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Extremely Efficient Cross-Coupling of Benzylic Halides with Aryltitanium Tris(isopropoxide) Catalyzed by Low Loadings of a Simple Palladium(II) Acetate/Tris(*p*-tolyl)phosphine System

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Abstract: Highly efficient coupling reactions of benzylic bromides or chlorides with aryltitanium tris(isopropoxide) [$ArTi(O\text{-}i\text{-}Pr)_3$] catalyzed by a simple palladium(II) acetate/tris(*p*-tolyl)phosphine [$Pd(OAc)_2$/$P(p\text{-tolyl})_3$] system are reported. The coupling reactions proceed in general at room temperature employing low catalyst loadings of 0.02 to 0.2 mol%, affording coupling products in excellent yields of up to 99%. For benzylic bromides bearing strong electron-withdrawing cyano (CN) or trifluoromethyl (CF_3) substituents, the reactions require a higher catalyst loading of 1 mol%, or the reactions are carried out at 60 °C. The catalytic system also tolerates (1-bromoethyl)benzene bearing β-hydrogen atoms while using a catalyst loading of 1 mol% to afford the coupling product in a 70% yield.

Keywords: aryltitanium species; benzyl halides; benzylic coupling; palladium; phosphines

Introduction

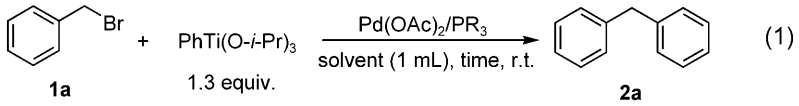
Catalytic cross-coupling reactions using a variety of organometallic reagents have been extensively studied over the past three decades.[1–6] Recent studies have focused on the development of catalytic systems for coupling reactions of inert substrates,[7–10] formation of the C–N,[11] C–O,[12] or C–S[13] bond, and catalytic systems with metal Cu,[14] Ni,[15] or Fe[16] centers. In addition, $ArTi(OR)_3$ compounds have been recently found to be excellent aryl sources. The aryl-aryl coupling reactions have been demonstrated in a few reports employing nickel or palladium catalysts at elevated temperatures by Hayashi[17] and by Kwong,[18] or even at room temperature by Knochel[19] and by us,[20] affording coupling products in good to excellent yields. In sharp contrast to the aryl-aryl coupling reactions, the coupling of benzylic halides with the organometallic reagents has been less reported. The scaffolds of diarylmethane and heteroaryl-arylmethane are key intermediates leading to bioactive compounds.[21] In addition, they are found as subunits in receptor molecules for molecular recognition.[22] Synthetically, the cross-coupling of benzyl derivatives with aryl- or heteroaryl-metallic reagents is the most straightforward route, and arylboron,[23] arylmagnesium,[24] arylzinc,[25] or aryltin[26] compounds have been used for this purpose. However, the coupling reactions need to be carried out, in general, either at elevated temperatures or with catalyst loadings of 1 mol% or greater.

In continuation of our efforts to develop organoaluminum or organotitanium compounds as efficient coupling reagents[20,27] or addition reagents in asymmetric catalysis,[28] we report herein the extremely efficient coupling reactions of benzylic bromides or chlorides with aryltitanium reagents of the formula $ArTi(O\text{-}i\text{-}Pr)_3$.

Results and Discussion

The coupling reaction of benzyl bromide (**1a**) and $PhTi(O\text{-}i\text{-}Pr)_3$ was first screened for palladium catalysts with a variety of phosphine ligands (supporting information, Table S1), and it was found that $Pd(OAc)_2$ and $P(p\text{-tolyl})_3$ in a ratio of 1 to 2 was the best catalytic system [Eq. (1)]. When a mixture of

Table 1. Optimization of the coupling reactions of benzyl bromide with PhTi(O-*i*-Pr)$_3$ catalyzed by Pd(OAc)$_2$/P(*p*-tolyl)$_3$ systems.[a]



Entry	Pd(OAc)$_2$ [mol%]	PR$_3$[b] [mol%]	Solvent	Time	Conversion [%][c]
1	1.0	2.0	toluene	5 min	>99
2	1.0	2.0	hexane	5 min	9
3	1.0	2.0	CH_2Cl_2	5 min	10
4	1.0	2.0	ether	5 min	34
5	1.0	2.0	THF	5 min	>99
6	1.0	1.0	toluene	5 min	>99
7	1.0	3.0	toluene	5 min	trace
8	0.1	0.1	toluene	0.5 h	>99
9	0.1	0.2	toluene	0.5 h	>99
10	0.02	0.04	toluene	2 h	>99
11	0.02	0.02	toluene	2 h	51
12	0.01	0.02	toluene	2 h	55
13[d]	0.02	0.04	toluene	2 h	>99

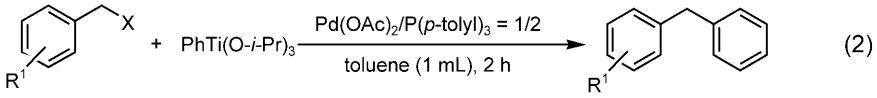
[a] Benzyl bromide/PhTi(O-*i*-Pr)$_3$ = 1.0/1.3 mmol.
[b] PR$_3$ = P(*p*-tolyl)$_3$.
[c] Conversions were determined by ^{1}H NMR spectra.
[d] PhTi(O-*i*-Pr)$_3$ = 1.1 mmol.

1 mol% Pd(OAc)$_2$ and 2 mol% P(*p*-tolyl)$_3$ was used as the catalyst, the coupling reaction took place efficiently in toluene at room temperature, affording coupling product **2a** in >99% yield in only 5 min (Table 1, entry 1). Coupling reactions carried out in different solvents were then studied (entries 2–5), and both toluene (entry 1) and THF (entry 5) were found to be suitable solvents. Subsequently, catalyst loadings and ratios of P(OAc)$_2$/P(*p*-tolyl)$_3$ were tuned in toluene (entries 6–12), and, to our surprise, the catalyst loading could be reduced down to 0.02 mol% Pd(OAc)$_2$ and 0.04 mol% P(*p*-tolyl)$_3$, producing **2a** in >99% conversion in 2 h at room temperature (entry 10). When the amount of PhTi(O-*i*-Pr)$_3$ was reduced to 1.1 equiv., the reaction still afforded **2a** in >99% yield (entry 13). This is an exceptionally good result compared to those of the previously reported aryl-benzyl coupling reactions.

Studies on the scope of the catalytic system with the optimized Pd(OAc)$_2$/P(*p*-tolyl)$_3$ ratio of 1:2 were performed on substituted benzyl bromides and chlorides employing 1.1 equiv. PhTi(O-*i*-Pr)$_3$ [Eq. (2)]. Depending on the substrates, catalyst loadings were tuned to afford the best results which are presented in Table 2. For substituted benzyl bromides containing electron-donating substituents on the aromatic ring as well as 3- and 4-phenylbenzyl bromides (entries 1–10), low catalyst loadings of 0.02 to 0.2 mol% were effective enough to produce diarylmethanes in excellent yields of ≥92% except for 3,5-dimethoxybenzyl bromide in which a higher catalyst loading of 0.5 mol% was needed (entry 10). However, the catalyst loading could be brought down to 0.05 mol% to afford **2j** in an excellent 96% yield when the reaction was conducted at 60 °C (entry 11). A catalyst loading of 0.1 mol% was also good enough for 4-chlorobenzyl bromide and 4-bromobenzyl bromide, affording **2k** and **2l** in 95% and 80% yields (entries 12 and 13), respectively. It is worth noting that the cross-coupling of 4-bromobenzyl bromide with PhTi(O-*i*-Pr)$_3$ also furnished 12% 4-benzylbiphenyl which is a product derived from a further coupling of **2l** with PhTi(O-*i*-Pr)$_3$ (entry 13). In contrast, the coupling reactions of substituted benzyl bromides containing strong electron-withdrawing substituents, such as 4-cyanobenzyl bromide or 3,5-bis(trifluoromethyl)benzyl bromide, required a higher catalyst loading of 1 mol% to afford **2m** and **2n** in 84% and 32% yields (entries 14 and 16), respectively. When the reactions were conducted at 60 °C, excellent yields could be achieved at low catalyst loadings of 0.2 to 0.1 mol% (entries 15 and 17). However, the higher reaction temperature also resulted in a homo-coupling product of 1,2-bis[3,5-bis(trifluoromethyl)phenyl]ethane derived from 6% of **1n** (entry 17).

We subsequently examined coupling reactions of benzylic chlorides (entries 18–27). The catalytic system exhibits similar reactivity toward benzylic chlorides compared to benzylic bromides. For example, a 0.05 mol% catalyst loading was used for benzyl chloride to afford coupling product **2a** in a 93% yield (entry 18) compared to the 0.02 mol% used for benzyl

Table 2. Coupling of substituted benzyl halides and $PhTi(O\text{-}i\text{-}Pr)_3$ catalyzed by $Pd(OAc)_2/P(p\text{-tolyl})_3$ systems.[a]



1: X = Br
1': X = Cl

2

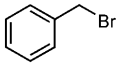
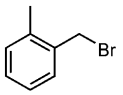
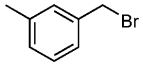
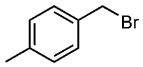
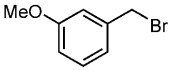
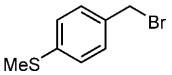
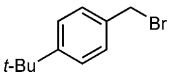
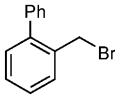
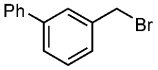
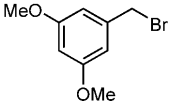
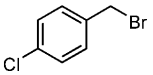
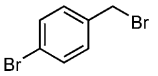
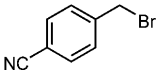
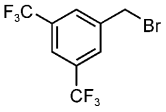
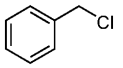
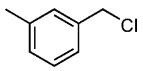
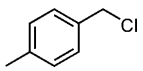
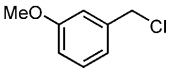
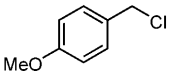
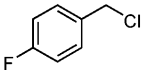
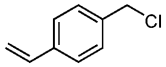
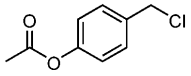
Entry	Substrate		$Pd(OAc)_2$ [mol%]	Temperature [°C]	Product **2**	Yield [%][b]
1		(**1a**)	0.02	25	**2a**	96
2		(**1b**)	0.2	25	**2b**	92
3		(**1c**)	0.1	25	**2c**	98
4		(**1d**)	0.1	25	**2d**	93
5		(**1e**)	0.1	25	**2e**	99
6		(**1f**)	0.1	25	**2f**	98
7		(**1g**)	0.1	25	**2g**	92
8		(**1h**)	0.1	25	**2h**	99
9		(**1i**)	0.1	25	**2i**	99
10		(**1j**)	0.5	25	**2j**	93
11		(**1j**)	0.05	60	**2j**	96
12		(**1k**)	0.1	25	**2k**	95
13		(**1l**)	0.1	25	**2l**	80 (12)[c]
14		(**1m**)	1	25	**2m**	84
15		(**1m**)	0.2	60	**2m**	98
16		(**1n**)	1	25	**2n**	32
17		(**1n**)	0.1	60	**2n**	94 (6)[d]
18		(**1a′**)	0.05	25	**2a**	93
19		(**1c′**)	0.1	25	**2c**	95
20		(**1d′**)	0.05	25	**2d**	97

Table 2. (Continued)

Entry	Substrate		$Pd(OAc)_2$ [mol%]	Temperature [°C]	Product **2**	Yield [%][b]
21		(**1e′**)	0.2	25	**2e**	99
22		(**1o′**)	0.05	25	**2o**	90
23		(**1p′**)	0.2	25	**2p**	93
24		(**1q′**)	1	25	**2q**	96
25		(**1q′**)	0.1	60	**2q**	93
26		(**1r′**)	1	25	**2r**[e]	95
27		(**1r′**)	0.1	60	**2r**[e]	94

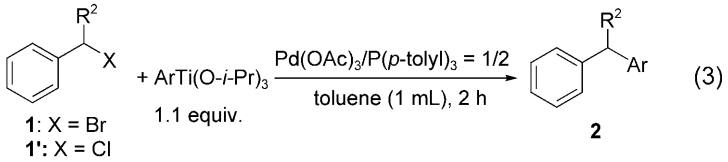
[a] Benzyl halide/$PhTi(O\text{-}i\text{-}Pr)_3$ = 1.0/1.1 mmol; solvent, toluene (1 mL); time, 2 h.
[b] Isolated yields are average values of two runs.
[c] Yield of 4-benzylbiphenyl in parenthesis.
[d] The value in parenthesis is a conversion of homo-coupling product derived from the substrate.
[e] **2r**: 4-benzylphenol.

bromide in the 96% yield (entry 1). Similarly, 0.05 to 0.2 mol% of the catalyst systems were used for methyl- or methoxy-substituted benzyl chlorides (entries 19–21) relative to 0.1 mol% of the catalyst for the corresponding substituted benzyl bromides (entries 3–5). For 4-fluorobenzyl chloride with an electron-withdrawing fluoro substituent, a 0.2 mol% loading of the catalyst was used to afford coupling product **2p** in 93% yield (entry 23). We also examined 4-(vinyl)benzyl chloride (**1q′**) and 4-(chloromethyl)phenyl acetate (**1r′**), and these two substrates required 1 mol% of the catalyst (entries 24 and 26). For the coupling reaction of **1r′**, the hydrolysis product 4-benzylphenol (**2r**) was obtained in a 95% yield after work-up procedures (entry 26). The hydrolysis is likely due to an effect of the Lewis acidic titanium compound present in the reaction solution. For **1q′** and **1r′**, a 0.1 mol% catalyst loading was effective enough when the reactions were conducted at 60 °C (entries 25 and 27), affording coupling products in 95 and 94% yields.

To extend the reaction scope, coupling reactions of benzylic halides with aryltitanium reagents were then studied [Eq. (3)], and results are listed in Table 3. Catalyst loadings of 0.05 to 0.1 mol% were employed for the coupling reactions of benzyl bromide with $ArTi(O\text{-}i\text{-}Pr)_3$ [Ar = 2-MeC_6H_4, 4-MeC_6H_4, 4-$(Me_3Si)C_6H_4$, or 2-naphthyl], affording products in 91 to 94% yields (entries 1–4). It is interestingly to note that the catalytic system tolerates benzylic bromides containing β-hydrogens. The coupling reaction of (1-bromoethyl)benzene (**1u**) with $(4\text{-}MeOC_6H_4)Ti(O\text{-}i\text{-}Pr)_3$ employing a 1 mol% catalyst loading produced **2u** in a 79% conversion with a 70% isolated yield (entry 5), and there was no observation of styrene which is the product derived from a β-hydrogen elimination process of **1u**. For coupling reactions of benzyl chloride with $ArTi(O\text{-}i\text{-}Pr)_3$ [Ar = 4-MeC_6H_4, 4-ClC_6H_4, 4-$(Me_3Si)C_6H_4$, or 2-naphthyl], a similar reactivity relative to coupling reactions of benzyl bromide was observed with the use of 0.05 to 0.1 mol% catalysts, affording the corresponding products in 90 to 92% yields (entries 6–9).

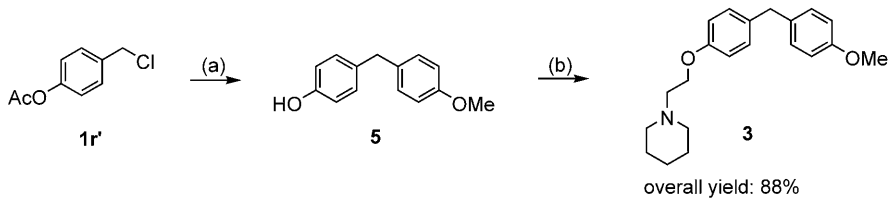
To demonstrate the application of the benzyl-aryl coupling reactions, the syntheses of bioactive diarylmethanes of **3** and **4** were conducted. Compound **3** has been tested for antitubercular activity,[29] and **4** shows activity as an HIV-1 integrase inhibitor.[21a] For the synthesis of **3**, the coupling reaction of (4-chloromethyl)phenyl acetate (**1r′**) with $(4\text{-}MeOC_6H_4)Ti(O\text{-}i\text{-}Pr)_3$ afforded diarylmethane **5** in one step. Compound **5** further reacted with 1-(2-chloroethyl)piperidine hydrochloride to furnish **3** (Scheme 1) in a superior overall yield of 88% in two steps. For compound **4** (Scheme 2), a benzyl-aryl coupling reaction of **1r′** with $PhTi(O\text{-}i\text{-}Pr)_3$ as the first step was conducted to give diarylmethane **2r**. Compound **2r** was converted to acetate **6** followed by a rearrangement reaction at 120 °C over 24 h to furnish **7**. Compound **7** was converted to 2-propoxo compound **8**, which reacted with dimethyl oxalate in the presence of NaOMe followed by hydrolysis to furnish the target compound **4**. This 5-step synthesis afforded **4** in an overall high yield of 42%. The molecular structure of **4** was determined to have the enol form in the solid state (Figure 1).

Table 3. Coupling of benzylic halides and $ArTi(O\text{-}i\text{-}Pr)_3$ catalyzed by the $Pd(OAc)_2/P(p\text{-tolyl})_3$ systems.[a]



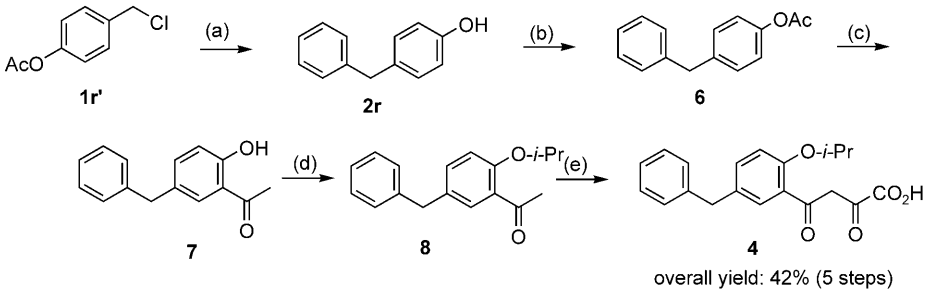
Entry	X	R^2	Ar	$Pd(OAc)_2$ [mol%]	Product **2**	Yield [%][b]
1[c]	Br	H	2-MeC_6H_4	0.1	**2b**	92
2	Br	H	4-MeC_6H_4	0.1	**2d**	92
3[d]	Br	H	4-$TMSC_6H_4$	0.1	**2s**	94
4	Br	H	2-naphthyl	0.05	**2t**	91
5	Br	Me	4-$MeOC_6H_4$	1	**2u**	70[e]
6	Cl	H	4-MeC_6H_4	0.05	**2d**	91
7	Cl	H	4-ClC_6H_4	0.05	**2k**	92
8	Cl	H	4-$TMSC_6H_4$	0.05	**2s**	92
9	Cl	H	2-naphthyl	0.1	**2t**	90

[a] Benzyl halide/$ArTi(O\text{-}i\text{-}Pr)_3$ = 1.0/1.1 mmol; solvent, toluene (1 mL); time, 2 h; room temperature.
[b] Isolated yields are average values of two runs.
[c] 2 mL toluene.
[d] 5 mL toluene.
[e] 79% conversion.



Reagents: (a) 0.5 mol% $Pd(OAc)_2$, 1 mol% $P(p\text{-tolyl})_3$, 1.1 equiv. $(4\text{-}MeOC_6H_4)Ti(O\text{-}i\text{-}Pr)_3$, 92.8%; (b) 1-(2-chloroethyl)piperidine hydrochloride, K_2CO_3, 94.6%.

Scheme 1.



Reagents: (a) 0.5 mol% $Pd(OAc)_2$, 1 mol% $P(p\text{-tolyl})_3$, 1.1 equiv. $PhTi(O\text{-}i\text{-}Pr)_3$, 95.1%; (b) AcCl, py, 93.6%; (c) $AlCl_3$, 1,2-dichlorobenzene, 81.6%; (d) *aq.* NaOH, HMPA, *i*-PrBr, 92.3%; (e) (1) $(CO_2CH_3)_2$, NaOMe; (2) NaOH; 63.2%.

Scheme 2.

Conclusions

In summary, a novel and extremely efficient benzyl-aryl coupling reaction of benzylic bromides or chlorides with $ArTi(O\text{-}i\text{-}Pr)_3$ is reported. $ArTi(O\text{-}i\text{-}Pr)_3$ reagents exhibit advantages over other organometallic compounds in terms of two features. First, the simple and economic catalytic system of $Pd(OAc)_2/P(p\text{-tolyl})_3$ is extremely efficient for the coupling reactions. The reactions proceed effectively at room tempera-

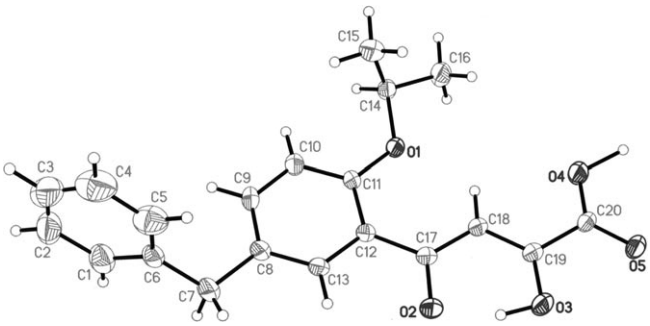


Figure 1. The molecular structure of **4**.

ture in short reaction times of ≤ 2 h. Second, low catalyst loadings of 0.02 to 0.2 mol% are good enough except for substrates containing strong electron-withdrawing substituents on the aromatic ring for which a higher reaction temperature of 60 °C is used to achieve the coupling products in excellent yields. In this study, a wide variety of benzylic bromides and chlorides have been examined, and the catalytic system shows similar reactivity toward both benzylic bromides and benzylic chlorides. The benzylic bromide containing β-hydrogens is also tolerated while using 1 mol% of the catalyst. Furthermore, concise syntheses of bioactive diarylmethane derivatives in high overall yields are also demonstrated.

Experimental Section

General Remarks

All syntheses and manipulations were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in a glovebox. Solvents were dried by refluxing for at least 24 h over P_2O_5 (dichloromethane) or sodium/benzophenone (THF, *n*-hexane or toluene) and were freshly distilled prior to use. ^{1}H NMR spectra were obtained with a Varian Mercury-400 (400 MHz) spectrometer, and ^{13}C NMR spectra were recorded with the Varian Mercury-400 (100.70 MHz) spectrometer. ^{1}H and ^{13}C chemical shifts were measured relative to TMS as the internal reference. ArTi(O-*i*-Pr)$_3$ reagents were prepared according to literature procedures.[20]

General Procedures for Coupling Reactions

Under a dry nitrogen atmosphere, to $Pd(OAc)_2$ and P(*p*-tolyl)$_3$ in 1:2 ratio and ArTi(O-*i*-Pr)$_3$ (1.10 mmol) in 1 mL of toluene was added a liquid benzylic halide (1.0 mmol), and the solution was stirred at room temperature for 2 h. The reaction mixture was quenched with water (10 mL) and was extracted with dichloromethane (3×30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated to dryness under reduced pressures. The coupling product was purified by column chromatography with hexane/EtOAc as eluent. For solid benzylic halides, $Pd(OAc)_2$, P(*p*-tolyl)$_3$, ArTi(O-*i*-Pr)$_3$, and the benzylic halide were placed in a reaction vessel and dissolved in 1 mL of toluene. The solution was stirred at room temperature for 2 h followed by the same work-up procedures as for the liquid benzylic halide.

Synthesis of 4-(4-Methoxybenzyl)phenol (5)[29]

(4-MeOC$_6$H$_4$)Ti(O-*i*-Pr)$_3$ (3.65 g, 11.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), and P(*p*-tolyl)$_3$ (30.5 mg, 0.100 mmol) were dissolved in 10 mL of toluene under a dry nitrogen atmosphere, followed by addition of 4-(chloromethyl)phenyl acetate (**1r′**) (1.54 mL, 10.0 mmol). The mixture was stirred at room temperature for 2 h and quenched with 10 mL of water. The solution was extracted with dichloromethane (3×30 mL). The combined organic phase was dried over $MgSO_4$, concentrated to dryness under reduced pressure, and purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 100/1) to give a pale yellow solid of **5**; yield: 1.99 g (92.8%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.10$–7.06 (m, 2H), 7.05–7.02 (m, 2H), 6.86–6.79 (m, 2H), 6.78–6.71 (m, *2*H), 4.79 (s, 1H), 3.85 (s, 2H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 157.4$, 153.6, 133.8, 133.5, 129.8, 129.6, 115.2, 113.8, 55.1, 39.9.

Synthesis of 1-{2-[4-(4-Methoxybenzyl)phenoxy]-ethyl}piperidine (3)[29]

A mixture of **5** (1.07 g, 5.00 mmol), anhydrous K_2CO_3 (3.46 g, 25.0 mmol), and 1-(2-chloroethyl)piperidine hydrochloride (1.38 g, 7.50 mmol) in dry acetone (100 mL) was refluxed for 7 h. The solution was filtered, and volatile materials of the filtrate were removed. To the residue was added water (50 mL) and the mixture was extracted with ethyl acetate (3×50 mL). The organic layer was washed with water (30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. The solution was dried under reduced pressures, and the residue was purified by column chromatography on basic silica gel (eluent: hexane/ethyl acetate = 65/35) to give the light yellow liquid **3**; yield: 1.54 g (94.6%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.09$–7.05 (m, 4H), 6.84–6.80 (m, 4H), 4.07 (t, $J = 6.0$ Hz, 2H), 3.85 (s, 2H), 3.77 (s, 3H), 2.75 (t, $J = 6.0$ Hz, 2H), 2.49 (br, 4H), 1.62–1.56 (m, 4H), 1.47–1.40 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 157.7$, 157.0, 133.5, 133.4, 129.51, 129.48, 114.3, 113.6, 65.7, 57.8, 54.9, 54.8, 39.9, 25.8, 24.0.

Synthesis of 4-Benzylphenol (2r)[30]

PhTi(O-*i*-Pr)$_3$ (3.32 g, 11.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), and P(*p*-tolyl)$_3$ (30.5 mg, 0.100 mmol) were dissolved in 10 mL of toluene under a dry nitrogen atmosphere followed by an addition of 4-(chloromethyl)phenyl acetate (**1r′**) (1.54 mL, 10.0 mmol). The mixture was stirred at room temperature for 2 h and quenched with 10 mL of water. The solution was extracted with dichloromethane (3×30 mL). The combined organic phase was dried over $MgSO_4$, concentrated to dryness under reduced pressures, and purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 100/1) to give **2r** as a white solid; yield: 1.75 g (95.1%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–7.24 (m, 2H), 7.20–7.14 (m, 3H), 7.03–7.01 (m, 2H), 6.73–6.71 (m, 2H), 4.91 (br, 1H), 3.88 (s, 2H); ^{13}C{^{1}H} NMR

(100 MHz, $CDCl_3$): $\delta = 153.4$, 141.4, 133.4, 130.0, 128.7, 128.4, 125.9, 115.3, 40.9.

Synthesis of 4-Benzylphenyl Acetate (6)

Acetyl chloride (0.282 mL, 4.0 mmol) was added dropwise to a solution of **2r** (0.608 g, 3.3 mmol) and pyridine (0.294 mL, 3.6 mmol) in dichloromethane (2.5 mL). After 3 h, the mixture was washed, in sequence, with water (10 mL), 10% aqueous HCl (10 mL), water (12 mL), and a saturated solution of $NaHCO_3$ (10 mL). The organic phase was dried and concentrated to give 4-benzylphenyl acetate **6** as a yellow oil; yield: 0.698 g (93.6%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.25 (m, 2H), 7.21–7.17 (m, 5H), 7.01–6.98 (m, 2H), 3.97 (s, 2H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 169.3$, 148.8, 140.5, 138.5, 129.6, 128.7, 128.3, 126.0, 121.3, 41.0, 20.8; HR-MS: $m/z = 226.0999$, calcd. for $C_{15}H_{14}O_2$: 226.0995 [M^+]; elemental analysis, calcd. for $C_{15}H_{14}O_2$: C 79.62, H 6.24%; found: C 79.35, H 6.02%.

Synthesis of 1-(5-Benzyl-2-hydroxyphenyl)ethanone (7)[31]

Aluminum chloride (0.411 g, 3.08 mmol) was added to a solution of **6** (0.698 g, 3.09 mmol) in 1,2-dichlorobenzene (10 mL) under a dry nitrogen atmosphere. After being heated at 120 °C for 24 h, the reaction mixture was allowed to cool to room temperature, treated with dichloromethane (25 mL), and poured into an ice cold 10% aqueous HCl (20 mL). The organic phase was separated, washed with 10% HCl (3×30 mL) and water (20 mL), dried over $MgSO_4$, and concentrated to dryness under reduced pressures to give an oily liquid. The liquid was distilled under vacuum (0.1 torr) at 90 °C to remove dichlorobenzene, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 20/1) to give **7** as a pale yellow solid; yield: 0.569 g (81.6%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.17$ (s, 1H), 7.51 (d, $J = 2.0$ Hz, 1H), 7.31–7.26 (m, 3H), 7.22–7.20 (m, 1H), 7.18–7.15 (m, 2H), 6.90 (d, $J = 8.4$ Hz, 1H), 3.92 (s, 2H), 2.55 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 204.4$, 160.7, 140.6, 137.3, 131.4, 130.4, 128.6, 128.5, 126.2, 119.4, 118.4, 40.8, 26.5.

Synthesis of 1-(5-Benzyl-2-isopropoxyphenyl)-ethanone (8)[32]

To a solution of **7** (0.330 g, 1.84 mmol) in 5 mL of HMPA was added 25% aqueous sodium hydroxide solution (0.589 g, 3.68 mmol), and the solution was stirred for 5 min followed by an addition of isopropyl bromide (0.702 mL, 7.47 mmol). After stirring for 2.5 h at room temperature, the reaction mixture was poured into 18 mL of 5% HCl, and the solution was extracted with diethyl ether (3×20 mL). The combined diethyl ether extract was washed with water (3×25 mL), dried over $MgSO_4$, and evaporated under reduced pressures to afford **8** as a pale yellow liquid; yield: 0.455 g (92.3%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 2.4$ Hz, 1H), 7.30–7.25 (m, 3H), 7.23–7.20 (m, 1H), 7.18–7.16 (m, 2H), 6.86 (d, $J = 8.4$ Hz, 1H), 4.63 (heptet, $J = 6.0$ Hz, 1H), 3.92 (s, 2H), 2.61 (s, 3H), 1.38 (d, $J = 6.0$ Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 200.0$, 155.6, 140.8, 133.7, 132.8, 130.4, 128.9, 128.6, 128.3, 125.9, 113.6, 70.4, 40.7, 32.9, 21.9.

Synthesis of 4-(5-Benzyl)-2-isopropoxyphenyl)-2,4-dioxobutanoic Acid (4)[21b]

To a cold solution (0 °C) of $NaOCH_3$ (0.216 g, 4.00 mmol) in dry toluene (50 mL) were added dimethyl oxalate (0.319 g, 2.70 mmol) and **8** (0.268 g, 1.00 mmol) in dry DME (5 mL) under a dry nitrogen atmosphere. The solution was stirred for 0.5 h at 0 °C and then heated to 80 °C for 1.5 h. The reaction mixture was quenched with 1.0 M HCl (50 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated to dryness under reduced pressures to give a residue which was purified by column chromatography (hexane/ethyl acetate = 4/1) to furnish the methyl ester of **4** (yield: 0.256 g, 75.0%). The methyl ester (0.080 g, 0.23 mmol) was dissolved in 4 mL of THF/CH_3OH (1:1) and stirred with 1 M NaOH (5.0 mL, 5.0 mmol) for 1 h at room temperature. The solution was then washed with diethyl ether (20 mL). The water phase was acidified with 2 M HCl to pH 1–2 and extracted with ethyl acetate (3×20 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (40 mL) and brine (40 mL), dried over $MgSO_4$, and evaporated to dryness under reduced pressures to give compound **4** as a light yellow solid; yield: 0.065 g (85.4%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 2.8$ Hz, 1H), 7.63 (s, 1H), 7.32–7.26 (m, 3H), 7.23–7.17 (m, 3H), 6.91 (d, $J = 8.8$ Hz, 1H,), 4.69 (heptet, $J = 6.0$ Hz, 1H), 3.96 (s, 2H), 1.44 (d, $J = 6.0$ Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 188.7$, 169.8, 164.5, 156.7, 140.6, 135.5, 133.3, 130.9, 128.8, 128.6, 126.2, 123.7, 114.2, 102.5, 71.5, 40.8, 21.9.

Chromatographic Condition and Spectroscopic Data of Coupling Products

Diphenylmethane (2a):[33] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.161 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.24 (m, 4H), 7.21–7.17 (m, 6H), 3.98 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta =$ 141.1, 128.9, 128.4, 126.0, 41.9.

1-Benzyl-2-methylbenzene (2b):[33] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.167 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–7.22 (m, 2H), 7.20–7.08 (m, 7H), 3.98 (s, 2H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 140.3$, 138.9, 136.5, 130.2, 129.9, 128.7, 128.3, 126.4, 126.0, 125.9, 39.4, 19.6.

1-Benzyl-3-methylbenzene (2c):[33] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.179 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.26 (m, 2H), 7.20–7.15 (m, 4H), 7.01–6.98 (m, 3H), 3.94 (s, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 141.2$, 141.0, 137.9, 129.7, 128.9, 128.4, 128.3, 126.8, 126.0, 125.9, 41.8, 21.3.

1-Benzyl-4-methylbenzene (2d):[33] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.169 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$–7.27 (m, 2H), 7.20–7.16 (m, 3H), 7.12–7.06 (m, 4H), 3.94 (s, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 141.4$, 138.0, 135.5, 129.1, 128.82, 128.78, 128.4, 125.9, 41.5, 21.0.

3-Benzylanisole (2e):[23a] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.196 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$–7.27 (m, 2H), 7.21–7.18 (m, 4H), 6.80–6.72 (m, 3H), 3.95 (s, 2H), 3.76 (s, 3H); $^{13}C\{^1H\}$

NMR (100 MHz, $CDCl_3$): δ = 159.6, 142.6, 140.8, 129.3, 128.8, 128.4, 126.0, 121.3, 114.7, 111.2, 54.9, 41.8.

4-Benzylthioanisole (2f):[34] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.210 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2H), 7.22–7.16 (m, 5H), 7.12–7.10 (m, 2H), 3.94 (s, 2H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 140.9, 138.1, 135.7, 129.4, 128.8, 128.4, 127.0, 126.1, 41.3, 16.1.

1-Benzyl-4-*tert*-butylbenzene (2g):[35] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.219 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.28 (m, 4H), 7.22–7.18 (m, 3H), 7.13–7.10 (m, 2H), 3.95 (s, 2H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 148.7, 141.2, 138.0, 128.9, 128.5, 128.4, 126.0, 125.3, 41.4, 34.3, 31.4.

2-Benzylbiphenyl (2h):[34] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.241 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.14 (m, 12H), 6.99–6.97 (m, 2H), 3.96 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 142.2, 141.6, 141.4, 138.1, 130.3, 130.1, 129.2, 128.8, 128.2, 128.0, 127.4, 126.8, 126.1, 125.7, 39.0.

3-Benzylbiphenyl (2i):[36] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.241 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2H), 7.41–7.36 (m, 4H), 7.35–7.24 (m, 4H), 7.21–7.14 (m, 4H), 4.02 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 141.6, 141.4, 141.2, 141.0, 128.91, 128.85, 128.7, 128.5, 127.9, 127.8, 127.19, 127.15, 126.1, 125.0, 42.0.

1-Benzyl-3,5-dimethoxybenzene (2j):[37] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.212 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 2H), 7.21–7.18 (m, 3H), 6.36–6.34 (m, 2H), 6.32–6.31 (m, 1H), 3.91 (s, 2H), 3.75 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 160.7, 143.3, 140.6, 128.8, 128.3, 126.0, 107.0, 97.8, 55.0, 42.0.

1-Benzyl-4-chlorobenzene (2k):[33] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.192 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 5H), 7.15 (d, J = 6.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 3.93 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 140.4, 139.5, 131.8, 130.2, 128.8, 128.48, 128.46, 126.2, 41.1.

1-Benzyl-4-bromobenzene (2l):[38] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.197 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2H), 7.31–7.25 (m, 2H), 7.23–7.19 (m, 1H), 7.15 (d, J = 7.2 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 3.93 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 140.3, 140.0, 131.4, 130.6, 128.8, 128.5, 126.2, 119.9, 41.2.

4-Benzylbenzonitrile (2m):[39] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.162 g (84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.55 (m, 2H), 7.33–7.22 (m, 5H), 7.17–7.14 (m, 2H), 4.03 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 146.6, 139.2, 132.1, 129.5, 128.8, 128.6, 126.5, 118.9, 109.8, 41.8.

5-Benzyl-1,3-bis(trifluoromethyl)benzene (2n):[23c] Eluent: hexane/ethyl acetate = 10/1; colorless liquid; yield: 0.097 g (32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.72 (m, 1H), 7.63 (s, 2H), 7.34–7.32 (m, 2H), 7.28–7.25 (m, 1H), 7.19–7.16 (m, 2H), 4.10 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 143.6, 138.8, 131.9 (q, J = 32.7 Hz), 128.9 (m), 127.3, 127.2, 126.9, 123.4 (q, J = 270 Hz), 120.3 (m), 41.5.

4-Benzylanisole (2o):[33] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.178 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 2H), 7.21–7.15 (m, 3H), 7.12–7.08 (m, 2H), 6.84–6.81 (m, 2H), 3.92 (s, 2H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.9, 141.5, 133.1, 129.7, 128.7, 128.3, 125.9, 113.8, 55.0, 40.9.

1-Benzyl-4-fluorobenzene (2p):[40] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.173 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 2H), 7.18–7.10 (m, 5H), 6.99–6.94 (m, 2H), 3.95 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.6, 160.2, 140.9, 136.8, 136.7, 130.3, 130.2, 128.8, 128.5, 126.2, 115.3, 115.1, 41.0.

1-Benzyl-4-vinylbenzene (2q):[41] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.186 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 4H), 7.21–7.13 (m, 5H), 6.69 (dd, J = 17.6, 11.2 Hz, 1H), 5.72 (dd, J = 17.6, 0.8 Hz, 1H), 5.20 (dd, J = 11.2, 0.8 Hz, 1H), 3.96 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 140.9, 140.7, 136.5, 135.4, 129.1, 128.8, 128.4, 126.3, 126.1, 113.2, 41.6.

4-Benzylphenol (2r):[30] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.175 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2H), 7.21–7.14 (m, 3H), 7.04–7.01 (m, 2H), 6.74–6.71 (m, 2H), 4.92 (br, 1H), 3.89 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.4, 141.4, 133.4, 130.0, 128.7, 128.4, 125.9, 115.3, 40.9.

(4-Trimethylsilylbenzyl)benzene (2s):[42] Eluent: hexane/ethyl acetate = 100/1; colorless liquid; yield: 0.225 g (94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2H), 7.31–7.24 (m, 2H), 7.21–7.17 (m, 5H), 3.97 (s, 2H), 0.24 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 141.7, 140.9, 137.7, 133.5, 129.0, 128.4, 128.3, 126.1, 41.9, −1.1.

2-Benzylnaphthalene (2t):[39] Eluent: hexane/ethyl acetate = 20/1; white solid; yield: 0.198 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.74 (m, 3H), 7.63 (s, 1H), 7.47–7.40 (m, 2H), 7.33–7.27 (m, 3H), 7.25–7.18 (m, 3H), 4.15 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 140.9, 138.5, 133.6, 132.0, 129.0, 128.4, 128.0, 127.6, 127.5, 127.1, 126.1, 125.9, 125.3, 42.0.

4-(1-Phenylethyl)anisole (2u):[43] Eluent: hexane/ethyl acetate = 20/1; colorless liquid; yield: 0.148 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.13 (m, 5H), 6.84–6.81 (m, 2H), 4.10 (q, J = 7.2 Hz, 1H), 3.77 (s, 3H), 1.60 (d, J = 7.2 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.8, 146.7, 138.5, 128.5, 128.3, 127.5, 125.9, 113.6, 55.1, 43.9, 22.0.

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