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Highly active, air-stable palladium catalysts for Kumada–Tamao–Corriu cross-coupling reaction of inactivated aryl chlorides with aryl Grignard reagents

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Abstract

Palladium(II) chlorides possessing phosphinous acid ligands have proved to be remarkably active and efficient catalysts for cross-coupling reactions of inactivated aryl chlorides with aryl Grignard reagents (Kumada–Tamao–Corriu reaction) at room temperature to yield the corresponding biaryls with isolated product yields ranging from 51 to 99%. ^{1}H- and ^{31}P-NMR studies argue that these phosphinous acid ligands in the complexes can be deprotonated to yield electron-rich anionic species, which is anticipated not only to accelerate the rate-determining oxidative addition of aryl chlorides in the catalytic cycle, but also to stabilize the transition-metal complexes. © 2002 Published by Elsevier Science B.V.

Keywords: $[(t\text{-Bu})_2P{-}OH)]_2PdCl_2$; $[(t\text{-Bu})_2P{-}OH)PdCl_2]_2$; Cross-coupling; Kumada–Tamao–Corriu reaction

1. Introduction

Carbon–carbon bond-forming reactions involving aryl halides are important synthetic transformations in synthetic chemistry [1], and the efficient cross-coupling reactions of aryl halides and Grignard reagents represent versatile and powerful approaches for constructing a diverse variety of biaryl compounds [2], which are important industrial intermediates for photo-materials, polymers, pharmaceuticals, agrochemicals, and homogeneous ligands. However, the lack of air-stable palladium-catalysts for cross-coupling of more readily available and less expensive aryl chlorides [3,4] with aryl Grignard reagents, and the necessity for elevated reaction temperatures to activate C–Cl bond of aryl chlorides, prompted us to search for new, highly active, and air-stable catalysts.

As part of our ongoing efforts to apply combinatorial technologies for the discovery of new industrial homogeneous catalysts [5–7], we reported the discovery of air-stable phosphine oxides [$R_2P(O)H$] and phosphine sulfides [$R_2P(S)H$] ligand precursors, for a variety of transition-metal-catalyzed cross-coupling reactions of inactivated aryl chlorides [8]. All these reactions are mediated by metal–phosphinous acid or metal–phosphinothious acid compounds [9] which are generated via tautomerization of $R_2P(O)H$ or $R_2P(S)H$ in the presence of transition metals. These air-stable complexes can be deprotonated in the presence of base to generate anionic species as catalysts for Cl–C bond activation of aryl chlorides (Scheme 1).

Herein, we report our results on the use of isolated air-stable palladium complexes as catalyst precursors for the C–C bond-forming reactions of aryl chlorides with aryl Grignard reagents in high yields at ambient temperature.

2. Results and discussion

The goal of this study was to employ new types of anionic palladium(II) catalysts for cross-coupling of aryl chlorides, to examine the scope, regiospecificity, catalytic activity, and mechanism of these isolated, air-stable palladium–phosphinous acids-catalyzed cross-coupling

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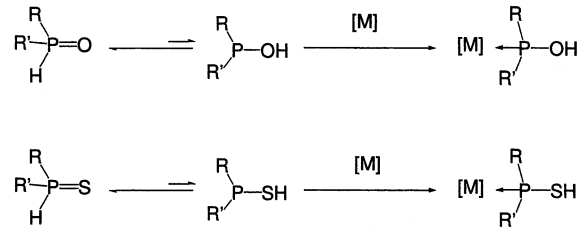
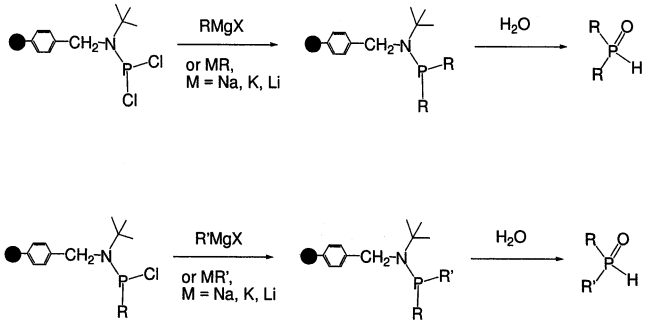


Scheme 1.

reaction of aryl chlorides and aryl Grignard reagents. To compare and contrast with the Kumada–Tamao–Corriu reaction of aryl chlorides mediated by nickel–(t-Bu)$_3$P [4], palladium–imidazolium chlorides [3] and nickel–phosphine oxides [8a], which are produced in-situ via a reaction of nickel or palladium and ligands, the present work focused on phosphinous acid ligand variation while transition metals and reagents were held constant, on catalytic regioselectivity, and on the factors affecting reaction rate and rate-limiting oxidative additions.

The ligand precursors used for cross-coupling reactions were straightforwardly synthesized by reaction of R_2PCl with H_2O in organic solvents [10], or by our previously reported polymer-supported approaches (Scheme 2) [5,7,8a].



Scheme 2.

The precatalysts were generated by treating $PdCl_2$ with phosphine oxides [$R_2P(O)H$] in organic solvents [11]. The catalytic cross-coupling reactions were carried out in organic solvents (e.g. THF, Et_2O, dioxane) under anhydrous | anaerobic (catalyst loading: 0.5–1.0 mol%). Isolated yields in Table 1 refer to products isolated by column chromatography. Known products were identified by comparison with literature data and/or with those of authentic samples. New compounds were characterized by 1-D and 2-D $^1H/^{13}C$-NMR, HRMS, or elemental analysis.

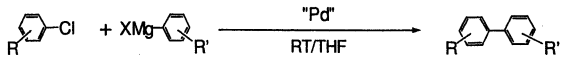
The results of Table 1 demonstrated that palladium(II) complexes of the type $(R_2POH)_nPdCl_m$ ($n = 1, 2$; $m = 1, 2$) and $\{[R_2PO\cdots H\cdots OPR_2]_2PdCl\}_2$ were capable of catalyzing the cross-coupling reactions of a variety of aryl chlorides and aryl Grignard reagents at room temperature to yield the desired biaryls in high isolated yields. Entries 1, 3, 4 and 5 illustrate that a variety of electron-rich chloroanisoles could be coupled with aryl Grignard reagents quantitatively. Entries 4 and 5 demonstrate that both more sterically demanding and electron-rich substrate 3-chloroanisole was coupled with aryl Grignard reagents to yield 3-(2,4,6-trimethylphenyl)anisole and 3-(2-tolyl)anisole, respectively. Entries 6, 7 and 8 illustrate that Grignard reagents are effective coupling groups with aryl chlorides yielding 2-phenyltoluene and biphenyl.

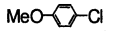
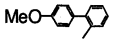
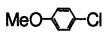
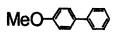
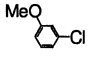
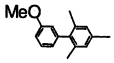
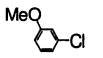
A number of aspects of the present palladium–phosphinous acid catalysts are noteworthy and offer both informative parallels and contrasts to the corresponding nickel–phosphine [4] and palladium–imidazolium chloride [3], as well as nickel–phosphinous acid ligands [8a] in the cross-coupling of aryl chlorides with aryl Grignard reagents. The present catalysts are capable of employing a diverse variety of air-stable phosphine oxides [RR′P(O)H] as ligand precursors for Pd-catalyzed cross-coupling reactions of aryl chlorides and aryl Grignard reagents (Kumada–Tamao–Corriu coupling reaction) at room temperature, and all the phosphine oxides can be easily synthesized via a polymer-supported combinatorial approach [5,7], all the cross-coupling results are comparable with those from the corresponding Ni–phosphinous acids [8a] at the same reaction conditions and from Ni–imidazolium salts [4]. Interestingly, and in marked contrast to the Pd–imidazolium salt [3] for Kumada–Tamao–Corriu cross-coupling of aryl chlorides, the present catalyst systems showed the cross-coupling can be carried out at room temperature in a low catalyst loading. It would thus appear that the oxidative addition (rate-limiting step) of aryl chlorides in the catalytic cycle is facilitated, presumably due to anionic palladium-species produced in the presence of a Grignard reagent (Scheme 3), which are employed to form more reactant-like transition states for such a rate-limiting process.

More importantly, from the standpoint of organic synthesis, the direct use of air-stable **POPd**, **POPd1** and **POPd2** as catalysts for cross-couplings of aryl chlorides would be more practical owing to the difficulties in generating in situ catalysts and in handling extremely air-sensitive phosphine ligands [4].

With regard to a plausible mechanism, ^{31}P-NMR studies of the reaction of **POPd** with Et_3N in $CDCl_3$ solution argue that in the presence of bases, **POPd** is subject to generate a chloro-bridged dinuclear species, and yielding an electron-rich phosphine-containing anionic complex [12], which is anticipated not only to accelerate the rate-determining oxidative addition of aryl chlorides in the catalytic cycle [13], but also to stabilize the transition metals via a O–P–M conjugation (Scheme 4). Direct evidence for this pathway derives

Table 1
Palladium-catalyzed Kumada–Tamao–Corriu cross-couplings of aryl chlorides

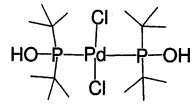


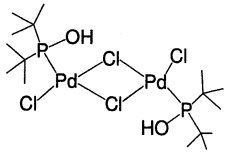
Entry	Halide	Coupling Partner	Catalyst	Time (h)	Product	Yield (%) (Isolated)
1			POPd	4		87
2			POPd	4		99
3			POPd1	4		57
4			POPd1	14		51
5			POPd2	4		88
6			$[(Ph_2PO...H...OPPh_2)PdCl]_2$	14		90
7			$[(Cy_2PO...H...OPCy_2)PdCl]_2$	14		60
8			$[(i\text{-}Pr)_2PO...H...OP(i\text{-}Pr)_2PdCl]_2$	4		93

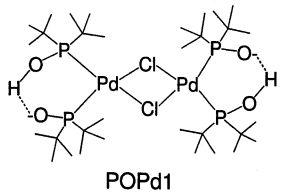
from the reaction of **POPd** with K_2CO_3 in THF, which generates an anionic dimer **POPd1** [8c,8d].

3. Conclusion

In conclusion, we have shown for the first time that air-stable palladium(II) complexes bearing phosphinous acid ligands are ideal catalyst precursors for the activation of C–Cl bonds of inactivated aryl chlorides, and that such processes can be incorporated into efficient catalytic cycles for cross-coupling reactions of aryl chlorides with aryl Grignard reagents. Of note is the efficiency for inactivated aryl chlorides; and ready accessibility for these catalyst precursors via polymer-supported approaches. Additional applications of these new, simple, readily accessible, air-stable, and efficient palladium(II) catalyst precursors for catalysis are currently under investigation.





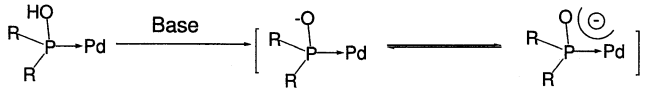


Scheme 3. Air-stable palladium complexes employed in Table 1.

4. Experimental

4.1. General considerations

All reagents were used as supplied commercially without further purification. Dihydrogen dichlorobis(di-*tert*-butylphosphinito-κ*P*)palladate(2-) $[(t\text{-}Bu)_2POH)_2PdCl_2$ referred as **POPd**], and dihydrogen di-μ-chlorodichlorobis(di-*tert*-butylphosphinito-κ*P*)dipalladate(2-) $\{[(t\text{-}Bu)_2P(OH)PdCl_2]_2$ referred as **POPd2**} are available exclusively from CombiPhos Catalysts, Inc. Alternatively, they may be prepared according to our reported procedures [8c,8d]. NMR spectra were recorded on either a Nicolet NMC-300 wide-bore (FT, 300 MHz, ^1H; 75 MHz, ^{13}C; 121 MHz, ^{31}P), or GE QM-300 narrow-bore (FT, 500 MHz, ^1H) instrument. Chemical shifts (δ) for ^1H, ^{13}C are referenced to internal solvent resonances and reported relative to $SiMe_4$. ^{31}P-NMR shifts are reported relative to external phosphoric acid. Mass spectral data were



Scheme 4.

obtained on a Kratos CONCEPT IH instrument at 70 eV.

4.2. Preparation of dihydrogen di-μ-chlorotetrakis(diphenylphosphinito-κP)dipalladate(2-) [14]

A solution of $Pd(OAc)_2$ (5.0 g, 22.27 mmol), Ph_2PCl (10.0 g, 45.3 mmol) and H_2O (0.816 g, 45.3 mmol) in 100 ml of 1,4-dioxane was refluxed under nitrogen condition overnight. After the mixture was cooled to room temperature (r.t.), the dioxane was removed under vacuum. The residue was washed with Et_2O (5 × 50 ml) and hexane (5 × 50 ml), purified by column chromatography on silica gel to afford 10.0 g (82% yield) of $\{[(Ph)_2PO\cdots H\cdots OP(Ph)_2]PdCl\}_2$. It was >95% pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 (m, 16H), 7.40 (m, 8H), 7.27 (m, 16H) ppm. ^{13}C-NMR (76 MHz, $CDCl_3$): δ 135.3 (d, $J = 71.3$ Hz), 132.0 (t, $J = 6.08$ Hz), 130.9 (s), 127.9 (t, $J = 5.96$ Hz) ppm. ^{3l}P-NMR (121 MHz, $CDCl_3$): δ 79.5 ppm. ^{1}H-coupled ^{31}P-NMR (121 MHz, $CDCl_3$): δ 79.5 (s) ppm. Anal. Calc. for $C_{48}H_{42}O_4Cl_2P_4Pd_2$: C, 52.87; H, 3.88; Cl, 6.50; P, 11.36. Found: C, 53.30; H, 3.68; Cl, 6.41; P, 10.76%. The crystallographic sample was obtained by slow recrystallization from a mixture of CH_2Cl_2 and hexane [8c,8d].

4.3. Preparation of dihydrogen di-μ-chlorotetrakis(dicyclohexylphosphinito-κP)dipalladate(2-)

A solution of $PdCl_2$ (1.90 g, 10.74 mmol), Cy_2PCl (5.0 g, 21.48 mmol) and H_2O (1.0 g, 55.6 mmol) in 100 ml of THF was refluxed under nitrogen condition overnight. After the mixture was cooled to r.t., the THF was removed under vacuum. The residue was washed with Et_2O (5 × 50 ml) and hexane (5 × 50 ml), purified by column chromatography on silica gel to afford 5.3 g (87% yield) of $\{[Cy_2PO\cdots H\cdots OPCy_2]PdCl\}_2$. It was > 95% pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.61 (m, 4H), 3.56–3.44 (m, 8H), 72.31–1.15 (m, 34H) ppm. ^{13}C-NMR (76 MHz, $CDCl_3$): δ 40.58 (d, $J = 28.27$ Hz), 40.46 (d, $J = 38.88$ Hz), 40.45 (d, $J = 28.28$ Hz), 29.0, 27.6, 26.8 (dt, $J = 49.69$ Hz, $J =$ 7.49 Hz) ppm. ^{31}P-NMR (202 MHz, $CDCl_3$): δ 113.5 ppm. ^{1}H-coupled ^{31}P-NMR (202 MHz, $CDCl_3$): δ 113.5 (s) ppm. Anal. Calc. for $C_{48}H_{90}O_4Cl_2P_4,Pd_2$: C, 50.62; H, 7.97; Cl, 6.23; P, 10.88. Found: C, 50.70; H, 8.10; Cl, 6.25; P, 10.99%.

4.4. Preparation of dihydrogen di-μ-chlorotetrakis(di-iso-propylphosphinito-κP)dipalladate(2-)

A solution of $PdCl_2$ (5.0 g, 28.2 mmol), $(i\text{-Pr})_2PCl$ (8.97 g, 56.4 mmol) and H_2O (1.2 g, 66.7 mmol) in 100 ml of THF was refluxed under nitrogen condition overnight. After the mixture was cooled to r.t., the THF was removed under vacuum. The residue was washed with Et_2O (5 × 50 ml) and hexane (5 × 50 ml), purified by column chromatography on silica gel to afford 5.9 g (51% yield) of $\{[(i\text{-Pr})_2PO\cdots H\cdots OP(i\text{-Pr})_2]PdCl\}_2$. It was >95% pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.19 (m, 4H), 1.36 (m, 12H), 1.22 (m, 12H) ppm, ^{13}C-NMR (126 MHz, $CDCl_3$): δ 31.2, 19.5, 17.4 ppm. ^{31}P-NMR (202 MHz, $CDCl_3$): δ 118.3 ppm. ^{1}H-coupled ^{31}P-NMR (202 MHz, $CDCl_3$): δ 118.3 (s) ppm. Anal. Calc. for $C_{24}H_{58}O_4Cl_2P_4Pd_2$: C, 35.22; H, 7.14; Cl, 8.66; P, 15.14. Found: C, 35.40; H, 7.24; Cl, 8.98; P, 15.24%.

4.5. Synthesis of 4-(2-tolyl)anisole

In the drybox, 25.0 mg (0.05 mm) of **POPd**, 1.43 g (10.0 mm) of 4-chloroanisol and 10.0 ml of THF were loaded into a reactor (50 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 15 ml (15.0 mm, 1.0 M in THF) of *O*-tolylmagnesium chloride at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 4 h before the reaction was quenched with 10.0 ml of H_2O, and the mixture was diluted with 300 ml of Et_2O. After separation of organic and aqueous phases, the organic phase was washed with 50 ml of H_2O, and 50 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel (100: 1-hexane: methyl *t*-butyl ether) to afford 1.72 g (87% yield) of 4-(*o*-tolyl)anisole. It was >95% pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33–7.00 (m, 8H), 3.91 (s, 3H), 2.34 (s, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 158.5, 141.5, 135.3, 134.3, 130.2, 130.1, 129.8, 126.8, 125.7, 113.4, 55.0, 20.4 ppm. HRMS Calc. For $C_{14}H_{14}O$: 199.1122. Found: 199.1121. Anal Calc. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.65; H, 6.98%.

4.6. Synthesis of 2-phenyltoluene

In the drybox, 50.0 mg (0.10 mm) of **POPd**, 1.13 g (10.0 mm) of chlorobenzene and 10.0 ml of THF were loaded into a reactor (50 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 15 ml (15.0 mm, 1.0 M in THF) of *O*-tolylmagnesium chloride at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 4 h before the reaction was quenched with 10.0 ml of H_2O, and the mixture was diluted with 300 ml of Et_2O. After separation of organic and aqueous phases, the organic phase was washed with 50 ml of H_2O, and 50 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column

chromatography on silica gel to afford 1.66 g (99% yield) of 2-phenyltoluene. It was >95% pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.6–7.47 (m, 9H), 2.50 (s, 3H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 142.0, 141.9, 135.2, 130.3, 129.7, 129.1, 128.0, 127.2, 126.7, 125.7, 20.4 ppm. HRMS Calc. for $C_{13}H_{12}$: 169.1017. Found: 169.1016. Anal Calc. for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.60; H, 7.08%.

4.7. Synthesis of 3-(2-tolyl)anisole [15]

In the drybox, 68.0 mg (0.10 mm) of **POPd2**, 1.43 g (10.0 mm) of 3-chloroanisol and 10.0 ml of THF were loaded into a reactor (50 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 15 ml (15.0 mm, 1.0 M in THF) of *O*-tolylmagnesium chloride at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 4 h before the reaction was quenched with 10.0 ml of H_2O, and the mixture was diluted with 300 ml of Et_2O. After separation of organic and aqueous phases, the organic phase was washed with 50 ml of H_2O, and 50 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel to afford 1.75 g (88% yield) of 3-(*o*-tolyl) anisole.

4.8. Synthesis of 2-phenyltoluene

In the drybox, 109 mg (0.10 mm) of $\{[(Ph)_2PO\cdots H\cdots OP(Ph)_2]PdCl\}_2$, 1.13 g (10.0 mm) of chlorobenzene and 10.0 ml of THF were loaded into a reactor (50 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 15 ml (15.0 mm, 1.0 M in THF) of *O*-tolylmagnesium chloride at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 14 h before the reaction was quenched with 10.0 ml of H_2O, and the mixture was diluted with 300 ml of Et_2O. After separation of organic and aqueous phases, the organic phase was washed with 50 ml of H_2O, and 50 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel to afford 1.52 g (90% yield) of 2-phenyltoluene.

4.9. Synthesis of 2-phenyltoluene

In the drybox, 114 mg (0.10 mm) of $\{[Cy_2PO\cdots H\cdots OPCy_2]PdCl\}_2$, 1.13 g (10.0 mm) of chlorobenzene and 10.0 ml of THF were loaded into a reactor (50 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 15 ml (15.0 mm, 1.0 M in THF) of *O*-tolylmagnesium chloride at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 14 h before the reaction was quenched with 10.0 ml of H_2O, and the mixture was diluted with 300 ml of Et_2O. After separation of organic and aqueous phases, the organic phase was washed with 50 ml of H_2O, and 50 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel to afford 1.1 g (60% yield) of 2-phenyltoluene.

4.10. Synthesis of biphenyl

In the drybox, 82.0 mg (0.10 mm) of $\{[(i\text{-}Pr)_2PO\cdots H\cdots OP(i\text{-}Pr)_2]PdCl\}_2$ and 1.13 g (10.0 mm) of chlorobenzene were loaded into a reactor (20 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 7.5 ml (15.0 mm, 2.0 M in THF) of phenylmagnesium chloride at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 4 h before the reaction was quenched with 10.0 ml of H_2O, and the mixture was diluted with 300 ml of hexane. After separation of organic and aqueous phases, the organic phase was washed with 70 ml of H_2O, and 100 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel to afford 1.44 g (93% yield) of biphenyl. It was >95% pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.77 (d, $J = 7.75$ Hz, 4H), 7.60 (t, $J = 7.65$ Hz, 4H), 7.50 (t, $J = 7.38$ Hz, 2H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 141.2, 128.7, 127.2, 127.1 ppm. HRMS: Calc. for $C_{12}H_{10}$: 154.0783. Found: 154.0785%.

4.11. Synthesis of 4-phenylanisole

In the drybox, 66.6 mg (0.050 mm) of **POPd1**, 1.43 g (10.0 mm) of 4-chloroanisol was loaded into a reactor (50 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 7.5 ml (15.0 mm, 2.0 M in THF) of phenylmagnesium chloride at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 4 h before the reaction was quenched with 10.0 ml of H_2O, and the mixture was diluted with 300 ml of Et_2O. After separation of organic and aqueous phases, the organic phase was washed with 50 ml of H_2O, and 50 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel to afford 1.05 g (57% yield) of 4-phenylanisole. It was >95% pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 4H), 7.32 (m, 2H), 7.21 (m, 1H), 6.88 (d, $J = 8.72$ Hz, 2H), 3.74 (s, 3H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.2, 140.8, 133.8, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3 ppm. Anal. Calc. for $C_{13}H_{12}O$: C, 84.75; H, 6.57; O, 8.68. Found: C, 84.81; H, 6.65; O, 8.62%.

4.12. Synthesis of 3-(2,4,6-trimethylphenyl)anisole

In the drybox, 47.0 mg (0.0505 mm) of **POPd1** and 2.86 g (20.0 mm) of 3-chlorideanisole were loaded into a reactor (50 ml) equipped with a magnetic stir bar. The resulting mixture was stirred when addition of 30 ml (30.0 mm, 1.0 M in THF) of 2-mesitylmagnesium bromide at r.t. over a period of 5 min. The resulting mixture was stirred at r.t. over 14 h before the reaction was quenched with 50.0 ml of H_2O, and the mixture was diluted with 300 ml of Et_2O. After separation of organic and aqueous phases, the organic phase was washed with 100 ml of H_2O, and 100 ml of brine, then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel (100: 1-hexane: Acetate) to afford 2.3 g (51% yield) of the title compound. It was $>95\%$ pure by ^{1}H-NMR and GC–MS. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 (m, 1H), 7.17 (s, 2H), 7.09–7.08 (m, 1H), 6.98–6.95 (m, 2H), 4.00 (s, 3H), 2.56 (s, 3H), 2.28 (s, 6H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.6, 142.5, 138.9, 136.4, 135.7, 129.3, 128.0, 121.6, 114.8, 111.9, 54.9, 20.9, 20.5 ppm. HRMS: Calc. for $C_{16}H_{18}O$: 227.1436. Found: 227.1434%.

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[12] A reaction of (t-Bu)$_2$POH)$_2$PdCl$_2$ (POPd), (50.0 mg, 0.10 mm) and Et$_3$N [20.0 mg, 0.198 mm) in 3.0 ml of $CDCl_3$ at room temperature for 2 h generates an insoluble mixture exhibiting ^{31}P-NMR resonance at δ 124.0 (singlet).

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