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Room-Temperature Benzylic Alkylation of Benzylic Carbonates: Improvement of Palladium Catalyst and Mechanistic Study

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Supporting Information

ABSTRACT: The palladium catalyst for the nucleophilic substitution of benzyl carbonates was improved by using 1,1′-bis(diisopropylphosphino)ferrocene (D*i*PrPF) as the ligand. The [Pd(η^3-C_3H_5)(cod)]BF_4–D*i*PrPF catalyst allows the benzylic substitution with soft carbanions to proceed even at 30 °C, affording the desired products in high yields (up to 99% yield). Thermally unstable pyridylmethyl esters are employable as the electrophilic substrates for the benzylic alkylation with the improved catalyst. Furthermore, we investigated the mechanism of the catalytic benzylic alkylation by means of D*i*PrPF ligand. The palladium(0) complex bearing D*i*PrPF activates the benzylic C–O bond to form the (benzyl)palladium(II) intermediate at room temperature. The coordination mode of the benzyl ligand would be equilibrium between the η^1- and η^3-manner. The nucleophile would preferentially react with the η^3-benzyl ligand to give the desired product.

KEYWORDS: *palladium, benzylic substitution, benzyl carbonate, active methine, (η^3-benzyl)metal complex*

INTRODUCTION

Nucleophilic substitution of benzylic electrophiles is frequently used in organic synthesis for protecting reactive functional groups as well as for constructing molecular frameworks. Benzylic bromides or chlorides are commonly employed as the electrophilic substrates for the reaction. In the benzylic electrophiles, their aryl groups lead to an increase in reactivity of the halide leaving group.[1] The enhanced leaving-group ability often causes significant decomposition of the substrate and/or undesirable side reactions. Sulfonates are also known as good leaving groups for the nucleophilic substitution, but their high reactivities would often cause significant formation of side products. Therefore, a less reactive functionality, such as acetate or hydroxide,[2] would be often required as the leaving group for the nucleophilic substitution of such reactive substrates. Moreover, use of the alkyl halide or sulfonate is disadvantageous for contributing to an environmentally benign chemical industry. Carboxylates and carbonates would have less impact on creatures than the halides and sulfonates.

For the nucleophilic substitution of allylic electrophiles, acetate or a related functionality is often chosen as the leaving group. Allylic carboxylates react with various nucleophiles in the presence of a palladium catalyst (Figure 1, path a)[3,4] In the catalytic process, the Tsuji–Trost reaction, palladium(0) species **A** activates the allylic C—O bond to form an electrophilic (η^3-allyl)palladium(II) intermediate **B**.[5] Coordination of the palladium to the C=C double bond would facilitate the elimination of the acyloxy group from allylic carbon. An allylic terminus of **B** undergoes the attack of nucleophile to give the alkylation product and regenerate **A**.[6] A structural analogy between allyl and benzyl groups might

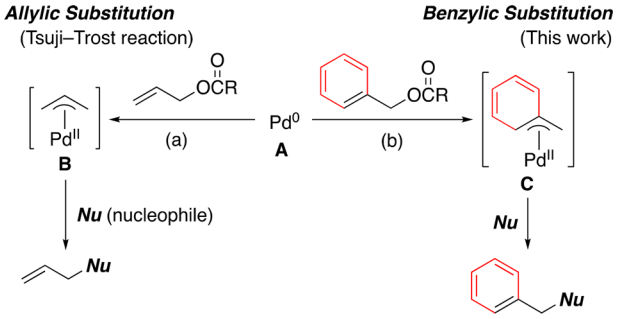

Figure 1. Allylic vs benzylic substitution.

suggest to us that benzylic carboxylates and carbonates are also activated with the palladium(0) complex to form (η^3-benzyl)palladium **C**,[7] which would be electrophilic (path b).[8] The benzylic esters might function as good substrates for the nucleophilic substitution in the presence of a palladium catalyst. However, the η^3-coordination of the benzyl ligand is thermodynamically unfavorable because it involves the dearomatization of the arene ring. Despite this difficulty, Fiaud and Legros had successfully developed the benzylic substitution of naphthylmethyl esters with a palladium catalyst in 1992.[9] The naphthyl group would facilitate generation of the η^3-benzyl intermediate because the fused-arene ring requires

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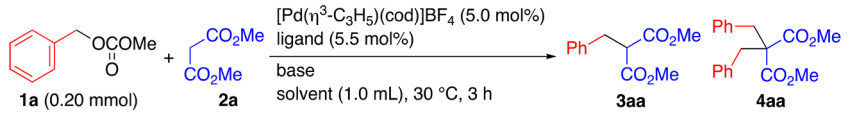
Table 1. Optimization of Reaction Conditions[a]



1a (0.20 mmol) 2a 3aa 4aa

entry	ligand	solvent	base	yield[b] (3aa)	yield[b] (4aa)
1	**L1**	THF	Cs_2CO_3	0	0
2	**L2**	THF	Cs_2CO_3	20	18
3	**L2**	DMF	Cs_2CO_3	49	44
4	**L2**	dioxane	Cs_2CO_3	44	24
5	**L2**	toluene	Cs_2CO_3	28	4
6	**L2**	DMF	K_2CO_3	0	0
7	**L2**	DMF	K_3PO_4	39	11
8	**L2**	DMF	DBU	31	7
9	**L2**	DMF		0	0
10	**L1**	DMF	Cs_2CO_3	5	2
11	**L3**	DMF	Cs_2CO_3	42	50
12	**L4**	DMF	Cs_2CO_3	0	0
13	**L5**	DMF	Cs_2CO_3	0	0
14	**L6**[c]	DMF	Cs_2CO_3	7	4
15	**L7**	DMF	Cs_2CO_3	29	33
16	**L8**	DMF	Cs_2CO_3	0	0
17	**L9**	DMF	Cs_2CO_3	0	0
18[d]	**L2**	DMF	Cs_2CO_3	43[e]	52[e]

[a]Reactions were conducted on a 0.20 mmol scale in a solvent (1.0 mL) at 30 °C for 3 h unless otherwise noted. The ratio of **1a**:**2a**:base:[Pd(η^3-C_3H_5)(cod)]BF_4:ligand was 20:30:30:1.0:1.1. [b]Yields were determined by GC analysis and calibrated with an internal standard, tetradecane (average of two runs). [c]Phosphonium tetrafluoroborate salt of **L6** was used as the ligand precursor. [d]The reaction was carried out on a 1.0 mmol scale with 1.0 mol % catalyst loading for 24 h. [e]Isolated yields.

relatively low energy for its dearomatization. Since then, the reaction has been studied and expanded by many researchers.[10] Enantioselective catalysts, nowadays, have been successfully developed for the benzylic substitution.[11] Meanwhile, the monocyclic benzyl esters are challenging substrates for palladium-catalyzed benzylic substitution as compared with the naphthylmethyl substrates,[12] because the benzene ring is more stabilized with its own aromaticity as compared to naphthalene.

We previously developed the nucleophilic substitution of the monocyclic benzyl carbonates[13] and acetates.[14] The benzylic esters were converted into the desired products in high yields with the palladium catalyst, which was generated from a palladium precursor and appropriate chelating bisphosphine ligand, e.g., DPPF or DPEphos. With the palladium catalyst, the reaction required mild heating to afford the desired benzylation products in high yields. However, the heating condition sometimes causes the significant decomposition of benzylic substrates. Herein, we report a highly active palladium catalyst for the benzylic alkylation of benzyl carbonates with soft carbanions. The catalyst, 1,1′-bis(diisopropylphosphino)-ferrocene (D*i*PrPF)−palladium complex, allows the reaction to give the desired products in high yields at room temperature. Under the mild condition, some thermally unstable benzylic carbonates are transformed into the substitution products in high yields. Furthermore, we investigated the mechanism of the catalytic reaction by means of the D*i*PrPF−palladium complex.

RESULTS AND DISCUSSION

Optimization of Catalyst toward the Room-Temperature Benzylic Substitution. We presumed that the oxidative addition of benzylic C−O bond to palladium(0) was sluggish and the rate-determining step in the benzylic substitution of benzyl carbonates through the DPPF (**L1**)−palladium catalysis.[13a,b] Use of an electron-donating ligand is known to facilitate oxidative addition to a low-valent metal complex in general.[15] The palladium catalyst might be improved by using a bidentate ligand bearing alkyl substituents on its phosphorus atoms. To confirm the working hypothesis, we attempted the reaction of benzyl methyl carbonate (**1a**) with dimethyl malonate (**2a**) by using D*i*PrPF[16] (**L2**) in place of **L1**. The reaction was conducted in THF at 30 °C in the presence of Cs_2CO_3 and 5.0 mol % of the catalyst, which was prepared *in situ* from [Pd(η^3-C_3H_5)(cod)]BF_4 and **L1** or **L2** (Table 1, entries 1 and 2). Use of **L1** resulted in the formation of neither the benzylated malonate **3aa** nor **4aa**, while the **L2**−palladium catalyst afforded a mixture of **3aa** and **4aa** in moderate combined yield. The rate of the benzylic substitution was enhanced by using a more polar solvent (entries 2−5). DMF is the solvent of choice for the present palladium catalysis (entry 3). The benzyl ester **1a** almost disappeared from the reaction mixture within 3 h to give **3a** and **4a** in 49% and 44%, respectively. The efficiency of the palladium catalyst significantly deteriorated by using bases other than Cs_2CO_3 (entries 6−8). No benzylation products were detected in the reaction conducted without any bases, although the methoxide stemming from **1a** might work as a base (entry 9). Choice of phosphine ligand is crucial for the palladium catalysis (see Chart 1). The catalysis was remarkably affected by the substituents on the phosphorus atoms in the ferrocenyl phosphine ligand. The DPPF−palladium complex could catalyze the present benzylic substitution in DMF, but products **3aa** and **4aa** were obtained in very low yields from the reaction at 30 °C (entry 10). DCyPF[17] (**L3**) as with **L2** functioned as a good spectator ligand for the palladium catalyst

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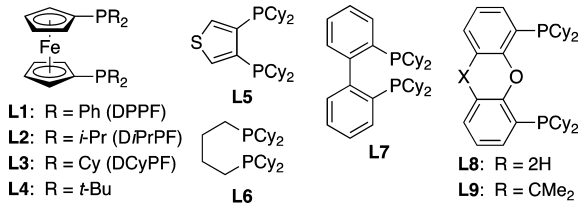
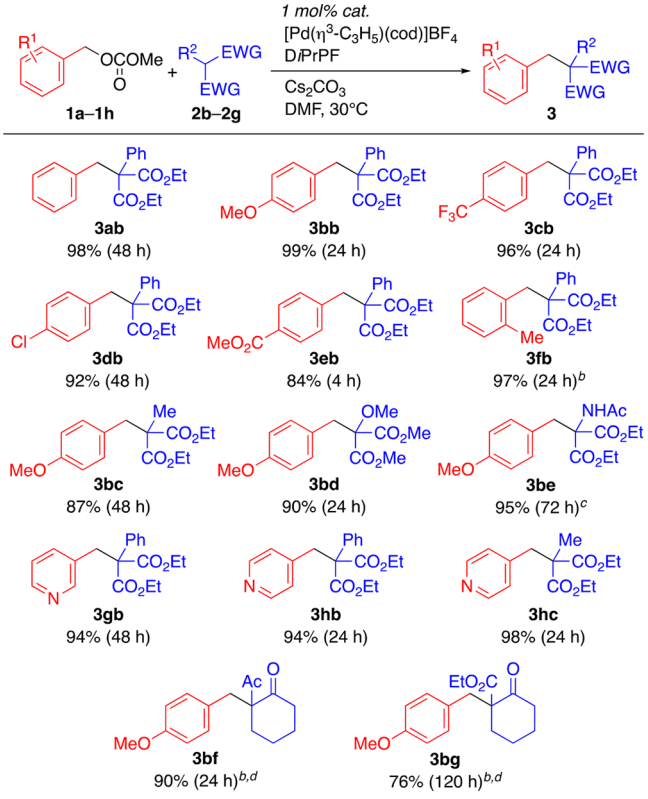
Chart 1. Structures of Phosphine Ligands



to give the benzylation products in high combined yield (entry 11). The catalytic activity disappeared by replacing the isopropyl or cyclohexyl by a *tert*-butyl group (entry 12). Furthermore, the reaction was attempted with a variety of chelating bis(dicyclohexylphosphino) ligands **L5**–**L9** to investigate effect of their bridged structure (entries 13–17). The bridged structure also impacted the catalytic benzylic substitution. Use of the ligands except **L7** resulted in no or little production of **3aa** and **4aa** at 3 h. No benzylic substitution was observed in the reactions using **L8** and **L9**, although the DPEphos– or xantphos–palladium complex often works as a good catalyst for the reactions involving the benzylic C–O bond activation.[13a,c–f,18] To our surprise, the **L7**–palladium catalyst bearing a biaryl backbone also could promote the reaction with good efficiency, while the ligand is inferior to **L2** or **L3**. Under the optimized conditions above, the benzylic substitution of **1a** with **2a** was carried out on a 1.0 mmol scale with 1.0 mol % catalyst loading (entry 18). The benzyl ester **1a** was completely consumed within 24 h to give **3aa** and **4aa** in 43% and 52% isolated yields, respectively.

Substrate Scope. As a result of the optimization of the reaction conditions, the benzylation of **2a** with **1a** proceeds with high efficiency in DMF by using Cs_2CO_3 as the base and the [Pd(η^3-C_3H_5)(cod)]BF_4–D*i*PrPF complex as the catalyst. As with **2a**, diethyl phenylmalonate (**2b**) was benzylated with **1a** at 30 °C to give benzylphenylmalonate **3ab** in 98% yield (see Table 2). Both electron-rich and electron-deficient benzyl esters **1b** and **1c** also worked as the good electrophilic substrates for the palladium-catalyzed benzylation to give the desired products **3bb** and **3cb** in high yields. The chloro and alkoxycarbonyl functionalities in the benzylic substrates, **1d** and **1e**, were compatible with the palladium catalysis. Remarkably, the reaction of **1e** was completed within 4 h to form the substitution product **3eb** in high yield. However, *o*-substituted benzyl ester **1f** is much less reactive than other benzyl esters. The methyl group might hamper the oxidative addition of the benzylic C–O bond to the palladium(0). The reaction of **1f** with **2b** required warming at 50 °C for the complete conversion to **3fb**. A range of α-substituted malonates also work as the nucleophiles for the catalytic benzylic substitution. Methyl- and methoxymalonates, **2c** and **2d**, were alkylated with **1b** in high yields under the optimized condition. (Acetylamino)malonate **2e** was converted into the benzylated product **3be** in high yield under a dilute condition (3.0 mL of DMF) because of the low solubility of **2e**. It is noteworthy that (pyridinyl)methyl carbonates **1g** and **1h** reacted with **2b** or **2c** in high yields through the present palladium catalysis. The carbonate substrates significantly decomposed during the catalytic benzylic substitution when DPPF (**L1**) was used in place of **L2** at 80 °C.[13a] The thermal decomposition of **1g** and **1h** might be avoided by carrying out the reaction at a lower temperature. With the **L2**–palladium complex, no benzylation was observed in the reaction of 1,3-

Table 2. Substrate Scope of Benzylic Substitution



[a]Reactions were conducted on a 1.0 mmol scale in DMF (1.0 mL) at 30 °C unless otherwise noted. The ratio of **1**:**2**:Cs_2CO_3:[Pd(η^3-C_3H_5)(cod)]BF_4:ligand was 100:110:110:1.0:1.1. [b]At 50 °C. [c]In 3.0 mL of DMF. [d]**L3** was used as the ligand in place of **L2**.

diketone **2f** or β-ketoester **2g** with **1b** at 30 °C. Coordination of **2f** or **2g** might obstruct the oxidative addition of **1b** to the palladium(0) species. The successful formations of **3bf** and **3bg** were achieved by using DCyPF (**L3**), whose cyclohexyl substituents might hamper the access of **2f** or **2g** to the palladium(0).

Mechanistic Study. A reaction pathway could be supposed for the present benzylic substitution by analogy to the Tsuji–Trost reaction as shown in Figure 2.[4] The catalytic cycle starts from the oxidative addition of the benzylic C–O bond of **1** to palladium(0) species **A** to form (η^3-benzyl)-palladium(II) intermediate **C**. The resulting electrophilic organometallic species undergoes the nucleophilic attack of

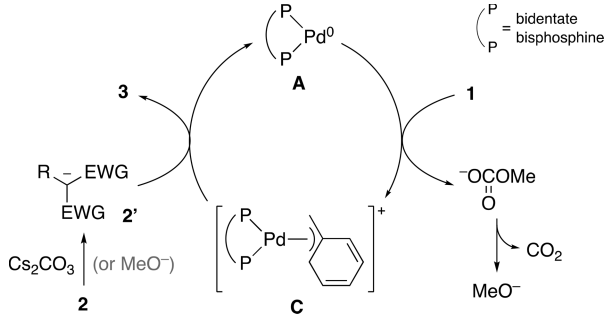


Figure 2. Supposed reaction pathway of the palladium-catalyzed benzylic substitution.

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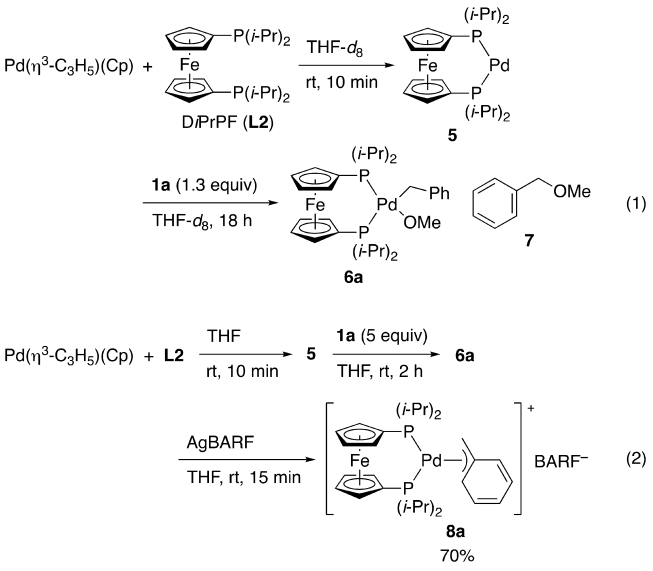
the soft carbanion **2′** to afford the benzylated product **3** and regenerate palladium(0) **A**.

To confirm the above postulation, the stoichiometric reaction of the **L2**−palladium(0) complex and benzyl methyl carbonate **1a** was monitored with NMR measurement (eq 1 in Scheme 1). The D*i*PrPF-ligated palladium(0) **5** was prepared

Scheme 1. Reactions of Palladium(0) 5 with Benzyl Ester 1a



in situ by mixing Pd(η^3-C_3H_5)(Cp) and **L2** in THF-d_8 at ambient temperature for 10 min.[19] The resonance of the palladium(0) species appeared as a broad peak **I** at 32.7 ppm in the ^{31}P NMR spectrum of the resulting mixture (Figure 3a). An allylcyclopentadiene, which formed through the reductive elimination from Pd(η^3-C_3H_5)(Cp), may cause the peak to broaden because of the weak interaction between the triene and palladium. The palladium(0) **5** gradually reacted with benzyl carbonate **1a** at ambient temperature to give new peaks **II**, and then, the signals **III** of benzyl methyl ether (**7**) gradually emerged in the ^{1}H NMR spectrum. The ^{31}P and ^{1}H NMR spectra of the reaction mixture at 18 h are given in Figures 3b and 4b, respectively. In the ^{31}P NMR spectrum, a pair of doublets **II** appeared at 35.1 and 46.5 ppm with 31 Hz of P−P spin coupling constant. The peaks **II** would be assigned to a (benzyl)palladium(II) complex, because the signal of the benzylic hydrogens was observed at 3.18 ppm in the ^{1}H NMR. Its H−P coupling disappeared when the spectrum was observed with ^{31}P decoupling (Figure 4c). The benzyl ligand would be bound to the palladium atom through η^1-coordination because the signal pattern of its aromatic protons is similar to those of (η^1-benzyl)palladium(II)s in the literature[20] and authentic Pd(η^1-benzyl)Cl(**L2**) (**6b**) (*vide infra*). These observations indicate that the benzylic C−O bond in **1a** is cleaved by the **L2**−palladium(0) **5** even at room temperature. As the result of the oxidative addition of the benzylic C−O bond, **5** would be converted to Pd(η^1-benzyl)(OMe)(**L2**) (**6a**) through the decarboxylation of the leaving group. The undesirable formation of **7** would be caused by the reductive elimination from **6a**.

Although no formation of (η^3-benzyl)palladium was detected in the above NMR analyses, (η^1-benzyl)palladium **6a** might be in equilibrium with the cationic η^3-benzyl complex. To eliminate the methoxide ligand from **6a**, silver tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (AgBARF) was added to *in situ* generated **6a**, which was prepared by the reaction of **L2**−palladium(0) **5** with excess **1a** in THF (eq 2, Scheme 1). Yellow precipitate was formed in the reaction mixture, and the resulting palladium complex was isolated in 70% yield. Its ^{31}P NMR spectrum was observed in CD_2Cl_2 at ambient temperature and consisted of a pair of broad peaks **IV** at 38.9 and 59.3 ppm (Figure 3c). The structure of the complex in the solid state was definitely confirmed to be [Pd(η^3-benzyl)(**L2**)]BARF (**8a**) by its X-ray crystallographic structure analysis (*vide infra*).

To elucidate the structures and dynamic behaviors of the above (benzyl)palladium species, authentic (η^1- and η^3-benzyl) palladium complexes bearing **L2** were prepared as shown in Scheme 2. Pd(η^1-benzyl)Cl(**L2**) (**6b**) was obtained from the reaction of Pd(η^1-benzyl)Cl(cod)[21] (**9**) with **L2** in CH_2Cl_2 (eq 3, Scheme 2). In the ^{31}P NMR spectrum of **6b**, a pair of doublet peaks appeared at 31.6 and 42.4 ppm with 28 Hz of P−P coupling constant. The resonances of the aromatic protons in the benzyl ligand clearly separated into three peaks at 6.90, 7.01, and 7.76 ppm, which are, respectively, assigned to

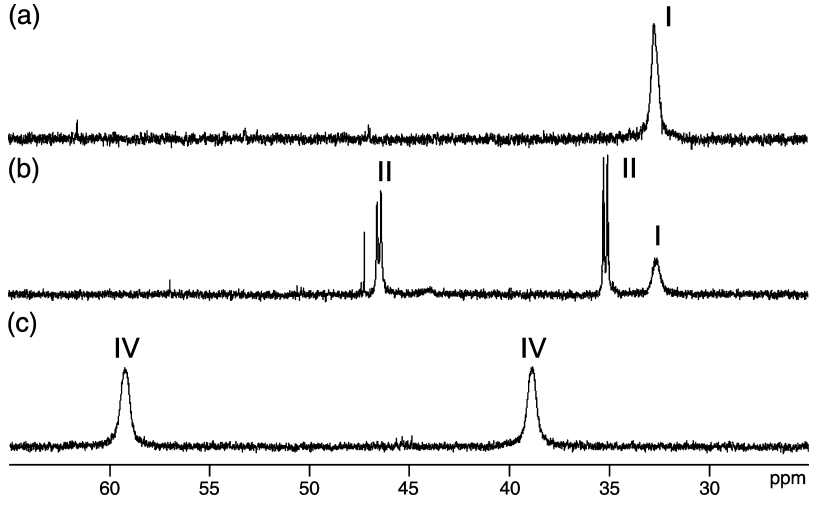


Figure 3. ^{31}P{^{1}H} NMR spectra (a) of the *in situ*-generated **5** in THF-d_8, (b) of the reaction mixture of **5** and **1a** in THF-d_8 after 18 h, and (c) of **8a** in CD_2Cl_2 at ambient temperature.

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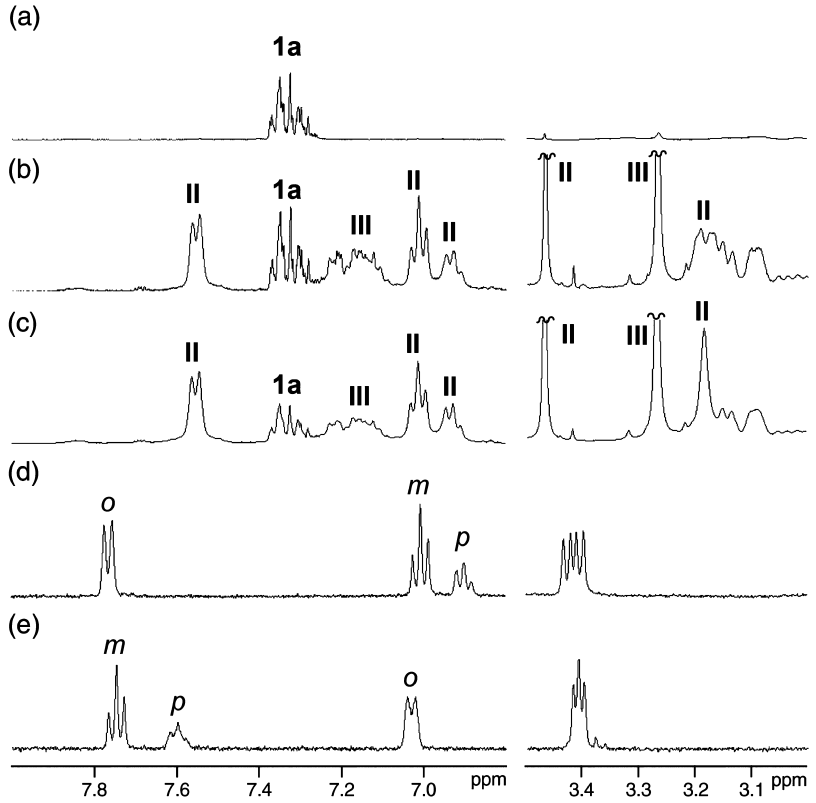
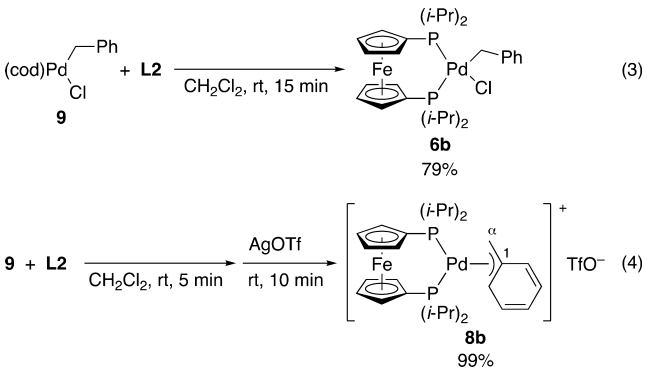


Figure 4. ^{1}H NMR spectra (a) of the reaction mixture of **5** and **1a** in THF-d_8 after 5 min, (b) of the reaction mixture after 18 h, (c) of the reaction mixture after 18 h with ^{31}P decoupling, (d) of authentic **6b**, and (e) of authentic **8b**.

Scheme 2. Preparation of Authentic (η^1- and η^3-Benzyl)palladium(II)s



the *p*-, *m*-, and *o*-protons from each splitting pattern and integral ratio (Figure 4d). The signal at 3.42 ppm was assigned to the benzylic protons and split into a double doublet because of the spin coupling with the two nonequivalent phosphorus atoms. Meanwhile, the authentic (η^3-benzyl)palladium(II) was prepared by treating the solution of *in situ* generated **6b** with AgOTf (eq 4, Scheme 2).[8] As with **8a**, the resulting [Pd(η^3-benzyl)(**L2**)]OTf (**8b**) exhibited a pair of broad peaks at 39.1 and 58.5 ppm in its ^{31}P NMR spectrum at ambient temperature. In the ^{1}H NMR spectrum of **8b**, the protons in the benzyl ligand provided relatively sharp peaks at 3.41, 7.03, 7.60, and 7.75 ppm (Figure 4e), while the signals of **L2** broadened. Each peak of the benzyl ligand was assigned to its benzylic, *o*-, *p*-, or *m*-protons, respectively. Furthermore, the ^{31}P and ^{1}H NMR spectra of **8b** were observed in THF-d_8 at various temperatures (see the SI). The broad peaks in the ^{31}P NMR spectrum turned to sharp doublet peaks below 0 °C, while the peak at 58.5 ppm shifted to upfield as the measurement temperature lowered. In the variable-temperature ^{1}H NMR measurements, the coalescent peak of isopropyl and ferrocene moiety in **L2** were clearly resolved to four double doublets and four singlets, respectively, at −10 °C. On the NMR time scale, the two benzylic protons are equivalent to each other and appeared as a triplet at 25 °C or a doublet below 0 °C. However, the signal started to collapse at −50 °C and disappeared at −70 °C. These observations suggest that the η^3−η^1−η^3 isomerization of the benzyl ligand through the Cα−C1 bond rotation rapidly occurs above −30 °C.[22] Although the equilibrium may be slow on the NMR time scale below −80 °C, we failed to observe the separated signals for the two benzylic protons in the variable-temperature NMR analysis.

The molecular structure of [Pd(η^3-benzyl)(**L2**)]BARF (**8a**) was determined with the single-crystal X-ray diffractometry. In the asymmetric unit, one formula unit of **8a** could be located with the (η^3-benzyl)palladium cation disordered over two sites, where the two sites had the occupation factors of 0.74 and 0.26, respectively (see the SI). The major structure of [Pd(η^3-benzyl)(**L2**)]$^+$ is shown in Figure 5. The crystal structure obviously indicates that the benzyl ligand is bound to the palladium atom with its three carbon atoms at benzylic, ipso, and ortho positions. The ortho C−Pd bond [2.531(6) or 2.37(4) Å] is longer than the benzylic C−Pd bond [2.087(6) or 2.093(13) Å]. The ligand **L2** chelates the palladium atom with the 106° bite angle, which is close to that reported for xantphos (**L9**) rather than that for DPPF (**L1**).[8] Steric repulsion between the isopropyl groups in **L2** is likely to be the cause of the larger bite angle. The delocalized benzyl anion is

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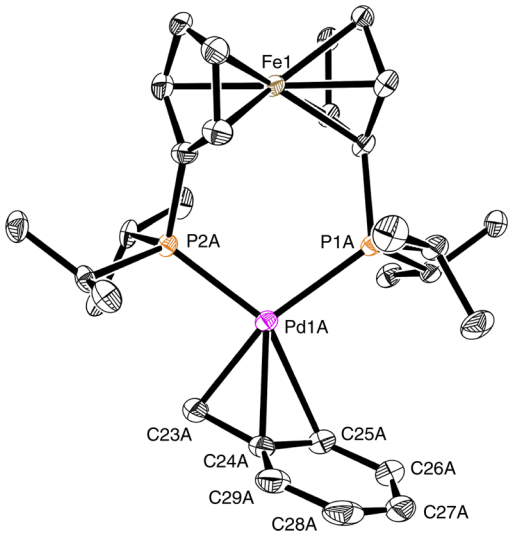

Figure 5. ORTEP plot of one of the two disordered structures of **8a** at the 30% probability level (0.74 in occupation). The hydrogen atoms and BARF counteranion have been omitted for clarity. Selected bond lengths and angles: Pd1A−C23A = 2.087(6) Å; Pd1A−C24A = 2.279(14) Å; Pd1A−C25A = 2.531(6) Å; Pd1A−P1A = 2.384(3) Å; Pd1A−P2A = 2.287(2) Å; P1A−Pd1A−P2A = 106.48(13)°; Pd1A−C23A−C24A = 78.3(6)°. Selected bond lengths and angles for the other structure (0.26 in occupation): Pd1B−C23B = 2.093(13) Å; Pd1B−C24B = 2.260(13) Å; Pd1B−C25B = 2.37(4) Å; Pd1B−P1B = 2.281(8) Å; Pd1B−P2B = 2.363(6) Å; P1B−Pd1B−P2B = 106.2(4)°; Pd1B−C23B−C24B = 76.8(8)°.

bound to the palladium atom through its π-orbital, although the distance between the ortho C and Pd atoms is much longer than the benzylic C−Pd bond distance. The angle of Pd1−C23−C24, 78.3(6)° or 76.8(8)°, is comparable to those reported for the related (η^3-allyl)palladium complexes,[8,23] indicating that the benzylic carbon is not sp^3-hybridized.

To investigate the reactivity of (benzyl)palladium intermediate **6a** with a nucleophile, the *in situ* generated **6a** was treated with dimethyl malonate (**2a**) in C_6D_6. The reaction was monitored by ^{31}P and ^{1}H NMR measurement (Figure 6). The solution of **6a** was prepared by mixing benzyl methyl carbonate **1a** and 0.2 equiv of *in situ* generated D*i*PrPF−palladium(0) **5** in C_6D_6 for 3 h (Figure 6a,b). The palladium species **5** and **6a** were assigned to the peaks **I** and **II** in the ^{31}P NMR spectra, respectively. Equimolar **2a** was added to the resulting mixture of **1a** and **6a**. Its methoxide would act as the base for generating the malonate carbanion, leading to the formation of **3aa**. Indeed, approximately 65% of **1a** was alkylated with **2a** at 5 h in the ^{1}H NMR analysis. Its ^{31}P NMR spectrum indicates that **6a** is the resting state in the catalytic benzylic substitution (Figure 6c). When the substrates **1a** and **2a** completely disappeared from the mixture at 24 h, the peaks **II** disappeared and **I** emerged again (Figure 6d). The further treatment of the resulting **5** with **1a** led to the regeneration of complex **6a** (Figure 6e). These observations indicate that the (η^1-benzyl)palladium **6a** participates as an intermediate in the mechanism of the benzylic substitution. However, the benzyl ligand on the palladium could react with the carbanion of **2a** through the η^1−η^3 isomerization, because the η^3-benzyl might be more electrophilic than the η^1-benzyl ligand in the analogy with the allyl complex. To evaluate the relative reactivities of the η^1- and η^3-benzyl complexes with nucleophiles, **6b** and **8b** were treated with excess dibutylamine (**10**), which worked as a nucleophile for the palladium-catalyzed benzylic substitution

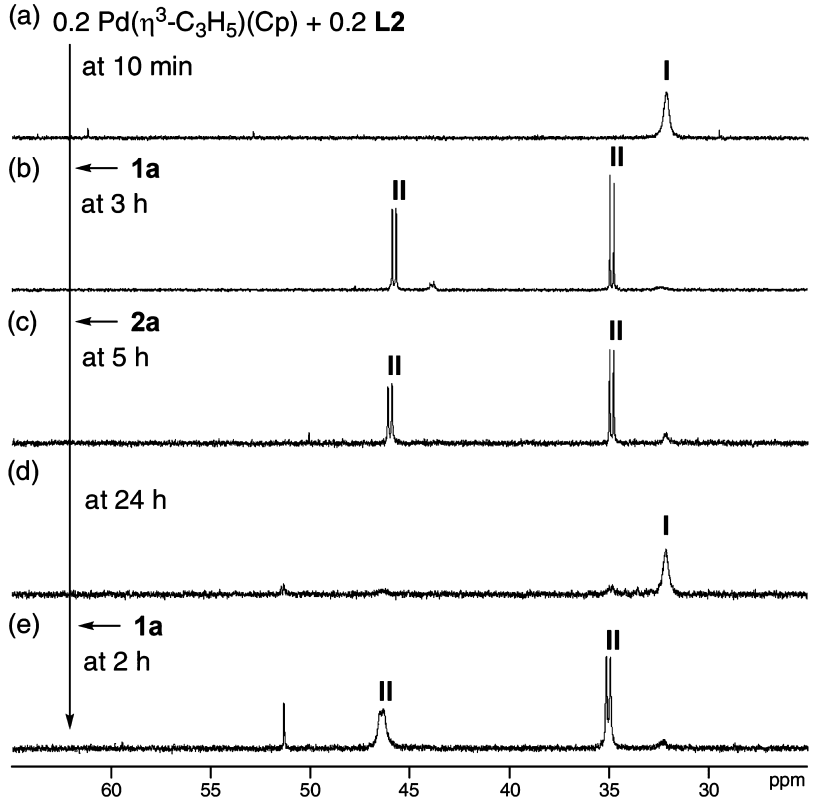

Figure 6. Monitoring the benzylic substitution of **1a** with **2a** through Pd(η^3-C_3H_5)(Cp)−**L2** catalyst with the $^{31}P\{^{1}H\}$ NMR measurement.

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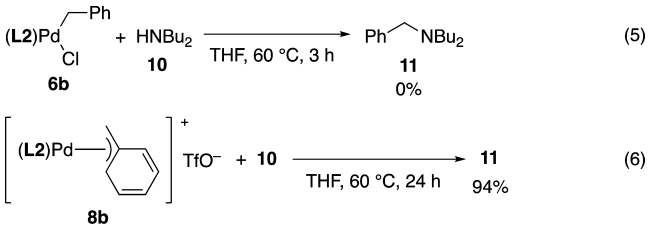
even in the absence of base (Scheme 3).[13a] The (η^3-benzyl)palladium **8b** gave the benzylamine **11** in 94% GC

Scheme 3. Reaction of (η^1- or η^3-Benzyl)palladium with Amine 10



yield for 3 h, while no formation of **11** was observed at 24 h in the reaction of **6b**. These observations suggest that the electrophilicity of the benzyl ligand is enhanced through the η^1–η^3 isomerization. The nucleophile would preferentially attack on the η^3-benzyl ligand.

On the basis of the above mechanistic studies, a reaction mechanism of the catalytic benzylic substitution is proposed as given in Figure 7. The palladium(0) species **5** is generated

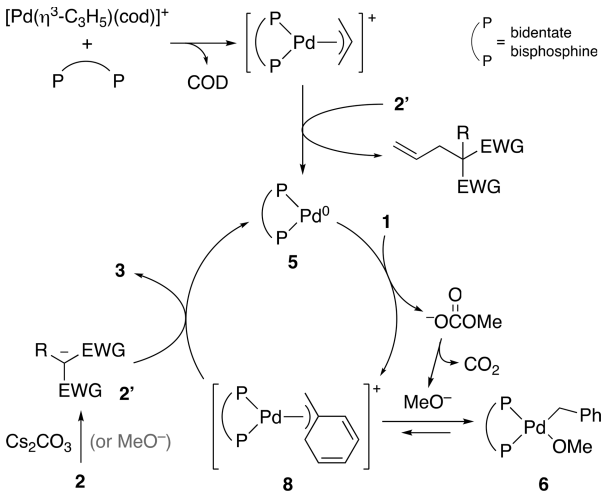


Figure 7. Proposed mechanism for the catalytic benzylic substitution of **1**.

from the nucleophilic attack of the stabilized carbanion **2′** on the cationic (η^3-allyl)palladium(II), which is generated *in situ* from [Pd(η^3-C_3H_5)(cod)]BF_4 and a bidentate bisphosphine. The catalytic cycle starts from the oxidative addition of benzyl ester **1** to **5**, which would lead to the formation of (η^3-benzyl)palladium intermediate **8** and the methyl carbonate anion. The leaving group from **1** liberates carbon dioxide to give methoxide. The mixture of **8** and methoxide is in equilibrium with (η^1-benzyl)palladium **6**, which is the resting state in the catalytic reaction.[22] Although the formation of **6** is thermodynamically favorable in THF, the (η^1-benzyl)-palladium isomerized into **8** to react with the nucleophile **2′**, which is generated through the deprotonation of **2** with Cs_2CO_3 or the methoxide. The attack of **2′** on the η^3-benzyl ligand forms the desired product **3** and regenerates the palladium(0) **5**. The formation of **8** from **6** would be unfavorable in less polar solvent such as THF because it is accompanied by charge separation. Use of polar solvent would cause an increase in the concentration of the (η^3-benzyl)-palladium intermediate. Therefore, the present benzylic alkylation of benzylic esters was facilitated even at room temperature in DMF.

CONCLUSIONS

We successfully improved the palladium catalyst for the benzylic alkylation of benzyl carbonates **1** by using 1,1′-bis(diisopropylphosphino)ferrocene (D*i*PrPF, **L2**) in place of DPPF (**L1**) as the ligand. The improved catalyst allowed the alkylation to proceed at room temperature, giving the desired products with high yields in various combinations of benzyl esters and active methine compounds. Although the **L2**–palladium complex failed to catalyze the reactions using an ortho-substituted benzyl ester, diketone, or β-keto ester as a substrate at 30 °C, such substrates are applicable to the catalytic benzylic substitution by heating at 50 °C.

The reaction mechanism was investigated with ^{1}H and ^{31}P NMR analyses by using the **L2**–palladium catalyst. The NMR studies suggested that the catalytic benzylic substitution starts from the oxidative addition of the benzylic C–O bond of **1** to the palladium(0) species **5** to form (benzyl)palladium(II). Although the benzyl ligand was mostly bound to the palladium atom through a σ-bond in the NMR spectra, the η^1-benzyl complex **6** would be in equilibrium in the cationic (η^3-benzyl)palladium **8**, which might preferentially undergo the nucleophilic attack of stabilized carbanion **2** to give **5** and the benzylated products **3**. Indeed, **8b** was much more reactive to the nucleophile attack of amine than **6b**. It is noteworthy that all signals of the benzyl ligand were fully assigned in the ^{1}H NMR study because **L2** has no benzene ring.

In this study, we successfully proved that palladium(0) species can activate the benzylic C–O bond in benzyl carbonate to give (benzyl)palladium(II) species. However, we failed to observe the direct formation of (η^3-benzyl)-palladium from the reaction of **1** with palladium(0) at this moment. Although we had treated **5** with **1a** in DMSO-d_6 or DMF-d_7, the reaction resulted in the formation of yellow precipitations. Furthermore, dynamic behavior of [Pd(η^3-benzyl)(**L2**)]$^+$ at room temperature would obstruct the NMR analysis of the reaction in polar solvent.

EXPERIMENTAL SECTION

General. [Pd(η^3-C_3H_5)(cod)]BF_4,[24] Pd(η^3-C_3H_5)(Cp),[25] Pd(η^1-benzyl)Cl(cod) (**9**),[8] and AgBARF[26] were prepared according to literature procedures. All other reagents were purchased from commercial suppliers.

Procedure for the Preparation of Benzyl Methyl Carbonates. Under a nitrogen atmosphere, a benzyl alcohol (10 mmol) and pyridine (0.96 mL, 12 mmol, *d* 0.985 g/mL) were added to a solution of 4-(dimethylamino)pyridine (122 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) under a N_2 atmosphere. Methyl chloroformate (0.92 mL, 12 mmol, *d* 1.23 g/mL) was carefully added dropwise to the reaction mixture. The resulting solution was stirred at ambient temperature. The reaction was quenched with 1 N HCl (20 mL) and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried with Na_2SO_4, and then evaporated under reduced pressure after filtration. The residue was purified with flash column chromatography on silica gel (EtOAc/hexane) to give the desired benzyl methyl carbonates **1**. Spectrum data of **1a**,[27] **1b**,[27] **1d**,[28] and **1e**[29] are accessible in the literature.

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Methyl 4-(Trifluoromethyl)benzyl Carbonate (1c). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.82 (s, 3H), 5.21 (s, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.1, 68.5, 123.9 (q, J = 272 Hz), 125.6 (q, J = 4 Hz), 128.1, 130.6 (q, J = 33 Hz), 139.2, 155.6. Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.29; H, 3.87. Found: C, 51.26; H, 3.82.

Methyl 2-Methylbenzyl Carbonate (1f). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.36 (s, 3H), 3.78 (s, 3H), 5.18 (s, 2H), 7.15−7.36 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 18.8, 54.7, 67.9, 125.9, 128.7, 129.3, 130.3, 133.2, 137.0, 155.7. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.58; H, 6.71.

Methyl Pyridin-3-ylmethyl Carbonate (1g). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.81 (s, 3H), 5.18 (s, 2H), 7.31 (ddd, J = 0.7, 4.8, 7.8 Hz, 1H), 7.73 (ddd, J = 1.7, 2.0, 7.8 Hz, 1H), 8.60 (dd, J = 1.7, 4.8 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.0, 66.9, 123.4, 130.8, 136.0, 149.7, 149.9, 155.4. Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.40; H, 5.42; N, 8.24.

Methyl Pyridin-4-ylmethyl Carbonate (1h). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.84 (s, 3H), 5.18 (s, 2H), 7.27 (d, J = 6.1 Hz, 2H), 8.62 (d, J = 6.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.2, 67.4, 121.7, 144.2, 150.1, 155.5. HRMS (FAB) Calcd for $C_8H_{10}NO_3$: 168.0661. Found: m/z = 168.0660 ($[M + H]^+$).

Procedure for Palladium-Catalyzed of Benzylation with Soft Carbanion. Under a nitrogen atmosphere, a mixture of 1,1′-bis(diisopropylphosphino)ferrocene (D*i*PrPF, **L2**) (4.6 mg, 11 μmol), $[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$ (3.4 mg, 10 μmol), and Cs_2CO_3 (358 mg, 1.1 mmol) in dry DMF (1.0 mL) was stirred at ambient temperature for 5 min. A benzyl carbonate **1** (1.0 mmol) and active methylene compound **2** (1.1 mmol) were added to the suspension. The resulting mixture was stirred at 30 °C. The mixture was diluted with hexane and water. The aqueous layer was extracted several times with hexane. The combined organic layer was washed with brine, dried with $MgSO_4$, and then evaporated under reduced pressure. The residue was purified with flash column chromatography on silica gel (EtOAc/hexane) or by preparative medium-pressure liquid chromatography (MPLC) after passing through a short column on silica gel to give the desired product.

Dimethyl 2-Benzylmalonate (3aa) and Dimethyl 2,2-Dibenzylmalonate (4aa) (Table 1, Entry 18). The procedure was followed with the use of benzyl methyl carbonate (**1a**) (164 mg, 0.99 mmol), dimethyl malonate (**2a**) (197 mg, 1.5 mmol), and Cs_2CO_3 (490 mg, 1.5 mmol). The reaction was carried out in DMF (3.0 mL) for 24 h. The crude product was purified with MPLC (EtOAc/hexane = 1/5) to give **3aa** (95.1 mg, 43%) and **4aa** (80.0 mg, 52%) as a colorless oil. **3aa**,[13a] ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.22 (d, J = 7.8 Hz, 2H), 3.68 (t, J = 7.8 Hz, 1H), 3.69 (s, 6H), 7.16−7.30 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 34.7, 52.5, 53.5, 126.7, 128.5, 128.7, 137.7, 169.1. **4aa**,[12d] ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.23 (s, 4H), 3.64 (s, 6H), 7.09−7.34 (m, 10H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 39.2, 52.2, 60.4, 127.0, 128.2, 130.0, 136.1, 171.3.

Diethyl 2-Benzyl-2-phenylmalonate (3ab). See ref 13a. The procedure was followed with the use of **1a** (164 mg, 0.99 mmol) and diethyl 2-phenylmalonate (**2b**) (259 mg, 1.1 mmol). The reaction was carried out for 48 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/10) to give **3ab** (316 mg, 98%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.20 (t, J = 7.1 Hz, 6H), 3.61 (s, 2H), 4.19 (q, J = 7.1 Hz, 4H), 6.86−6.91 (m, 2H), 7.10−7.17 (m, 3H), 7.23−7.28 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.8, 42.9, 61.5, 64.2, 126.7, 127.4, 127.73, 127.76, 128.3, 130.4, 136.0, 137.0, 170.1.

Diethyl 2-(4-Methoxybenzyl)-2-phenylmalonate (3bb). See ref 13a.The procedure was followed with the use of 4-methoxybenzyl methyl carbonate (**1b**) (196 mg, 1.0 mmol) and **2b** (260 mg, 1.1 mmol). The reaction was carried out for 24 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/5) to give **3bb** (354 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.21 (t, J = 7.2 Hz, 6H), 3.54 (s, 2H), 3.73 (s, 3H), 4.20 (q, J = 7.2 Hz, 4H), 6.67 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 7.22−7.28 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 42.1, 55.0, 61.5, 64.3, 113.1, 127.3, 127.7, 127.9, 128.3, 131.4, 137.0, 158.4, 170.1.

Diethyl 2-[4-(Trifluoromethyl)benzyl]-2-phenylmalonate (3cb). See ref 13a. The procedure was followed with the use of 4-(trifluoromethyl)benzyl methyl carbonate (**1c**) (234 mg, 1.0 mmol) and **2b** (259 mg, 1.1 mmol). The reaction was carried out for 24 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/10) to give **3cb** (379 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.20 (t, J = 7.1 Hz, 6H), 3.65 (s, 2H), 4.20 (q, J = 7.1 Hz, 4H), 7.01 (d, J = 8.1 Hz, 2H), 7.23−7.30 (m, 5H), 7.39 (d, J = 8.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.8, 42.6, 61.8, 64.1, 124.2 (q, J = 272 Hz), 124.6 (q, J = 4 Hz), 127.7, 128.0, 128.1, 129.0 (q, J = 32 Hz), 130.8, 136.6, 140.4, 169.8.

Diethyl 2-(4-Chlorobenzyl)-2-phenylmalonate (3db). See ref 13a. The procedure was followed with the use of 4-chlorobenzyl methyl carbonate (**1d**) (200 mg, 1.0 mmol) and **2b** (259 mg, 1.1 mmol). The reaction was carried out for 48 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/10) to give **3db** (332 mg, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.20 (t, J = 7.1 Hz, 6H), 3.56 (s, 2H), 4.20 (q, J = 7.1 Hz, 4H), 6.81 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 7.24−7.30 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 42.3, 61.7, 64.1, 127.5, 127.86, 127.91, 128.2, 131.8, 132.7, 134.6, 136.7, 169.9.

Diethyl 2-[4-(Methoxycarbonyl)benzyl]-2-phenylmalonate (3eb). See ref 13a. The procedure was followed with the use of 4-(methoxycarbonyl)benzyl methyl carbonate (**1e**) (225 mg, 1.0 mmol) and **2b** (259 mg, 1.1 mmol). The reaction was carried out for 4 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/10) to give **3eb** (322 mg, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.21 (t, J = 7.1 Hz, 6H), 3.64 (s, 2H), 3.88 (s, 3H), 4.21 (q, J = 7.1 Hz, 4H), 6.95 (d, J = 8.3 Hz, 2H), 7.20−7.29 (m, 5H), 7.81 (d, J = 8.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 42.9, 52.0, 61.8, 64.1, 127.6, 128.0, 128.2, 128.6, 129.0, 130.5, 136.6, 141.6, 167.0, 169.9.

Diethyl 2-(2-Methylbenzyl)-2-phenylmalonate (3fb). See ref 13b. The procedure was followed with the use of 2-methylbenzyl methyl carbonate (**1f**) (182 mg, 1.0 mmol) and **2b** (259 mg, 1.1 mmol). The reaction was carried out at 50 °C for 24 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/5) to give **3fb** (331 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.24 (t, J = 7.1 Hz, 6H), 1.61 (s, 3H), 3.64 (s, 2H), 4.26 (q, J = 7.1 Hz, 4H), 6.96 (d, J = 7.0 Hz, 1H), 7.00−7.10 (m, 5H),

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7.16−7.25 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 19.0, 38.7, 61.7, 64.2, 125.6, 126.7, 127.4, 127.7, 128.5, 129.6, 130.1, 134.6, 136.2, 138.3, 170.4.

Diethyl 2-(4-Methoxybenzyl)-2-methylmalonate (3bc). See ref 13b. The procedure was followed with the use of **1b** (197 mg, 1.0 mmol) and diethyl 2-methylmalonate (**2c**) (190 mg, 1.1 mmol). The reaction was carried out for 48 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/5) to give **3bc** (256 mg, 87%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.25 (t, *J* = 7.1 Hz, 6H), 1.33 (s, 3H), 3.16 (s, 2H), 3.77 (s, 3H), 4.19 (q, *J* = 7.1 Hz, 4H), 6.79 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.0, 19.6, 40.2, 54.8, 55.1, 61.2, 113.5, 128.1, 131.1, 158.5, 172.0.

Dimethyl 2-Methoxy-2-(4-methoxybenzyl)malonate (3bd). See ref 13a. The procedure was followed with the use of **1b** (195 mg, 1.0 mmol) and dimethyl 2-methoxymalonate (**2d**) (179 mg, 1.1 mmol). The reaction was carried out for 24 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/2) to give **3bd** (252 mg, 90%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 3.29 (s, 2H), 3.45 (s, 3H), 3.73 (s, 6H), 3.74 (s, 3H), 6.78 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 38.1, 53.0, 53.8, 54.8, 85.6, 113.4, 126.2, 130.8, 158.4, 168.4.

Diethyl 2-(Acetylamino)-2-(4-methoxybenzyl)-malonate (3be). See ref 13a. The procedure was followed with the use of **1b** (193 mg, 0.98 mmol) and diethyl 2-(acetylamino)malonate (**2e**) (243 mg, 1.1 mmol). The reaction was carried out in DMF (3.0 mL) for 72 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/1) to give **3be** (312 mg, 95%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.29 (t, *J* = 7.1 Hz, 6H), 2.03 (s, 3H), 3.59 (s, 2H), 3.77 (s, 3H), 4.25 (dq, *J* = 10.7, 7.1 Hz, 2H), 4.28 (dq, *J* = 10.7, 7.1 Hz, 2H), 6.53 (br s, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.0, 23.0, 36.9, 55.1, 62.5, 67.3, 113.7, 127.1, 130.8, 158.7, 167.6, 169.0.

Diethyl 2-Phenyl-2-(pyridin-3-ylmethyl)malonate (3gb). The procedure was followed with the use of methyl pyridin-3-ylmethyl carbonate (**1g**) (166 mg, 0.99 mmol) and **2b** (260 mg, 1.1 mmol). The reaction was carried out for 48 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/1) to give **3gb** (303 mg, 94%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.21 (t, *J* = 7.0 Hz, 6H), 3.58 (s, 2H), 4.21 (q, *J* = 7.0 Hz, 4H), 7.06 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.18−7.31 (m, 6H), 8.14 (d, *J* = 1.8 Hz, 1H), 8.40 (d, *J* = 4.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 40.2, 61.8, 64.1, 122.6, 127.7, 128.1, 131.8, 136.6, 137.8, 148.1, 151.6, 169.8. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.81; H, 6.41; N, 4.28.

Diethyl 2-Phenyl-2-(pyridin-4-ylmethyl)malonate (3hb). The procedure was followed with the use of methyl pyridin-4-ylmethyl carbonate (**1h**) (164 mg, 0.98 mmol) and **2b** (260 mg, 1.1 mmol). The reaction was carried out for 24 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/1) to give **3hb** (303 mg, 94%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.20 (t, *J* = 7.1 Hz, 6H), 3.59 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 4H), 6.84 (d, *J* = 5.9 Hz, 2H), 7.22−7.31 (m, 5H), 8.37 (d, *J* = 5.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.8, 42.0, 61.9, 63.6, 125.6, 127.7, 128.1, 136.4, 145.3, 149.2, 169.7. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.83; H, 6.49; N, 4.29.

Diethyl 2-Methyl-2-(pyridin-4-ylmethyl)malonate (3hc). The procedure was followed with the use of **1h** (168 mg, 1.0 mmol) and **2c** (182 mg, 1.0 mmol). The reaction was carried out for 24 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 2/1) to give **3hc** (227 mg, 85%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.22 (t, *J* = 7.2 Hz, 6H), 1.35 (s, 3H), 3.21 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 4H), 7.08 (d, *J* = 5.9 Hz, 2H), 8.50 (d, *J* = 5.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 19.7, 40.4, 54.2, 61.5, 125.4, 145.3, 149.5, 171.3. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.05; H, 7.29; N, 5.23.

2-Acetyl-2-(4-methoxybenzyl)cyclohexanone (3bf). See ref 13b. The procedure was followed with the use of **1b** (196 mg, 1.0 mmol), 2-acetylcyclohexanone **2f** (140 mg, 1.1 mmol), and DCyPF (**L3**) (7.1 mg, 12 μmol). The reaction was carried out at 50 °C for 24 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/5) to give **3bf** (234 mg, 90%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.42 (ddd, *J* = 4.3, 12.4, 13.8 Hz, 1H), 1.54−1.77 (m, 3H), 1.91−2.01 (m, 1H), 2.09 (s, 3H), 2.24 (ddd, *J* = 6.0, 12.6, 14.1 Hz, 1H), 2.32−2.39 (m, 1H), 2.46−2.54 (m, 1H), 3.03 (d, *J* = 14.2 Hz, 1H), 3.09 (d, *J* = 14.2 Hz, 1H), 3.77 (s, 3H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.2, 26.8, 27.0, 33.9, 39.1, 42.1, 55.1, 68.8, 113.6, 128.0, 131.2, 158.4, 205.9, 209.6.

Ethyl 1-(4-Methoxybenzyl)-2-oxocyclohexanecarboxylate (3bg). See ref 13b. The procedure was followed with the use of **1b** (196 mg, 1.0 mmol), ethyl 2-oxocyclohexanecarboxylate **2g** (188 mg, 1.1 mmol), and **L3** (6.6 mg, 11 μmol). The reaction was carried out at 50 °C for 120 h. The crude product was purified with flash column chromatography (EtOAc/hexane = 1/5) to give **3bg** (221 mg, 76%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.19 (t, *J* = 7.12 Hz, 3H), 1.44 (ddd, *J* = 5.0, 11.7, 13.6 Hz, 1H), 1.54−1.78 (m, 3H), 1.95−2.05 (m, 1H), 2.36−2.51 (m, 3H), 2.83 (d, *J* = 13.9 Hz, 1H), 3.23 (d, *J* = 13.9 Hz, 1H), 3.77 (s, 3H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.13 (dq, *J* = 10.8, 7.1 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.0, 22.5, 27.6, 35.8, 39.5, 41.3, 55.2, 61.2, 62.2, 113.4, 128.5, 131.3, 158.3, 171.1, 207.5.

Reaction of L2−Palladium(0) 5 with 1a (Scheme 1, Equation 1). In a nitrogen-filled dry-box, Pd(η^3-C_3H_5)(Cp) (3.1 mg, 15 μmol) and **L2** (6.5 mg, 16 μmol) were dissolved in THF-d_8 (0.7 mL) in a vial. The resulting solution was transferred into a screw-capped NMR tube. The tube was sealed with a cap containing a septum and then removed from the dry-box. The solution was analyzed with NMR measurements. Benzyl ester **1a** (3.2 mg, 19 μmol) was added to the solution which was then mixed well with shaking. Its ^1H, $^1H\{^{31}P\}$, and $^{31}P\{^1H\}$ NMR spectra were observed after 5 min and 1, 2, 3, 6, and 18 h.

Reaction of 5, 1a, and Silver Tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (AgBARF) (Scheme 1, Equation 2). Under a nitrogen atmosphere, a solution of Pd(η^3-C_3H_5)(Cp) (4.3 mg, 20 μmol) and **L2** (8.8 mg, 21 μmol) in dry THF (0.5 mL) was stirred for 10 min. Benzyl ester **1a** (16.7 mg, 0.10 mmol) was added to the solution. After 2 h, AgBARF (21.3 mg, 22 μmol) was added to the mixture. After 15 min, the solvent was removed *in vacuo*. The residue

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was dissolved in dry CH_2Cl_2. The resulting suspension was filtered through a Cerite pad. The filtrate was condensed to ca. 0.5 mL under reduced pressure, and layered with dry Et_2O. The Et_2O was allowed to diffuse into the CH_2Cl_2 solution at −30 °C. The yellow−orange crystals of [Pd(η^3-benzyl)(D*i*PrPF)]BARF (**8a**) (20.3 mg, 70%) were collected with filtration and used for the X-ray diffraction study. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.6−1.5 (br, 24 H), 1.8−2.2 (br, 2H), 2.2−2.7 (br, 2H), 3.11 (t, J = 3.8 Hz, 2H), 4.2−4.6 (br, 4H), 4.53 (br s, 4H), 6.77 (d, J = 7.0 Hz, 2H), 7.55−7.62 (m, 5H), 7.66 (t, J = 7.4 Hz, 2H), 7.73 (s, 8H). ^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2, 85% H_3PO_4 aq.): δ 38.9 (br, 1P), 59.3 (br, 1P). Anal. Calcd for $C_{61}H_{55}BF_{24}FeP_2Pd$: C, 49.54; H, 3.75. Found: C, 49.61; H, 3.73.

Pd(η^1-benzyl)Cl(D*i*PrPF) (6b) (Scheme 2, Equation 3). Under a nitrogen atmosphere, dry CH_2Cl_2 (1.0 mL) was added to a mixture of Pd(η^1-benzyl)Cl(cod)[8,21] (34.2 mg, 0.10 mmol) and **L2** (41.8 mg, 0.10 mmol). The solution was stirred at ambient temperature for 15 min. The mixture was filtered through a Cerite pad. The filtrate was condensed to ca. 0.2 mL under reduced pressure and layered with dry hexane. The hexane was allowed to diffuse into the CH_2Cl_2 solution at −30 °C. The yellow−orange crystals of **6b** (51.3 mg, 79%) were collected with filtration. ^{1}H NMR (400 MHz, THF-d_8): δ 1.02 (dd, J = 7.1, 16.0 Hz, 6H), 1.14 (dd, J = 7.0, 13.0 Hz, 6H), 1.19 (dd, J = 6.8, 14.4 Hz, 6H), 1.48 (dd, J = 7.2, 15.6 Hz, 6H), 2.57 (octet, J = 7.1 Hz, 2H), 2.77 (octet, J = 7.4 Hz, 2H), 3.42 (dd, J = 5.1, 9.1 Hz, 2H), 4.35−4.46 (m, 8H), 6.90 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 7.6 Hz, 2H), 7.76 (d, J = 7.7 Hz, 2H). ^{31}P{^{1}H} NMR (162 MHz, THF-d_8, 85% H_3PO_4 aq.): δ 31.6 (d, J = 28 Hz, 1P), 42.4 (d, J = 28 Hz, 1P).

[Pd(η^1-benzyl)(D*i*PrPF)]OTf (8b) (Scheme 2, Equation 4). Under a nitrogen atmosphere, dry CH_2Cl_2 (1.0 mL) was added to a mixture of Pd(η^1-benzyl)Cl(cod)[8,21] (34.0 mg, 0.10 mmol) and **L2** (42.0 mg, 0.10 mmol). After the solution was stirred at ambient temperature for 5 min, silver triflate (27.3 mg, 0.11 mmol) was added to the mixture. After 10 min, the resulting mixture was filtered through a Cerite pad. The filtrate was condensed to ca. 0.2 mL under reduced pressure and layered with dry Et_2O. The Et_2O was allowed to diffuse into the CH_2Cl_2 solution at −30 °C. The yellow−orange crystals of **8b** (75.8 mg, 99%) were collected with filtration. ^{1}H NMR (400 MHz, THF-d_8, at −10 °C): δ 0.91 (dd, J = 7.1, 17.1 Hz, 6H), 1.13 (dd, J = 6.6, 14.6 Hz, 6H), 1.18 (dd, J = 6.6, 16.1 Hz, 6H), 1.40 (dd, J = 7.1, 17.5 Hz, 6H), 2.12 (octet, J = 7.1 Hz, 2H), 2.61−2.75 (m, 2H), 3.44 (d, J = 7.8 Hz, 2H), 4.47 (s, 2H), 4.56 (s, 2H), 4.61 (s, 2H), 4.68 (s, 2H), 7.02 (dd, J = 4.2, 7.0 Hz, 2H), 7.56−7.62 (m, 1H), 7.76 (t, J = 7.5 Hz, 2H). ^{31}P{^{1}H} NMR (162 MHz, THF-d_8, 85% H_3PO_4): δ 39.1 (br, 1P), 58.5 (br, 1P). ^{31}P{^{1}H} NMR (162 MHz, THF-d_8, 85% H_3PO_4, at −10 °C): δ 36.6 (d, J = 33 Hz, 1P), 55.6 (d, J = 33 Hz, 1P). Anal. Calcd for $C_{30}H_{43}F_3FeO_3P_2PdS$: C, 47.11; H, 5.67. Found: C, 46.86; H, 5.65.

Monitoring the Catalytic Benzylic Substitution of 1a with 2a with NMR Measurement (Figure 6). In a nitrogen-filled dry-box, Pd(η^3-C_3H_5)(Cp) (4.4 mg, 21 μmol) and **L2** (9.2 mg, 22 μmol) were dissolved in dry C_6D_6 (0.7 mL) in a vial. The resulting solution was transferred into a screw-capped NMR tube. The tube was sealed with a cap containing a septum and then removed from the dry-box. The *in situ* generated **5** was analyzed with ^{31}P{^{1}H} NMR measurement. Benzyl ester **1a** (17.2 mg, 0.10 mmol) was added to the solution of **5** and mixed well with shaking. After 3 h, the solution was analyzed with ^{1}H and ^{31}P{^{1}H} NMR measurements. Then, malonate **2a** (14.8 mg, 0.11 mmol) was added to the mixture. The NMR spectra of the mixture were observed after 5 and 24 h. The mixture was treated with **1a** (14.1 mg, 87 μmol) again and analyzed with NMR measurements after 2 h.

Reaction of 6b or 8b with Dibutylamine (10) (Scheme 3). Under a nitrogen atmosphere, dibutylamine (**10**) (6.3 mg, 49 μmol) was added to a solution of **6b** (3.3 mg, 5.1 μmol) or **8b** (3.8 mg, 5.0 μmol) and tetradecane (7.5 mg) in dry THF (0.5 mL) at ambient temperature. The mixture was stirred at 60 °C and analyzed with GC. The GC yields of benzyldibutylamine (**11**) were calibrated with tetradecane as the internal standard.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00210.

ORTEP plots of **8a** and a copy of ^{1}H, ^{13}C, and ^{31}P NMR spectra for new compounds and the benzylic substitution products (PDF)

X-ray data for **8a** (CIF)

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Notes

The authors declare no competing financial interest.

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