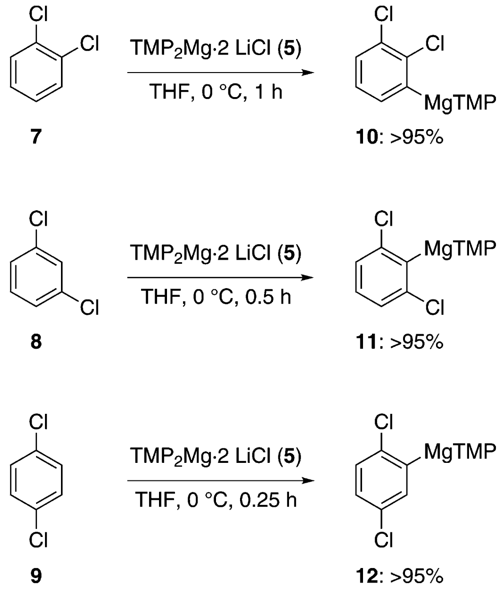


Figure 1.

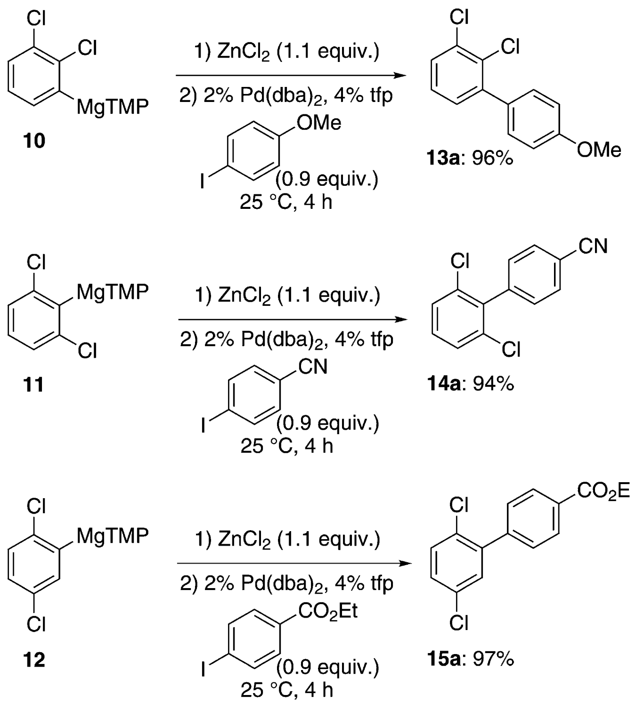
strates a regioselective magnesiation using TMP$_2$Mg·2LiCl (**5**) is achieved at 0°C within 15–60 min, leading to the expected *Grignard* reagents **10–12** in >95% yield. Less active TMP bases, such as TMP$_2$Mn·2MgCl$_2$·4LiCl,[14] TMP$_2$Zn·2MgCl$_2$·2LiCl[15] or TMPZnCl·LiCl[16] proved not to be suitable for such metallations. Side reactions like Wurtz coupling,[17] halogen dance[18] or elimination of HCl[19] are not observed in the course of the magnesiation (Scheme 1).

These Grignard reagents can be transmetallated to the corresponding organozinc reagents which undergo at room temperature readily a Negishi cross-coupling[20] using 2 mol% Pd(dba)$_2$ and 4 mol% tfp[21] [tfp = tri(2-furyl)phosphine] as catalyst. The desired functionalized dichlorobiphenyl derivatives **13a**, **14a** and **15a** are obtained in excellent yields (Scheme 2).



Scheme 1. Magnesiation of dichlorobenzenes **7-9**.

A broad range of electrophiles react with the dichlorophenylmagnesium reagents **10–12** leading to the expected products **13b–e**, **14b, c** and **15b–h** in moderate to excellent yields (Table 1). It should be noticed that this type of products can also be prepared *via* a Br/Mg exchange with *i*-PrMgCl·LiCl[22] starting, however, from the incomparably more expensive corresponding bromides.



Scheme 2. Negishi cross-coupling of the metallated dichlorobenzenes **10-12**.

Table 1. Products obtained after directed magnesiation of dichlorobenzenes **7–9**.

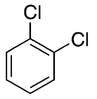
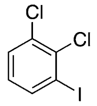
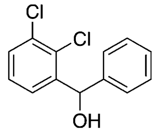
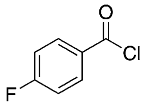
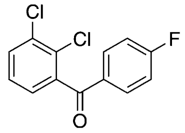
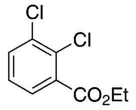
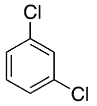
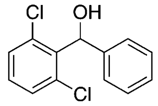
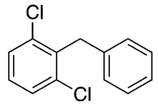
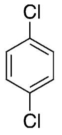
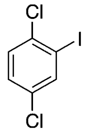
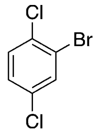
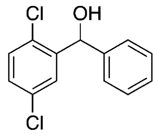
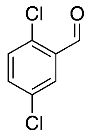
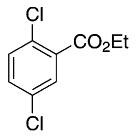
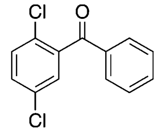
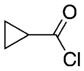
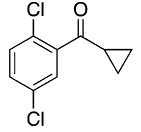
Entry	Substrate	E^+	Product: Yield[a]
1	 **7**	I_2	 **13b:** 78%
2	**7**	PhCHO	 **13c:** 94%
3	**7**		 **13d:** 87%[b]
4	**7**	$ClCO_2Et$	 **13e:** 81%[c]
5	 **8**	PhCHO	 **14b:** 90%
6	**8**	$PhCH_2Br$	 **14c:** 74%
7	 **9**	I_2	 **15b:** 78%
8	**9**	Br_2	 **15c:** 54%
9	**9**	PhCHO	 **15d:** 89%
10	**9**	DMF	 **15e:** 74%
11	**9**	$ClCO_2Et$	 **15f:** 88%[c]

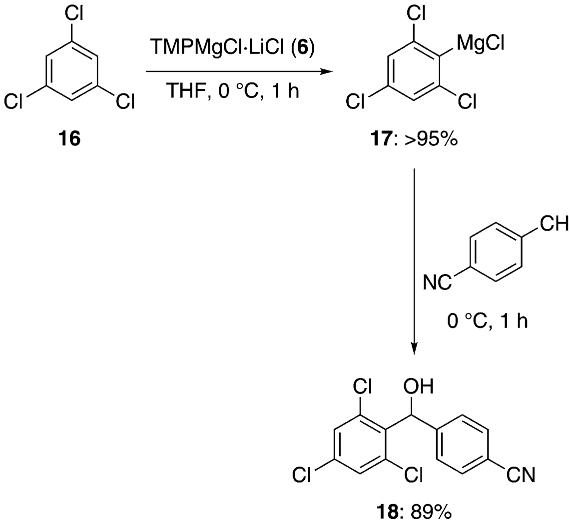
Table 1. (Continued)

Entry	Substrate	E$^+$	Product: Yield[a]
12	**9**	PhCOCl	 **15g:** 97%[c]
13	**9**		 **15h:** 58%[c]

[a] Isolated yield of analytically pure product.
[b] A transmetallation with $ZnCl_2$ (1.1 equiv.) and CuCN•2 LiCl (1.1 equiv.) was performed.
[c] A transmetallation with $ZnCl_2$ (1.1 equiv.) and 2 mol% $Pd(PPh_3)_4$-catalyzed acylation were performed.

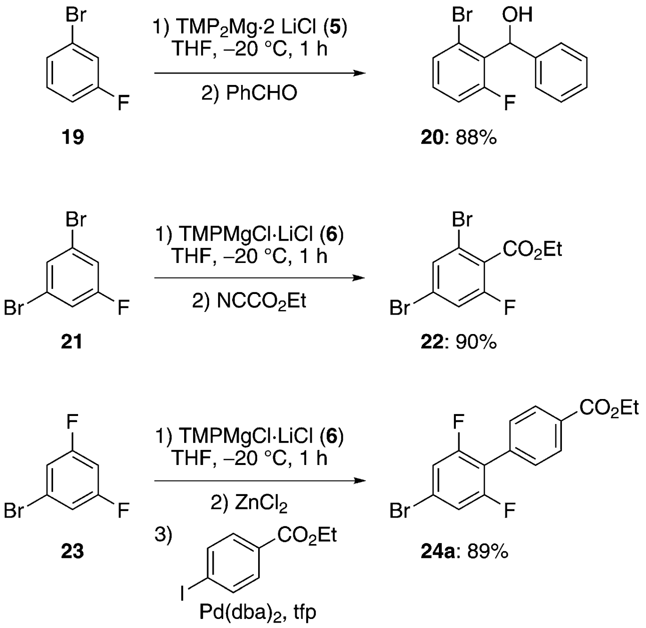
Thus, the iodolysis of Grignard reagent **10** produces 1,2-dichloro-3-iodobenzene (**13b**) in 78% (Table 1, entry 1). Addition of **10** to benzaldehyde gives the expected alcohol **13c** in 94% yield (Table 1, entry 2). After a transmetallation using CuCN·2 LiCl[23] and acylation with 4-fluorobenzoyl chloride the desired ketone **13d** is obtained in 87% yield (Table 1, entry 3). Whereas, after a transmetallation with $ZnCl_2$, Negishi acylation[24] with ethyl chloroformate furnishes the desired ethyl ester **13e** in 81% yield (Table 1, entry 4). Similarly the Grignard reagent **11** reacts with benzaldehyde or benzyl bromide yielding the corresponding alcohol **14b** or diphenylmethane **14c** in respective yields of 90 and 74% (Table 1, entries 5 and 6). In the same way, the arylmagnesium species **12** reacts with a range of electrophiles, like iodine, bromine, benzaldehyde, dimethylformamide or after transmetallation to zinc with various acid chlorides under palladium catalysis. The desired products **15b–h** are obtained in 54–97% (Table 1, entries 7–13). Remarkably, the reactions can also be run conveniently on a larger scale, as the reaction described in entry 8 was performed on a 40-mmol scale.

If the benzene ring is more electron-poor, like in 1,3,5-trichlorobenzene (**16**) magnesiation is best achieved using TMPMgCl·LiCl (**6**, 0 °C, 1 h), again degradation products have not been observed during the reaction course. In this case the use of $TMP_2Mg·2LiCl$ (**5**) is not required due to the higher activity of **16**. Furthermore whereas $TMP_2Mg·2LiCl$ (**5**) has only limited thermal stability, TMPMgCl·LiCl (**6**) is indefinitely stable at 25 °C and therefore more practical. The resulting phenylmagnesium derivative **17** reacts smoothly with electrophiles like 4-cyanobenzaldehyde, providing alcohol **18** in 89% yield (Scheme 3)



Scheme 3. Metallation of 1,3,5-trichlorobenzene **16**.

Similarly mixed bromofluoroarenes[25] are regioselectively magnesiated with $TMP_2Mg·2LiCl$ (**5**) or TMPMgCl·LiCl (**6**) depending on the number of halogen substituents attached to the aromatic ring. Remarkably, all these bromofluoroarenes are selectively metallated under mild conditions without any subsequent halogen dance, Wurtz coupling or elimination of HX. Thus, 1-bromo-3-fluorobenzene (**19**) is magnesiated at −20 °C using $TMP_2Mg·2LiCl$ (**5**) within 1 h. Subsequent reaction with benzaldehyde provides the diphenylmethanol **20** in 88% yield. The more electron-deficient 1,3-dibromo-5-fluorobenzene (**21**) is metallated regioselectively by TMPMgCl·LiCl (**6**) at −20 °C within 1 h. The resulting Grignard reagent reacts with ethyl cyanoformate yielding ethyl 2,4-dibromo-6-fluorobenzoate (**22**) in 90% yield. Also 1-bromo-3,5-difluorobenzene (**23**) is metallated regioselectively by TMPMgCl·LiCl (**6**) at −20 °C within 1 h. After transmetallation to zinc and palladium-catalyzed cross-coupling the desired biphenyl **24a** is obtained in 89% yield (Scheme 4).

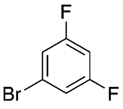
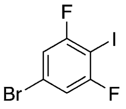
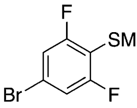
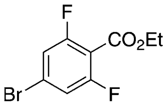
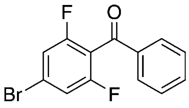
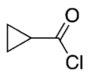
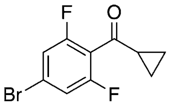
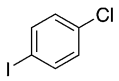
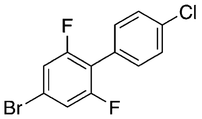


Scheme 4. Metallation of various bromofluorobenzenes with the TMP-magnesium bases **5** and **6**.

Furthermore, the Grignard reagent derived from **23** reacts with various other electrophiles. Quenching with iodine or *S*-methyl methanesulfonothioate affords 5-bromo-1,3-difluoro-2-iodobenzene (**24b**) and (4-bromo-2,6-difluorophenyl)(methyl)sulfane (**24c**) in respective yields of 61 and 88% (Table 2, entries 1 and 2). Similarly, the desired ethyl ester **24d** is obtained in 72% by an addition reaction to ethyl cyanoformate (Table 2, entry 3). Copper-catalyzed acylation provides the ketones **24e** and **24f** in 63–71% (Table 2, entries 4 and 5). After transmetallation to zinc and Negishi cross-coupling with 1-chloro-4-iodobenzene the polyhalogenated biphenyl **24g** is obtained in 84% yield (Table 2, entry 6).

We noticed that the magnesiation of 1,4-dibromobenzene[26] (**25**) with $TMP_2Mg{\cdot}2LiCl$ (**5**) leads mainly to aryne formation. This can be avoided by the following experimental protocol using $ZnCl_2$ *in situ*.[27]. Thus, 1,4-dibromobenzene was dissolved in $ZnCl_2$ solution (1 M in THF) and then treated with $TMP_2Mg{\cdot}2LiCl$ (**5**), furnishing full metallation after 12 h at room temperature. The resulting zincate can

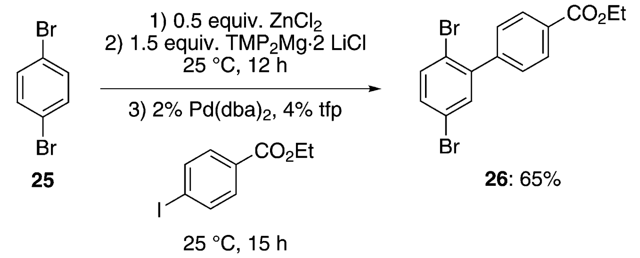
Table 2. Products obtained after directed magnesiation of 1-bromo-3,5-difluorobenzene (**23**).

Entry	Substrate	E+	Product: Yield[a]
1	 **23**	I_2	 **24b:** 61%
2	**23**	$MeSO_2SMe$	 **24c:** 88%
3	**23**	$NCCO_2Et$	 **24d:** 72%
4	**23**	PhCOCl	 **24e:** 71%[b]
5	**23**		 **24f:** 63%[c]
6	**23**		 **24g:** 84%[c]

[a] Isolated yield of analytically pure product.

[b] A transmetallation with $ZnCl_2$ (1.1 equiv.) and CuCN•2 LiCl (1.1 equiv.) was performed.

[c] A transmetlalation with $ZnCl_2$ (1.1 equiv.) and Pd-catalyzed cross-coupling using 2 mol% $Pd(dba)_2$ 4 mol% and tfp were performed.



Scheme 5. Functionalization of 1,4-dibromobenzene (**25**).

be cross-coupled with ethyl 4-iodobenzoate in the presence of 2% Pd(dba)$_2$ and 4% tfp yielding the desired functionalized unsymmetrical dibromobiphenyl **26** in 65% yield (Scheme 5).

To demonstrate the synthetic potential of our methodology, we have prepared the antimicrobial bibenzylphenol **4** found in the New Zealand liverwort *Riccardia marginata*.

Thus, we have performed a metallation of 1,3-dichlorobenzene (**8**) with TMP$_2$Mg·2LiCl (**5**) in the presence of isopropoxyboronic acid pinacol ester[28] yielding 2,6-dichlorophenylboronic acid pinacol ester (**27**) in 93%. Subsequent metallation following the procedure for 1,4-dibromobenzene (**25**) yielded the bimetallic zincate **28** that could be selectively cross-coupled with (*E*)-(2-iodovinyl)benzene under Pd(PPh)$_4$ catalysis to afford the diphenylstyrene **29**. The latter was used without purification in the following steps and oxidized under basic conditions with hydrogen peroxide. Then the resulting styrylphenol was directly reduced with molecular hydrogen, providing the natural product 2,6-dichloro-3-phenethylphenol (**4**) in 63% over 3 steps (Scheme 6).

Conclusions

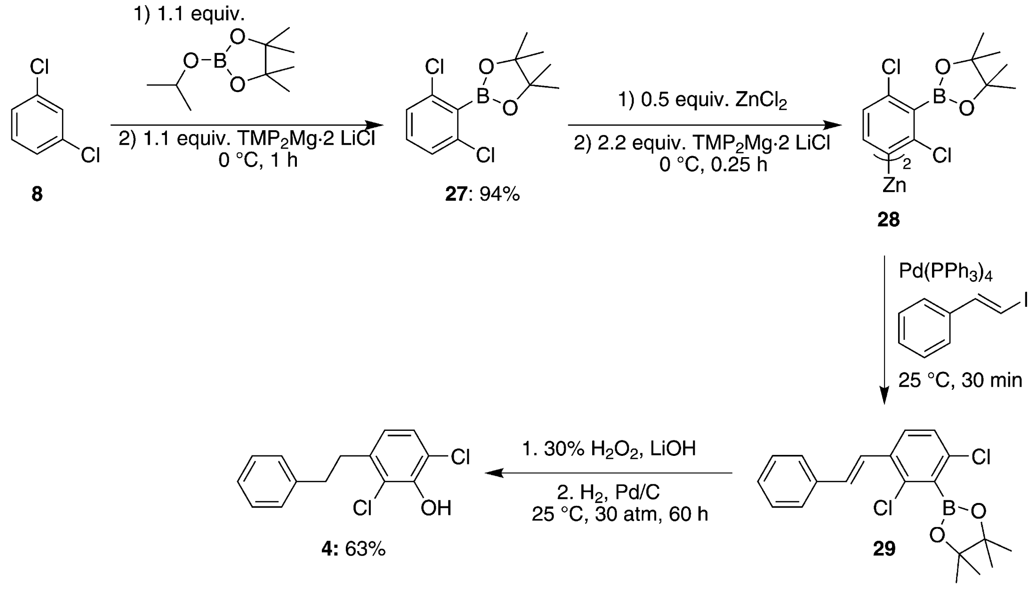
We have shown that various polyhaloaromatics can be regioselectively metallated by using TMP$_2$Mg·2LiCl (**5**) or TMPMgCl·LiCl (**6**) under mild conditions. The resulting Grignard reagents can be combined with a large number of electrophiles to provide attractive new building blocks, particularly functionalized derivatives, in good to excellent yields.

We also succeeded in preparing a mixed bimetallic zinc-boron reagent by metallation of a phenylboronic acid pinacol ester derivative and have successfully applied this method in the first preparation of 2,6-dichloro-3-phenethylphenol (**4**), a antimicrobial natural product isolated from the New Zealand liverwort *Riccardia marginata*. Further studies on the preparation of mixed bimetallic reagents *via* metallation are currently underway.

Experimental Section

Synthesis of Ethyl 2′,5′-Dichloro-[1,1′-biphenyl]-4-carboxylate (15a)

A flame-dried and argon-flushed Schlenk tube equipped with a rubber septum and a magnetic stirring bar was charged with a solution of 1,4-dichlorobenzene (294 mg, 2.0 mmol) in dry THF (2 mL) as well as 50 μL of tetradecane (internal standard for GC analysis). The mixture was cooled to 0 °C, then TMP$_2$Mg·2LiCl (0.7 M in THF, 3.14 mL, 2.2 mmol) was added dropwise through a syringe and the mixture was stirred at 0 °C for 0.25 h. Complete metallation was detected by GC analysis of reaction aliquots quenched with I$_2$ in dry THF. Then ZnCl$_2$ (2.4 mL, 1 M in THF, 2.4 mmol, 1.2 equiv.) was added at 0 °C. The reaction mix-



Scheme 6. Total synthesis of 2,6-dichloro-3-phenethylphenol (**4**).

ture was stirred for 10 min before Pd(dba)$_2$ (23 mg, 2 mol%), P(*o*-furyl)$_3$ (19 mg, 4 mol%) and ethyl 4-iodobenzoate (497 mg, 1.8 mmol) were added. Then the solution was warmed to room temperature over 3 h. The reaction mixture was quenched by the addition of a saturated aqueous NH_4Cl solution (30 mL), extracted with diethyl ether (3×50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by column chromatography (pentane:-diethyl ether = 20:1) to give **15a** as a colorless solid; yield: 513 mg (97%).

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