JOC The Journal of Organic Chemistry

Note

Cobalt-Catalyzed, N–H Imine-Directed Arene C–H Benzylation with Benzyl Phosphates

Roshayed Ali Laskar, and Naohiko Yoshikai

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b01775 • Publication Date (Web): 07 Aug 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

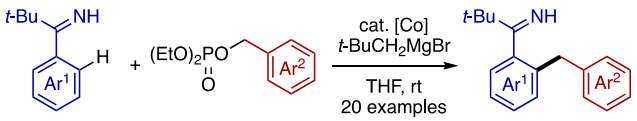
Cobalt-Catalyzed, N–H Imine-Directed Arene C–H Benzylation with Benzyl Phosphates

*Roshayed Ali Laskar and Naohiko Yoshikai**

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

E-mail: nyoshikai@ntu.edu.sg

Abstract. A cobalt-catalyzed *ortho* C–H benzylation reaction of pivalophenone N–H imines with benzyl phosphates is reported. The reaction is promoted at room temperature by a ternary catalytic system comprised of $Co(acac)_3$, a pyridylphosphine ligand, and a Grignard reagent, and tolerates a series of substituted pivalophenone imines and benzyl phosphates to afford various diarylmethane derivatives in moderate yields.

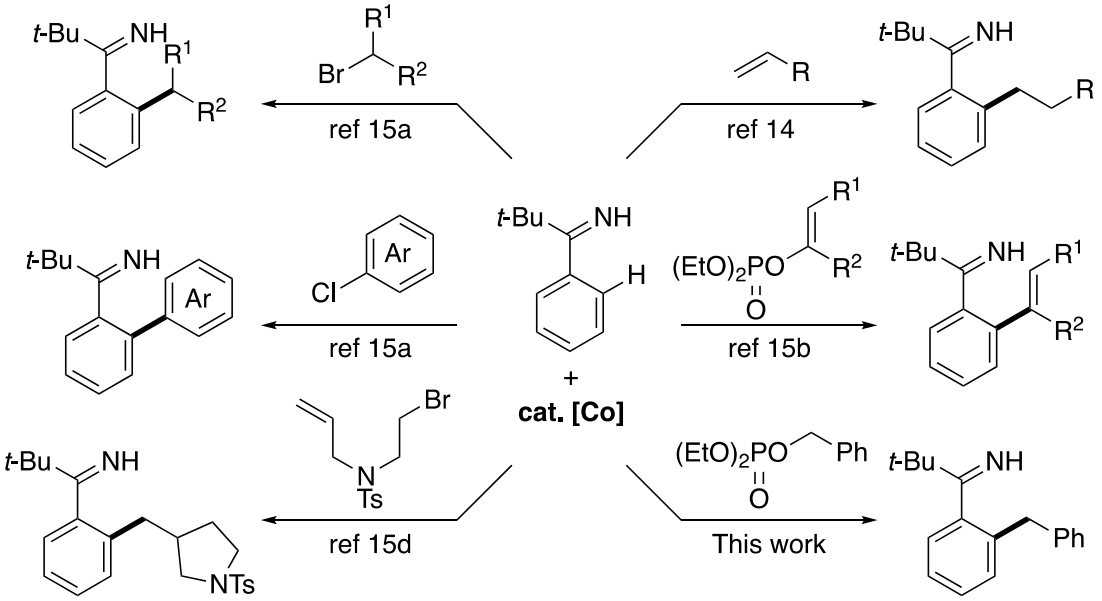


Diarylmethane skeletons are prevalent in biologically active compounds and pharmaceuticals, such as papaverine and beclobrate, and hence their efficient and selective construction represents an important subject in synthetic organic chemistry. A representative classical approach to access diarylmethanes is the Friedel–Crafts-type, acid-catalyzed electrophilic aromatic substitution (S_EAr) reactions of electron-rich aromatic compounds with benzyl halides.[1] Meanwhile, the transition metal-catalyzed cross-coupling between aryl halides and benzylmetal reagents or between benzyl halides and arylmetal reagents has been developed as an alternative approach.[2] Nevertheless, these well-established approaches have some intrinsic drawbacks. Despite notable progress in benzylating agents,[3] the scope of the Friedel–Crafts approach is inherently limited by the requirement for electron-rich arenes, and also by the difficulty of regiocontrol. The cross-coupling reaction necessitates two prefunctionalized starting materials, while the reductive, cross-electrophile coupling approach has emerged to allow for bypassing the preparation of organometallic reagents.[4] In this context, the transition metal-catalyzed C–H benzylation of arenes has attracted interest as another viable approach to diarylmethanes.[5,6] In particular, benzylations involving directing group-assisted C–H activation have been achieved with precious transition metals such as ruthenium,[7] palladium,[8] and rhodium,[9] as well as with earth-abundant transition metals such as cobalt,[10] nickel,[11] and iron.[12]

Over the last decade, we and others have developed a series of directed arene C–H functionalizations with organic electrophiles under low-valent cobalt catalysis.[13] As for C–H benzylation, a C2-benzylation reaction of N-pyridylindole with benzyl phosphate, reported by Ackermann in 2012, represents the first example.[10a] Later in 2015, our group disclosed *ortho*-benzylation of N-aryl imines derived from aryl alkyl ketones with benzyl phosphates.[10b] Meanwhile, our recent studies have demonstrated that N–H imine, that of pivalophenone in particular, serves as a powerful and transformable directing group for a variety of cobalt-catalyzed C–H functionalization reactions including hydroarylation to alkenes[14] as well as alkylation, arylation, and alkenylation with the corresponding electrophiles (Scheme 1).[15,16] Prompted by the need for efficient benzylation methods

and the utility of N–H imine directing group, we have developed a cobalt-catalyzed directed C–H benzylation reaction of pivalophenone N–H imines, which is reported herein.

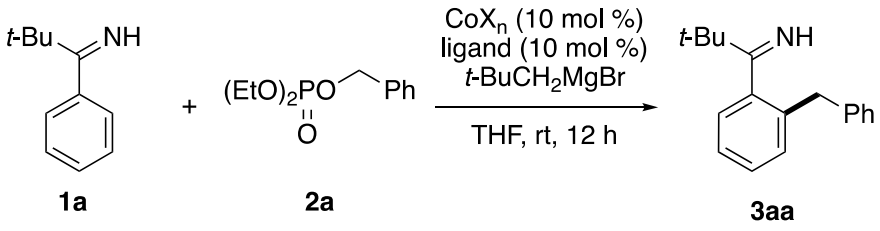
Scheme 1. Cobalt-Catalyzed N–H Imine-Directed C–H Functionalization



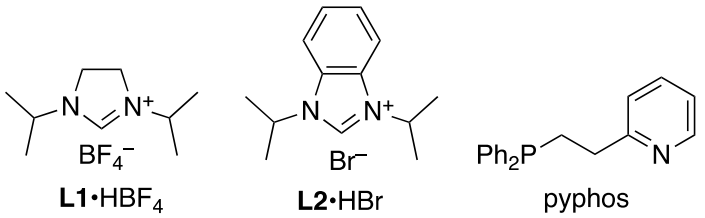
The present study began with a screening of reaction conditions for the coupling between pivalophenone N–H imine **1a** and benzyl diethyl phosphate **2a** (Table 1). A catalytic system comprised of $CoBr_2$ (10 mol %), IMes•HCl (10 mol %), and *t*-$BuCH_2MgBr$ (2 equiv) promoted the reaction at room temperature to afford the desired benzylation product **3aa** in 14% yield (entry 1). Other NHC preligands such as IPr•HCl and *N*,*N*'-diisopropyl derivatives **L1** and **L2** displayed similar performances as IMes•HCl (entries 2–4). No particular improvement was observed using monodentate phosphines such as PPh_3 and bidentate nitrogen ligands such as 1,10-phenanthroline (entries 5 and 6). A slight but finite improvement was observed using 2-(2-(diphenylphosphanyl)ethyl)pyridine (pyphos), which afforded **3aa** in 21% yield (entry 7). Using pyphos as the ligand, the use of CoI_2 or $Co(acac)_3$ as the cobalt source improved the yield of **3aa** to 31% or 40%, respectively (entries 8 and 9). Finally, the yield of the latter reaction was further improved to 50% (51% isolated yield) using a slightly larger amount (2.4 equiv) of the Grignard reagent (entry 10). Outside this optimization table, we have extensively

screened various reaction conditions and parameters including cobalt sources, ligands, Grignard reagents, temperatures, equivalences, and concentrations. Nevertheless, we were unable to improve the reaction efficiency further. The difficulty appears to be partly due to the background reaction, both catalyzed and uncatalyzed,[17] between the Grignard reagent and the benzyl phosphate. In fact, **2a** was generally fully consumed, while the conversion of **1a** reached only 80% even under the optimized conditions. Under the optimized conditions, the desired product was accompanied by *ortho*-neopentylation of **1a** (10%), cross-coupling between the Grignard reagent and **2a** (3%), and homocoupling of **2a** (4%).

Table 1. Benzylation of Pivalophenone N–H Imine **1a** with Benzyl Phosphate **2a**[a]



1a **2a** **3aa**



L1•HBF_4 **L2**•HBr pyphos

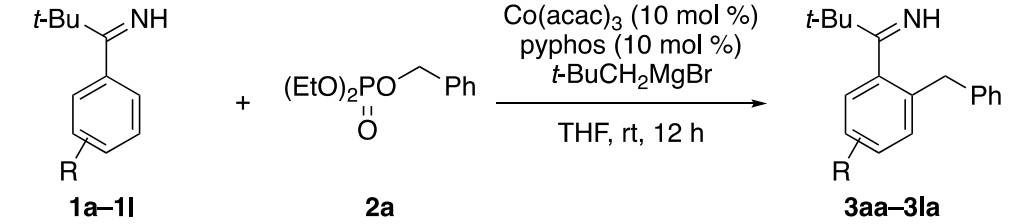
Entry	CoX_n	Ligand	Yield (%)[b]
1	$CoBr_2$	IMes•HCl	14
2	$CoBr_2$	IPr•HCl	17
3	$CoBr_2$	**L1**•HBF_4	16
4	$CoBr_2$	**L2**•HBr	15
5	$CoBr_2$	PPh_3	11
6	$CoBr_2$	1,10-phenanthroline	13
7	$CoBr_2$	pyphos	21
8	CoI_2	pyphos	31
9	$Co(acac)_3$	pyphos	40
10[c]	$Co(acac)_3$	pyphos	50 (51)[d]

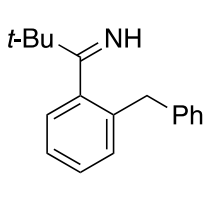
[a]The reaction was performed using 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 0.2 mmol of *t*-$BuCH_2MgBr$. [b]Determined by GC using *n*-tridecane as an internal standard. [c]0.24 mmol of *t*-$BuCH_2MgBr$ was used. [d]Isolated yield for a 0.4 mmol-scale reaction.

With the best reaction conditions in hand, we explored the scope of the present C–H benzylation. First, a variety of substituted pivalophenone N–H imines were subjected to the benzylation with the parent benzyl phosphate **2a** (Scheme 2). A variety of *para*-substituted imines participated in the reaction to afford the desired benzylation products **3ba**–**3ha** in 40–65% yields, showing tolerance to electron-donating groups such as tert-butyl and methoxy groups and electron-withdrawing groups such as trifluoromethoxy, fluoro, and chloro groups. No cross-coupling between the chloro-substituted imine

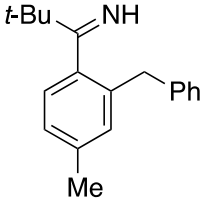
and the Grignard reagent was observed (see **3ha** and **3ka**). The reaction between **1a** and **2a** could be scaled up to 4 mmol scale to afford **3aa** in a higher yield (58%) than that of the small-scale reaction (51%). The imines bearing *meta*-methyl or –chloro substituent underwent regioselective benzylation at the less hindered *ortho* position, affording the corresponding products **3ia** and **3ka**, respectively, in modest yields. On the other hand, the *meta*-fluorinated imine was benzylated at the proximity of the fluorine atom, presumably due to the secondary directing effect (see the product **3ja**).[14b,15b] The *ortho*-methyl-substituted imine failed to participate in the present benzylation reaction. Note also that the reaction between benzophenone N–H imine and **2a** under the present conditions was sluggish, affording the corresponding monobenzylated product in low yield (15% as estimated by GC analysis; not isolated) along with substantial recovery of the imine (43%).

Scheme 2. Benzylation of Substituted Pivalophenone N–H Imines with **2a**[a]

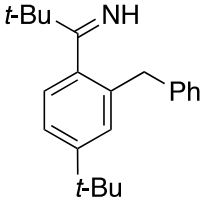




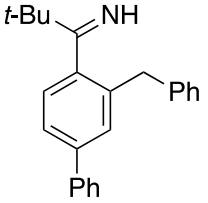
3aa, 51%
(58% on 4 mmol)



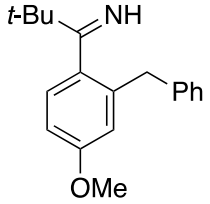
3ba, 62%



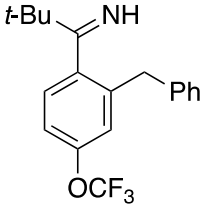
3ca, 40%



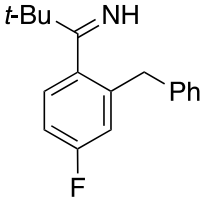
3da, 46%



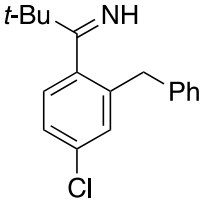
3ea, 53%



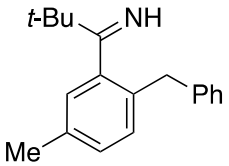
3fa, 65%



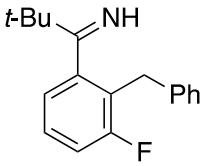
3ga, 54%



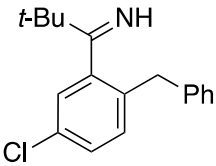
3ha, 54%



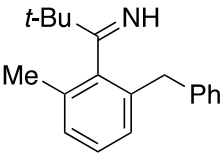
3ia, 28%



3ja, 52%



3ka, 42%

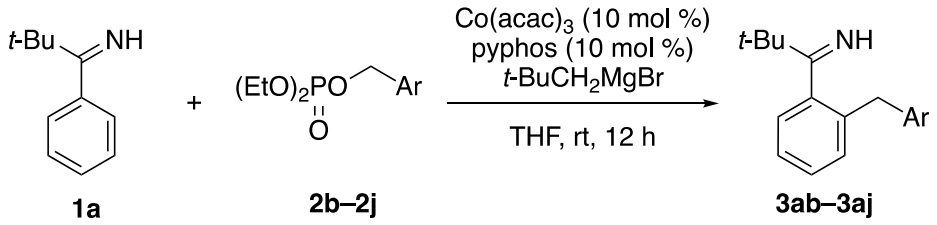


3la, 0%

[a]The reaction was performed on a 0.4 mmol scale under the conditions in Table 1, entry 10.

Next, we examined the reaction of the N–H imine **1a** with different benzyl phosphates (Table 2). Benzyl phosphates derived from para-substituted benzyl alcohols participated in the reaction to afford the corresponding diarylmethane products in 48–66% yields (entries 1–4). Phopshates derived from *meta*-substituted benzyl alcohols also afforded the desired products in somewhat lower yields (entries 5–8). The benzyl phosphate derived from *ortho*-chlorobenzyl alcohol furnished the benzylation product in a lower yield of 29%, presumably due to the steric effect (entry 9). Nonetheless, these examples again demonstrated the tolerance of the present reaction to an aryl–Cl moiety, which did not undergo cross-coupling with the Grignard reagent (see entries 4, 8, and 9).

Table 2. Benzylation of **1a** with Different Benzyl Phosphates[a]



1a **2b–2j** **3ab–3aj**

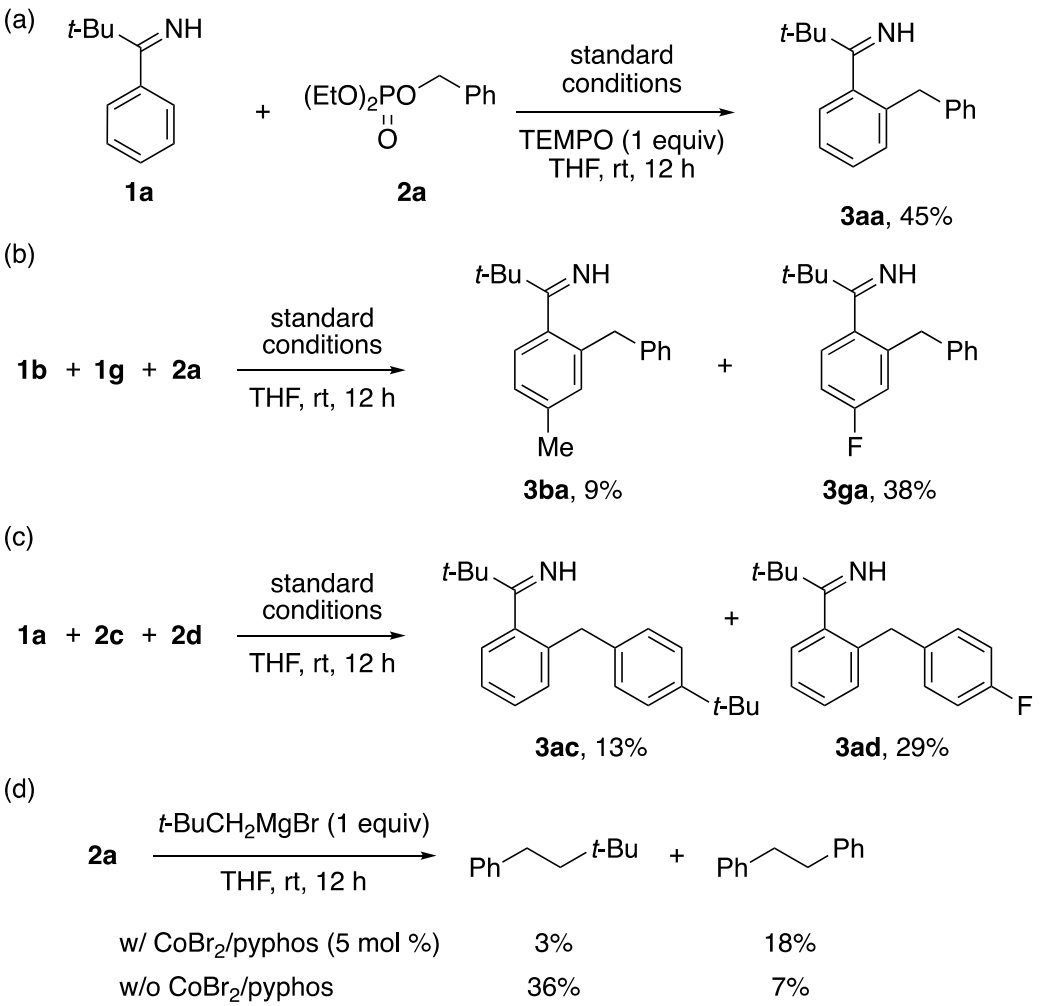
Entry	Ar	Yield (%)[b]
1	4-MeC_6H_4 (**2b**)	66 (**3ab**)
2	4-*t*-BuC_6H_4 (**2c**)	50 (**3ac**)
3	4-FC_6H_4 (**2d**)	57 (**3ad**)
4	4-ClC_6H_4 (**2e**)	48 (**3ae**)
5	3-MeC_6H_4 (**2f**)	53 (**3af**)
6	3-$MeOC_6H_4$ (**2g**)	42 (**3ag**)
7	3-FC_6H_4 (**2h**)	39 (**3ah**)
8	3-ClC_6H_4 (**2i**)	35 (**3ai**)
9	2-ClC_6H_4 (**2j**)	29 (**3aj**)

[a]The reaction was performed on a 0.4 mmol scale under the conditions in Table 1, entry 10. [b]Isolated yield.

To gain mechanistic insight, several control experiments were performed. First, the benzylation reaction in the presence of a free radical scavenger, TEMPO, afforded the desired product in 45% yield (Scheme 3a). Interestingly, this observation is in sharp contrast to our previously reported *ortho*-benzylation of N-aryl imines, where the reaction was completely shut down by TEMPO.[10b] This may suggest that the mechanism of the benzylic C–O cleavage and/or the nature of the resulting benzylic species is substantially different between the present and the previous benzylation reactions. Second, comparison of parallel individual reactions of **1a** and its deuterated analogue **1a**-d_5 indicated virtually no kinetic isotope effect (Figure 1). Thus, C–H activation is unlikely to be the rate-determining step. This is also distinct from the benzylation of N-aryl imine, where a sizable KIE of 1.6 was observed.[10b] A competition reaction using a mixture of the *para*-methyl- and fluoro-substituted imines (**1b** and **1g**)

resulted in predominant benzylation of the latter, demonstrating more facile activation of the electron-deficient C–H bond (Scheme 3b). Another competition reaction using a mixture of the *para*-*tert*-butyl- and -fluoro-substituted benzyl phosphates (**2c** and **2d**) preferentially afforded the product of the latter, more electron-poor phosphate (Scheme 3c). We also probed the background reaction between **2a** and *t*-$BuCH_2MgBr$, which produced 3,3-dimethylbutylbenzene and bibenzyl through cross-coupling and homocoupling, respectively (Scheme 3d). While the cross-coupling was dominant in the absence of the cobalt catalyst, the homocoupling outcompeted the cross-coupling under the catalytic conditions. In either case, high conversion of **2a** (>95%) was observed.

Scheme 3. Control Experiments



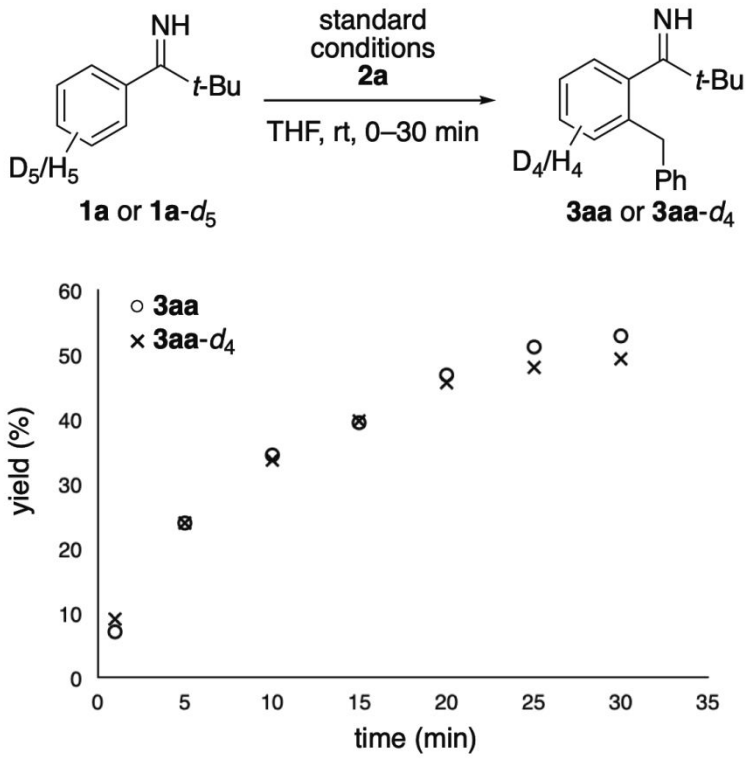
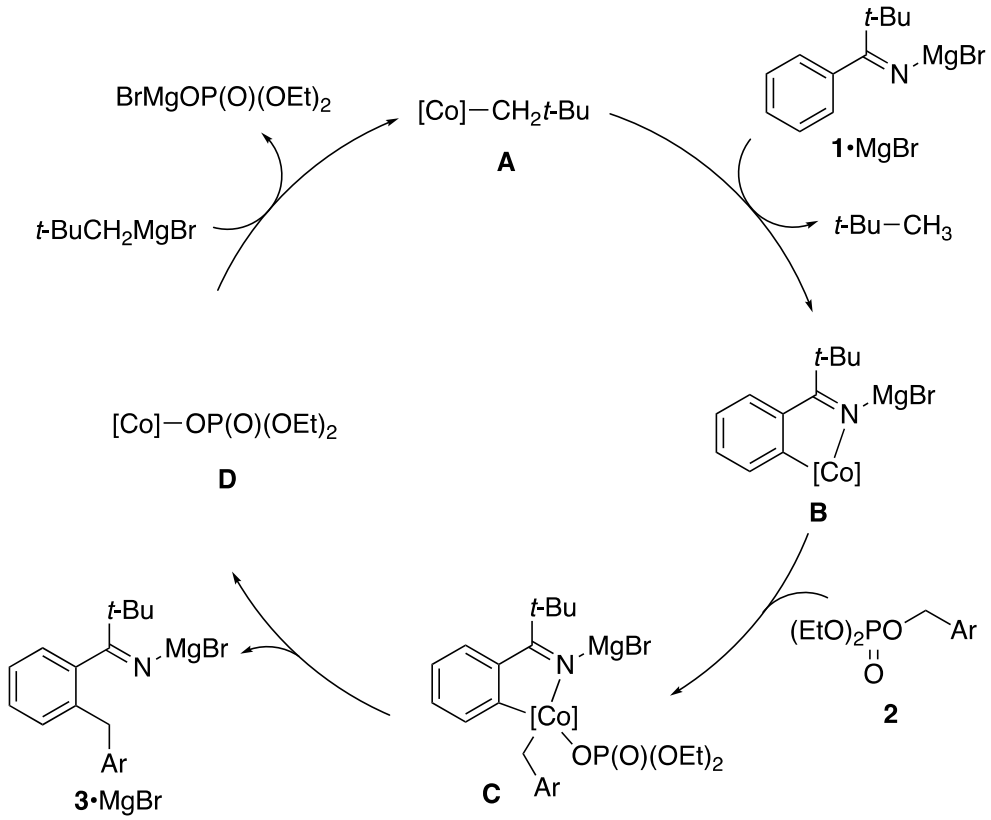


Figure 1. Comparison of individual benzylation reactions of **1a** and **1a**-d_5.

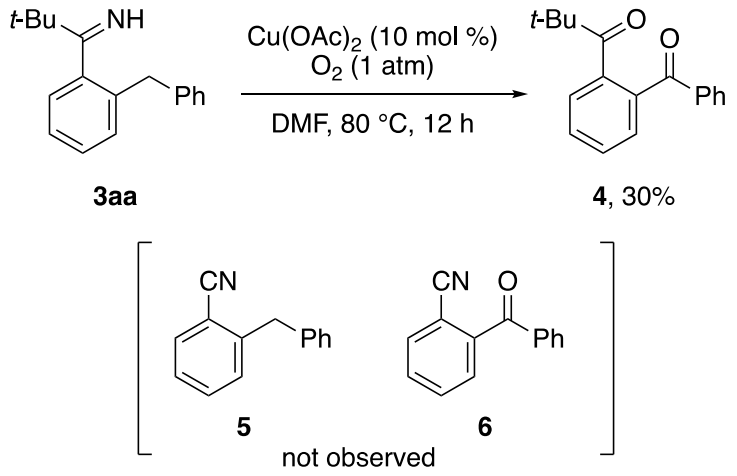
A possible catalytic cycle for the present benzylation reaction is shown in Scheme 4. As was proposed for the alkylation and arylation reactions,[15a] we assume that the present reaction is initiated by cyclometalation of a magnesium alkylideneamide **1**•MgBr, generated by the deprotonation of the N–H imine with the Grignard reagent, with a neopentylcobalt species **A**. The resulting cobaltacycle intermediate **B** would undergo oxidative addition of the benzyl phosphate **2**, followed by reductive elimination of the aryl(benzyl)cobalt species **C** to give the product **3**•MgBr. The alkylcobalt species **A** would be regenerated through transmetalation between cobalt phosphate **D** and the Grignard reagent. The lack of inhibition by TEMPO may suggest a two-electron mechanism for the oxidative addition, while an alternative mechanism involving single electron transfer and rapid cobalt/benzyl radical recombination may not be excluded.

Scheme 4. Possible Catalytic Cycle



Finally, we attempted on transformation of the imine functionality of the benzylation product under aerobic copper-catalyzed conditions (Scheme 5). Unlike the imine-to-nitrile conversion achieved for the *ortho*-alkylated and –arylated pivalophenone imines,[15a,d,18] exposure of the product **3aa** to catalytic $Cu(OAc)_2$ under O_2 atmosphere in DMF at 80 °C resulted in the formation of diketone **4** in 30% yield, accompanied by other intractable products. Benzonitrile derivative **5** and oxygenated benzonitrile derivative **6** were not detected. The formation of **4** would be rationalized by a mechanism for analogous benzylic oxygenation reaction developed by Chiba,[19] which is proposed to involve the formation of iminylcopper(II) species, its oxidation by O_2, benzyl-to-N 1,5-hydrogen atom transfer, and interception of benzyl radical by peroxycopper(II) species.

Scheme 5. Aerobic Benzylic C–H Oxygenation of **3aa**



In summary, we have developed a cobalt-catalyzed, N–H imine-directed aromatic C–H benzylation reaction with benzyl phosphates. The reaction proceeds at room temperature and tolerates a range of substituted pivalophenone imines and benzyl phosphates to afford diarylmethane derivatives in moderate yields. The N–H imine moiety of the product can be used to trigger oxygenation of the benzylic C–H bond, allowing access to a 1,2-diacylbenzene derivative. Further exploration of N–H imine-directed C–H functionalization reactions is underway.

Experimental Section

General Methods. All the reactions dealing with air- and moisture-sensitive compounds were performed in oven-dried reaction vessels under nitrogen atmosphere. Thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash column chromatography was performed using 40-63 μm silica gel (Si 60, Merck). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker AV-300 (300 MHz), AV-400 (400 MHz), or AV-500 (500 MHz) NMR spectrometers. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm), and 31P NMR spectra are reported in reference to 85% H_3PO_4 (ppm) as an external standard. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 system equipped with glass capillary column DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-Tof Premier LC HR mass spectrometer. Melting points

were determined using a capillary melting point apparatus and are uncorrected. Unless otherwise noted, commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. $Co(acac)_3$ and 2-(2-(diphenylphosphanyl)ethyl)pyridine were purchased from Alfa Aesar and Strem Chemicals, respectively, and were used as received. THF was distilled over Na/benzophenone. Neopentylmagnesium bromide was prepared from neopentyl bromide and magnesium turnings in THF, and titrated before use.

Preparation of N–H Imines: General Procedure. An oven-dried Schlenk flask (100 mL) equipped with a stir bar was charged with aryl nitrile (20 mmol), CuBr (58 mg, 0.4 mmol), and THF (20 mL) under N_2 atmosphere. To the mixture was added *tert*-butylmagnesium chloride (11 mL, 2 M in THF, 22 mmol), and the reaction mixture was stirred at 80 °C for 16 h. The resulting solution was cooled in an ice bath and quenched with methanol (20 mL). After stirring for 10 min, the ice bath was removed and the mixture was stirred for additional 1 h. The volatile materials were evaporated under reduced pressure. The residue was diluted with Et_2O (50 mL) and filtered thorough Celite. The resulting filtrate was concentrated under reduced pressure, and the crude oil was purified with Kugelrohr distillation to afford the desired N–H imine as light yellow oil. Except **1c**, the N–H imines (**1a**,[20] **1b**,[15a] **1d**,[15a] **1e**,[21] **1f-g**,[15a] **1h**,[18a] **1i**,[15a] **1j-1k**,[18a] and **1l**[18b]) are known compounds and their spectral data showed good agreement with the literature data.

1-(4-(*tert*-Butyl)phenyl)-2,2-dimethylpropan-1-imine (1c). Light green solid (1.96 g, 90%); m.p. 62.7-62.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (brs, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.5 Hz, 2H), 1.32 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 151.0, 139.5, 126.3, 124.9, 34.7, 31.4, 28.7; HRMS (ESI) Calcd for $C_{15}H_{24}N$ $[M + H]^+$ 218.1909, found 218.1911.

Preparation of Benzyl Phosphates. Benzyl phosphates were prepared from the corresponding benzyl alcohols and diethyl chlorophosphates according to the literature procedure[22] and purified using silica gel chromatography. Except **2j**, the benzyl phosphates (**2a**,[22] **2b**,[22] **2c**,[10b] **2d**,[23] **2e**,[22] and **2f-i**,[10b]) are known compounds and their spectral data showed good agreement with the literature data.

2-Chlorobenzyl diethyl phosphate (2j). Colorless oil (1.30 g, 47%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.50 (m, 1H), 7.38-7.33 (m, 1H), 7.30-7.24 (m, 2H), 5.17 (d, J = 7.2 Hz, 2H), 4.17-4.07 (m, 4H), 1.32 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 133.0, 129.7, 129.6, 129.4, 127.0, 66.2 (d, $^2J_{C\text{-}P}$ = 4.9 Hz), 64.1 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 16.2 (d, $^3J_{C\text{-}P}$ = 6.6 Hz); ^{31}P (121 MHz, $CDCl_3$) δ -0.4; HRMS (ESI) Calcd for $C_{11}H_{17}ClO_4P$ $[M + H]^+$ 279.0553, found 279.0565.

General Procedure for C–H Benzylation. A dry 10 mL Schlenk tube equipped with a stir bar was charged with $Co(acac)_3$ (14.3 mg, 0.040 mmol) and 2-(2-(diphenylphosphanyl)ethyl)pyridine (pyphos, 11.7 mg, 0.040 mmol), and THF (1.0 mL) under N_2 atmosphere. The resulting solution was cooled in an ice bath, followed by dropwise addition of t-$BuCH_2MgBr$ (1.0 M in THF, 0.96 mL, 0.96 mmol). After stirring for 30 min, N–H imine (0.40 mmol) and benzyl phosphate (0.80 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The resulting mixture was filtered through a short pad of silica gel while washing with EtOAc (10 mL x 3). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluent: hexane/EtOAc/NEt_3 = 50/1/1) to afford the benzylation product.

1-(2-Benzylphenyl)-2,2-dimethylpropan-1-imine (3aa). Light yellow oil (51 mg, 51%); R_f 0.50 (hexane/EtOAc = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (brs, 1H), 7.26-7.10 (m, 8H), 7.06 (dd, J = 1 Hz, 1H), 3.86 (s, 2H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 141.6, 140.8, 137.0, 130.5, 129.1, 128.6, 127.9, 126.32, 126.26, 125.6, 40.6, 39.5, 28.8; HRMS (ESI) Calcd for $C_{18}H_{22}N$ $[M + H]^+$ 252.1752, found 252.1747.

Preparative-Scale Synthesis of 3aa. A dry 50 mL Schlenk tube equipped with a stir bar was charged with $Co(acac)_3$ (143 mg, 0.40 mmol), pyphos (117 mg, 0.40 mmol), and THF (10.0 mL) under N_2 atmosphere. The resulting solution was cooled in an ice bath, followed by dropwise addition of t-$BuCH_2MgBr$ (1.0 M in THF, 9.6 mL, 9.6 mmol). After stirring for 30 min, 2,2-dimethyl-1-phenylpropan-1-imine (**1a**, 645 mg, 4.0 mmol) and benzyl diethyl phosphate (**2a**, 1.96 g, 8.0 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The resulting mixture was filtered through a short pad of silica gel while washing with EtOAc (50

mL x 3). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluent: hexane/EtOAc/NEt_3 = 50/1/1) to afford 1-(2-benzylphenyl)-2,2-dimethylpropan-1-imine (**3aa**) as a light yellow oil (587 mg, 58%).

1-(2-Benzyl-4-methylphenyl)-2,2-dimethylpropan-1-imine (3ba). Light yellow oil (66 mg, 62%); R_f 0.50 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (brs, 1H), 7.26 - 7.23 (m, 2H), 7.18-7.09 (m, 3H), 6.95-6.91(m, 3H), 3.82 (s, 2H), 2.25(s, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 141.0, 139.0, 137.6, 136.8, 131.1, 129.1, 128.6, 126.33, 126.28, 126.22, 40.7, 39.5, 28.9, 21.3; HRMS (ESI) Calcd for $C_{19}H_{24}N$ $[M + H]^+$ 266.1909, found 266.1915.

1-(2-Benzyl-4-(*tert*-butyl)phenyl)-2,2-dimethylpropan-1-imine (3ca). Light yellow oil (49 mg, 40%); R_f 0.55 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (brs, 1H), 7.29-7.25 (m, 2H), 7.20-7.18 (m, 3H), 7.12 (d, J = 7.2 Hz, 2H), 7.01 (d, J = 8 Hz, 1H), 3.89 (s, 2H), 1.26 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 150.7, 141.1, 139.0, 129.0, 128.6, 127.7, 126.2, 126.0, 122.5, 40.7, 39.8, 34.6, 31.4, 28.9; HRMS (ESI) Calcd for $C_{22}H_{30}N$ $[M + H]^+$ 308.2378, found 308.2382.

1-(3-Benzyl-[1,1'-biphenyl]-4-yl)-2,2-dimethylpropan-1-imine (3da): Light yellow oil (60 mg, 46%); R_f 0.45 (hexane/EtOAc = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (brs, 1H), 7.54-7.52 (m, 2H), 7.44-7.40 (m, 4H), 7.36-7.28 (m, 3H), 7.23-7.18 (m, 4H), 3.97 (s, 2H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 140.8, 140.7, 140.6, 137.5, 129.3, 129.1, 128.9, 128.7, 127.6, 127.2. 126.8, 126.4, 124.4, 40.7, 39.7, 28.9; HRMS (ESI) Calcd for $C_{24}H_{26}N$ $[M + H]^+$ 328.2065, found 328.2059.

1-(2-Benzyl-4-methoxyphenyl)-2,2-dimethylpropan-1-imine (3ea): Light yellow oil (60 mg, 53%); R_f 0.43 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (brs, 1H), 7.31-7.26 (m, 2H), 7.21-7.18 (m, 1H), 7.17-7.13 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.73 (dd, J = 8.4, 2.7 Hz, 1H), 6.66 (d, J = 2.4 Hz, 1H), 3.87 (s, 2H), 3.73 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 159.0, 140.6, 138.8, 134.4, 129.1, 128.6, 127.4, 126.4, 116.0, 110.8, 55.3, 40.8, 39.7, 28.9; HRMS (ESI) Calcd for $C_{19}H_{24}NO$ $[M + H]^+$ 282.1858, found 282.1862.

1-(2-Benzyl-4-(trifluoromethoxy)phenyl)-2,2-dimethylpropan-1-imine (3fa): Light yellow oil (87 mg, 65%); R_f 0.43 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (brs, 1H), 7.32-7.21 (m, 4H), 7.14-7.11 (m, 3H), 7.06-7.04 (m, 1H), 6.95 (d, J = 1.2 Hz, 1H), 3.89 (s, 2H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 148.8, 139.7, 129.1, 128.9, 127.8, 126.8, 122.8, 121.8, 119.3, 118.0, 40.8, 39.4, 28.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -57.8; HRMS (ESI) Calcd for $C_{19}H_{21}F_3NO$ $[M + H]^+$ 336.1575, found 336.1583.

1-(2-Benzyl-4-fluorophenyl)-2,2-dimethylpropan-1-imine (3ga): Light yellow oil (59 mg, 54%); R_f 0.45 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (brs, 1H), 7.38-7.20 (m, 3H), 7.13 (d, J = 7.2 Hz, 2H), 7.07 (dd, J = 8.4, 6 Hz, 1H), 6.89 (td, J = 8.4, 2.4 Hz, 1H), 6.80 (dd, J = 9.9, 2.4 Hz, 1H), 3.87 (s, 2H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 162.2 (d, $^1J_{C\text{-}F}$ = 245.1 Hz), 140.1 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 139.9, 137.5 (d, $^3J_{C\text{-}F}$ = 3.1 Hz), 129.2, 128.8, 127.9 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 126.7, 117.1 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 112.7(d, $^2J_{C\text{-}F}$ = 21.5 Hz), 40.8, 39.5, 28.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.8; HRMS (ESI) Calcd for $C_{18}H_{21}NF$ $[M + H]^+$ 270.1658, found 270.1660.

1-(2-Benzyl-4-chlorophenyl)-2,2-dimethylpropan-1-imine (3ha): Light yellow oil (62 mg, 54%); R_f 0.44 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (brs, 1H), 7.32-7.22 (m, 3H), 7.20-7.10 (m, 4H), 7.05-7.02 (m, 1H), 3.86 (s, 2H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 139.9, 139.8, 139.4, 133.8, 130.4, 129.1, 128.9, 127.7, 126.7, 125.9, 40.8, 39.4, 28.7. HRMS (ESI) Calcd for $C_{18}H_{21}NCl$ $[M + H]^+$ 286.1363, found 286.1357.

1-(2-Benzyl-5-methylphenyl)-2,2-dimethylpropan-1-imine (3ia); Light yellow oil (30 mg, 28%); R_f 0.65 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (brs, 1H,), 7.31-7.27 (m, 2H), 7.23-7.13 (m, 3H), 7.08-7.01 (m, 2H), 6.91 (s, 1H), 3.86 (s, 2H), 2.34 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3 (NH=*C*), 141.7, 141.1, 135.1, 133.9, 130.4, 129.1, 128.7, 128.6, 126.8, 126.3, 40.6, 39.2, 28.9, 21.2; HRMS (ESI) Calcd for $C_{19}H_{24}N$ $[M + H]^+$ 266.1909, found 266.1911.

1-(2-Benzyl-5-fluorophenyl)-2,2-dimethylpropan-1-imine (3ja): Light yellow oil (56 mg, 52%); R_f 0.45 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (brs, 1H), 7.36-7.32 (m, 3H), 7.3-7.28 (m, 1H), 7.23-7.21 (m, 2H), 7.14 (t, J = 8.4 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 4.03 (s, 2H), 1.30 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 161.8 (d, $^1J_{C\text{-}F}$ = 245.6 Hz), 143.8, 139.8, 128.6, 128.3, 127.6 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 126.3, 122.2 (d, $^3J_{C\text{-}F}$ = 2.8 Hz), 115.0 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 40.6, 33.3, 28.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1; HRMS (ESI) Calcd for $C_{18}H_{21}NF$ $[M + H]^+$ 270.1658, found 270.1651.

1-(2-Benzyl-5-chlorophenyl)-2,2-dimethylpropan-1-imine (3ka): Light yellow oil (48 mg, 42%); R_f 0.43 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (brs, 1H), 7.34-7.29 (m, 2H), 7.26-7.22 (m, 2H), 7.15-7.07 (m, 4H), 3.88 (s, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 140.2, 131.9, 131.5, 129.1, 128.8, 128.1, 126.6, 40.7, 39.0, 28.7; HRMS (ESI) Calcd for $C_{18}H_{21}NCl$ $[M + H]^+$ 286.1363, found 286.1357.

2,2-Dimethyl-1-(2-(4-methylbenzyl)phenyl)propan-1-imine (3ab); Light yellow oil (70 mg, 66%); R_f 0.50 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (brs, 1H), 7.25-7.00 (m, 8H), 3.84 (s, 2H), 2.31 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 141.7, 137.8, 137.3, 135.8, 130.5, 129.3, 129.0, 127.9, 126.2, 125.5, 40.7, 39.2, 28.9, 21.1; HRMS (ESI) Calcd for $C_{19}H_{24}N$ $[M + H]^+$ 266.1909, found 266.1913.

1-(2-(4-(*tert*-Butyl)benzyl)phenyl)-2,2-dimethylpropan-1-imine (3ac): Light yellow oil (62 mg, 50%); R_f 0.53 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (brs, 1H), 7.33-7.29 (m, 2H), 7.27-7.23 (m, 1H), 7.21-7.17 (m, 2H), 7.11-7.07 (m, 3H), 3.87 (s, 2H), 1.31 (s, 9H), 1.27(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 149.1, 141.6, 137.7, 137.2, 130.6, 128.7, 127.9, 126.2, 125.5, 40.6, 39.1, 34.5, 31.5, 28.9; HRMS (ESI) Calcd for $C_{22}H_{30}N$ $[M + H]^+$ 308.2378, found 308.2384.

1-(2-(4-Fluorobenzyl)phenyl)-2,2-dimethylpropan-1-imine (3ad): Light yellow oil (62 mg, 57%); R_f 0.43 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (brs, 1H), 7.26-7.16 (m, 2H), 7.11-7.07 (m, 4H), 7.00-6.93 (m, 2H), 3.86 (s, 2H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 161.6 (d, $^1J_{C\text{-}F}$ = 242.8 Hz), 136.8, 136.5, 136.4, 130.5 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 128.0, 126.4, 125.8, 115.4 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 40.7, 38.7, 28.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -117.0; HRMS (ESI) Calcd for $C_{18}H_{21}NF$ $[M + H]^+$ 270.1658, found 270.1665.

1-(2-(4-Chlorobenzyl)phenyl)-2,2-dimethylpropan-1-imine (3ae): Light yellow oil (55 mg, 48%); R_f 0.47 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (brs, 1H), 7.31-7.21 (m, 4H), 7.15-

7.10 (m, 4H), 3.90 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 141.6, 139.3, 136.4, 132.2, 130.4, 128.7, 128.1, 126.4, 125.8, 40.7, 38.9, 28.8; HRMS (ESI) Calcd for $C_{18}H_{21}NCl$ $[M + H]^+$ 286.1373, found 286.1370.

2,2-Dimethyl-1-(2-(3-methylbenzyl)phenyl)propan-1-imine (3af): Light yellow oil (55 mg, 53%); R_f 0.50 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (brs, 1H), 7.26-7.09 (m, 5H), 7.02 (d, J = 7.5 Hz, 1H), 6.97-6.93 (m, 2H), 3.87 (s, 2H), 2.32 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 141.7, 140.7, 138.2, 137.1, 130.5, 129.9, 128.5, 127.9, 127.1, 126.2, 125.5, 40.6, 39.4, 28.9, 21.6; HRMS (ESI) Calcd for $C_{19}H_{24}N$ $[M + H]^+$ 266.1909, found 266.1912.

1-(2-(3-Methoxybenzyl)phenyl)-2,2-dimethylpropan-1-imine (3ag): Light yellow oil (47 mg, 42%); R_f 0.33 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (brs, 1H), 7.32-7.14 (m, 5H), 6.82-6.75 (m, 3H), 3.93 (s, 2H), 3.83 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 159.8, 142.4, 141.7, 136.7, 130.5, 129.6, 127.9, 126.2, 125.6, 121.6, 115.1, 111.5, 55.2, 40.7, 39.5, 28.9; HRMS (ESI) Calcd for $C_{19}H_{24}NO$ $[M + H]^+$ 282.1858, found 282.1859.

1-(2-(3-Fluorobenzyl)phenyl)-2,2-dimethylpropan-1-imine (3ah): Light yellow oil (42 mg, 39%); R_f 0.43 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (brs, 1H), 7.34-7.24 (m, 3H), 7.19-7.15 (m, 2H), 6.98-6.87 (m, 3H), 3.94 (s, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 163.1 (d, $^1J_{C\text{-}F}$ = 244.4 Hz), 143.4 (d, $^3J_{C\text{-}F}$ = 7.3 Hz), 136.2, 130.5, 130.0 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 128.1, 126,5, 125.9, 124.8 (d, $^3J_{C\text{-}F}$ = 2.8 Hz), 116.0 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 113.3 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 40.7, 39.2, 28.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.3; HRMS (ESI) Calcd for $C_{18}H_{21}NF$ $[M + H]^+$ 270.1658, found 270.1660.

1-(2-(3-Chlorobenzyl)phenyl)-2,2-dimethylpropan-1-imine (3ai): Light yellow oil (40 mg, 35%); R_f 0.43 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (brs, 1H), 7.27-7.17 (m, 4H), 7.11 (d, J = 8.0 Hz, 3H), 7.01 (d, J = 6.4 Hz, 1H), 3.87 (s, 2H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 142.9, 141.7, 136.1, 134.4, 130.5, 129.9, 129.2, 128.1, 127.3, 126.6, 126.5, 125.9, 40.7, 39.1, 28.8; HRMS (ESI) Calcd for $C_{18}H_{21}NCl$ $[M + H]^+$ 286.1363, found 286.1369.

1-(2-(2-Chlorobenzyl)phenyl)-2,2-dimethylpropan-1-imine (3aj): Light yellow oil (34 mg, 29%), R_f 0.51 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (brs, 1H), 7.40-7.37 (m, 1H), 7.23-7.10 (m, 5H), 7.03-6.96 (m, 2H), 4.00 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 138.3, 135.5, 134.4, 131.1, 129.9, 129.7, 128.0, 127.9, 127.0, 126.4, 125.8, 40.8, 37.0, 28.9; HRMS (ESI) Calcd for $C_{18}H_{21}NCl$ $[M + H]^+$ 286.1363, found 286.1367.

1-(2-Benzoylphenyl)-2,2-dimethylpropan-1-one (4). In a 25 mL Schlenk tube equipped with a stir bar were placed **3aa** (0.6 mmol) and $Cu(OAc)_2$ (11 mg, 0.06 mmol), followed by the addition of DMF (6 mL). An oxygen balloon was attached to the Schlenk tube, and the reaction mixture was stirred at 80 °C in an oil bath for 12 h. The mixture was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography to afford the title compound as a light yellow oil (48 mg, 30%). R_f 0.33 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.76 (m, 2H), 7.60-7.53 (m, 3H), 7.48-7.42 (m, 4H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 196.7, 137.5, 137.2, 132.9, 131.0, 130.9, 130.2, 128.5, 128.3, 126.3, 44.7, 27.9; HRMS (ESI) Calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ 267.1385, found 267.1383.

Supporting Information Available. The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra (PDF)

Corresponding Author

*E-mail: nyoshikai@ntu.edu.sg.

ORCID

Naohiko Yoshikai: 0000-0002-8997-3268

Notes

The authors declare no competing financial interest.

Acknowledgments. This work was supported by Nanyang Technological University and Singapore Ministry of Education (MOE2016-T2-2-043).

References

( ) Rueping, M.; Nachtsheim, B. J. A Review of New Developments in the Friedel–Crafts Alkylation – from Green Chemistry to Asymmetric Catalysis. *Beilstein J. Org. Chem.* **2010**, *6*, 6.

(2) Liegault, B.; Renaud, J. L.; Bruneau, C. Activation and Functionalization of Benzylic Derivatives by Palladium Catalysts. *Chem. Soc. Rev.* **2008**, *37*, 290-299.

(3) (a) Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J. F. Friedel-Crafts Reaction of Benzyl Fluorides: Selective Activation of C-F Bonds as Enabled by Hydrogen Bonding. *Angew. Chem., Int. Ed.* **2014**, *53*, 13835-13839. (b) Schafer, G.; Bode, J. W. Friedel-Crafts Benzylation of Activated and Deactivated Arenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 10913-10916.

(4) (a) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp(2) Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767-1775. (b) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem. Eur. J.* **2014**, *20*, 6828-6842.

(5) Ackermann, L. Metal-Catalyzed Direct Alkylations of (Hetero)Arenes Via C-H Bond Cleavages with Unactivated Alkyl Halides. *Chem. Commun.* **2010**, *46*, 4866-4877.

(6) (a) Vasilopoulos, A.; Zultanski, S. L.; Stahl, S. S. Feedstocks to Pharmacophores: Cu-Catalyzed Oxidative Arylation of Inexpensive Alkylarenes Enabling Direct Access to Diarylalkanes. *J. Am. Chem. Soc.* **2017**, *139*, 7705-7708. (b) Zhang, W.; Chen, P.; Liu, G. Copper-Catalyzed Arylation of Benzylic C-H Bonds with Alkylarenes as the Limiting Reagents. *J. Am. Chem. Soc.* **2017**, *139*, 7709-7712. (c) Sha, S.-C.; Tcyrulnikov, S.; Li, M.; Hu, B.; Fu, Y.; Kozlowski, M. C.; Walsh, P. J. Cation-Pi Interactions in the Benzylic Arylation of Toluenes with Bimetallic Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 12415-12423. (d) Dewanji, A.; Krach, P. E.; Rueping, M. The Dual Role of Benzophenone in Visible-Light/Nickel Photoredox-Catalyzed C-H Arylations: Hydrogen-Atom Transfer and Energy Transfer. *Angew. Chem., Int. Ed.* **2019**, *58*, 3566-3570.

(7) Ackermann, L.; Novak, P. Regioselective Ruthenium-Catalyzed Direct Benzylations of Arenes through C-H Bond Cleavages. *Org. Lett.* **2009**, *11*, 4966-4969.

(8) (a) Nadres, E. T.; Santos, G. I.; Shabashov, D.; Daugulis, O. Scope and Limitations of Auxiliary-Assisted, Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 C-H Bonds. *J. Org. Chem.* **2013**, *78*, 9689-9714. (b) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. Ligand-Enabled Meta-C-H Activation Using a Transient Mediator. *Nature* **2015**, *519*, 334-338. (c) Wiest, J. M.; Pothig, A.; Bach, T. Pyrrole as a Directing Group: Regioselective Pd(II)-Catalyzed Alkylation and Benzylation at the Benzene Core of 2-Phenylpyrroles. *Org. Lett.* **2016**, *18*, 852-855.

(9) (a) Wang, H.; Yu, S.; Qi, Z.; Li, X. Rh(III)-Catalyzed C-H Alkylation of Arenes Using Alkylboron Reagents. *Org. Lett.* **2015**, *17*, 2812-2815. (b) Lu, M.-Z.; Wang, C.-Q.; Song, S.-J.; Loh, T.-P. Rhodium(III)-Catalyzed Directed C–H Benzylation and Allylation of Indoles with Organosilicon Reagents. *Org. Chem. Front.* **2017**, *4*, 303-307.

(10) (a) Song, W.; Ackermann, L. Cobalt-Catalyzed Direct Arylation and Benzylation by C-H/C-O Cleavage with Sulfamates, Carbamates, and Phosphates. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251-8254. (b) Xu, W.; Paira, R.; Yoshikai, N. Ortho-C-H Benzylation of Aryl Imines with Benzyl Phosphates under Cobalt-Pyphos Catalysis. *Org. Lett.* **2015**, *17*, 4192-4195.

(11) (a) Aihara, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. Ni(II)-Catalyzed Oxidative Coupling between C(sp^2)-H in Benzamides and C(sp^3)-H in Toluene Derivatives. *J. Am. Chem. Soc.* **2014**, *136*, 15509-15512. (b) Aihara, Y.; Wuelbern, J.; Chatani, N. The Nickel(II)-Catalyzed Direct Benzylation, Allylation, Alkylation, and Methylation of C-H Bonds in Aromatic Amides Containing an 8-Aminoquinoline Moiety as the Directing Group. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 438-446.

(12) (a) Fruchey, E. R.; Monks, B. M.; Cook, S. P. A Unified Strategy for Iron-Catalyzed Ortho-Alkylation of Carboxamides. *J. Am. Chem. Soc.* **2014**, *136*, 13130-13133. (b) Cera, G.; Haven, T.;

Ackermann, L. Expedient Iron-Catalyzed C-H Allylation/Alkylation by Triazole Assistance with Ample Scope. *Angew. Chem., Int. Ed.* **2016**, *55*, 1484-1488.

(13) (a) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C-H Functionalization. *Acc. Chem. Res.* **2014**, *47*, 1208-1219. (b) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C-H Activation. *ACS Catal.* **2016**, *6*, 498-525.

(14) (a) Xu, W.; Yoshikai, N. N-H Imine as a Powerful Directing Group for Cobalt-Catalyzed Olefin Hydroarylation. *Angew. Chem., Int. Ed.* **2016**, *55*, 12731-12735. (b) Xu, W.; Yoshikai, N. Cobalt-Catalyzed, N-H Imine-Directed Hydroarylation of Styrenes. *Org. Lett.* **2018**, *20*, 1392-1395.

(15) (a) Xu, W.; Yoshikai, N. Pivalophenone Imine as a Benzonitrile Surrogate for Directed C-H Bond Functionalization. *Chem. Sci.* **2017**, *8*, 5299-5304. (b) Xu, W.; Yoshikai, N. Cobalt-Catalyzed Directed C–H Alkenylation of Pivalophenone N–H Imine with Alkenyl Phosphates. *Beilstein J. Org. Chem.* **2018**, *14*, 709-715. (c) Sun, Q.; Yoshikai, N. Cobalt-Catalyzed Directed Ortho-Methylation of Arenes with Methyl Tosylate. *Org. Chem. Front.* **2018**, *5*, 2214-2218. (d) Sun, Q.; Yoshikai, N. Cobalt-Catalyzed Tandem Radical Cyclization/C−C Coupling Initiated by Directed C−H Activation. *Org. Lett.* **2019**, *21*, 5238-5242.

(16) For other selected examples of N–H imine-directed C–H functionalization reactions, see: (a) Tran, D. N.; Cramer, N. Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Racemic Allenes by the [3+2] Annulation of Aryl Ketimines. *Angew. Chem., Int. Ed.* **2013**, *52*, 10630-10634. (b) Zhang, J.; Ugrinov, A.; Zhao, P. Ruthenium(II)/N-Heterocyclic Carbene Catalyzed [3+2] Carbocyclization with Aromatic N–H Ketimines and Internal Alkynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 6681-6684. (c) Jia, T.; Zhao, C.; He, R.; Chen, H.; Wang, C. Iron-Carbonyl-Catalyzed Redox-Neutral [4+2] Annulation of N–H Imines and Internal Alkynes by C–H Bond Activation. *Angew. Chem., Int. Ed.* **2016**, *55*, 5268-5271. (d) Jin, X.; Yang, X.; Yang, Y.; Wang, C. Rhenium and Base Co-Catalyzed [3 + 2] Annulations of N–H Ketimines and Alkynes to Access Unprotected Tertiary Indenamines through C–H Bond Activation. *Org. Chem. Front.* **2016**, *3*, 268-272.

(17) Berlin, K. D.; Peterson, M. E. Nucleophilic Displacement Reaction on Organophosphorus Esters by Grignard Reagents. II. Evidence for Competitive Displacement on Carbon and Phosphorus in the Reaction of Grignard Reagents with Simple Phosphates. *J. Org. Chem.* **1967**, *32*, 125-129.

(18) (a) Xu, W.; Pek, J. H.; Yoshikai, N. Iron-Catalyzed Directed C-H Silylation of Pivalophenone N-H Imines. *Asian J. Org. Chem.* **2018**, *7*, 1351-1354. (b) Xu, W.; Yoshikai, N. Iron-Catalyzed Ortho C-H Arylation and Methylation of Pivalophenone N-H Imines. *ChemSusChem* **2019**, *12*, 3049-3053.

(19) Zhang, L.; Ang, G. Y.; Chiba, S. Copper-Catalyzed Benzylic C-H Oxygenation under an Oxygen Atmosphere Via N-H Imines as an Intramolecular Directing Group. *Org. Lett.* **2011**, *13*, 1622-1625.

(20) Weiberth, F. J.; Hall, S. S. Copper(I)-Activated Addition of Grignard Reagents to Nitriles. Synthesis of Ketimines, Ketones, and Amines. *J. Org. Chem.* **1978**, *52*, 3901-3904.

(21) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. Manganese-Catalyzed Dehydrogenative [4+2] Annulation of N-H Imines and Alkynes by C-H/N-H Activation. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950-4953.

(22) McLaughlin, M. Suzuki-Miyaura Cross-Coupling of Benzylic Phosphates with Arylboronic Acids. *Org. Lett.* **2005**, *7*, 4875-4878.

(23) Trost, B. M.; Czabaniuk, L. C. Benzylic Phosphates as Electrophiles in the Palladium-Catalyzed Asymmetric Benzylation of Azlactones. *J. Am. Chem. Soc.* **2012**, *134*, 5778-5781.