Studies on Palladium-Catalyzed Benzylic Arylation **Takashi Niwa 2009**

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Takashi Niwa

2009

Contents

Abbreviations

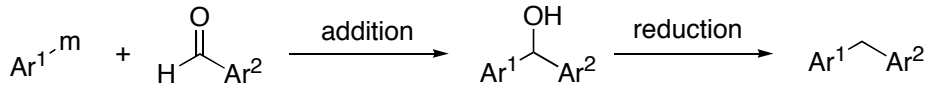
Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bs	broad singlet (spectral)
Bu	butyl
Bz	benzoyl
c	cyclo
°C	degrees Celsius
calcd	calculated
cat.	catalytic
cm	centimeter(s)
Co.	company
conc.	concentrated
δ	chemical shift in parts per million
d	doublet (spectral)
dba	dibenzylideneacetone
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPE-phos	bis[2-(diphenylphosphino)phenyl] ether
DPPE (dppe)	1,2-bis(diphenylphosphino)ethane
DPPF (dppf)	1,1'-bis(diphenylphosphino)ferrocene
DPPP (dppp)	1,3-bis(diphenylphosphino)propane
Ed(s).	editor(s)
eq(s)	equation(s), equivalent(s)
Et	ethyl
et al.	*et alii* (and others)
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HRMS	high-resolution mass spectrum
Hz	hertz (s^{-1})
i	iso
IR	infrared (spectral)
J	coupling constant (spectral)
m	multiplet (spectral)
M	molar (1 M = 1 mol dm^{-3})
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
μL	microliter(s)
mL	milliliter(s)
mmol	millimole
m.p.	melting point
MW	microwave
n	normal
NMR	nuclear magnetic resonance
Nu	nucleophile
pp.	page(s)
Ph	phenyl
ppm	parts per million (spectral)
Pr	propyl
q	quartet (spectral)
rac	racemic
ref	reference
rt.	room temperature (25 ± 3 °C)
s	singlet (spectral)
s (sec)	secondary
sep	septet (spectral)
t	triplet (spectral)
t (*tert*)	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
tol	tolyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

General Introduction

1. Palladium-Catalyzed Benzylation of Aryl Halide

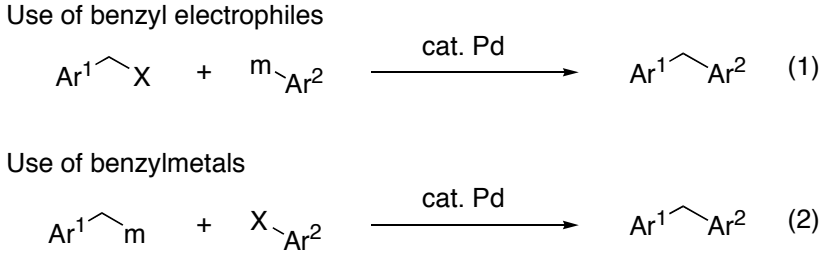
Diarylmethanes are an important class of compounds that often appear in organic chemistry.[1] Furthermore, some diarylmethane derivatives have interesting biological and physiological properties.[2] The common method for the synthesis of diphenylmethane derivatives has been the Friedel–Crafts-type alkylation of arenes with benzyl halides historically, which suffers from polyalkylation.[3] So far, the most popular route to diarylmethanes is the addition of organometallic reagents to aromatic aldehydes and subsequent reduction (Scheme 1).[4]

Scheme 1.



Palladium-catalyzed cross-coupling reaction is also a powerful method for straightforward synthesis of diarylmethane derivatives. In principle, the synthesis of diarylmethanes using cross-coupling strategy can be achieved by one of two processes, that is, the reaction of arylmetals with benzyl halides or the reaction of benzylmetals with aryl halides (Scheme 2).

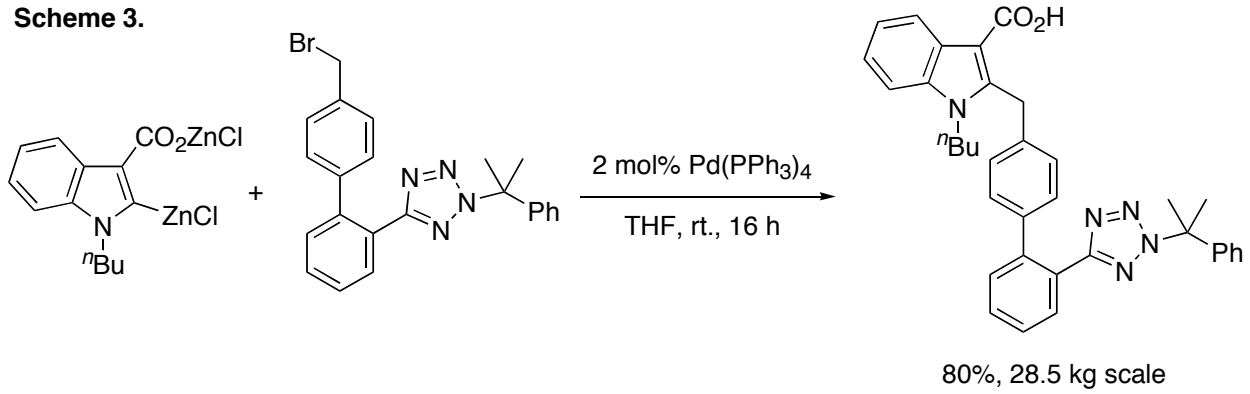
Scheme 2.



Palladium-catalyzed arylation of benzyl electrophiles has been widely explored (Scheme 2, eq 1).[5] Various benzyl chlorides and bromides are readily available, and they are therefore the reagents of choice in most cases. A variety of combinations of benzyl electrophiles and arylmetals allow for the synthesis of complex diarylmethanes. For instance, Fisher *et al.*

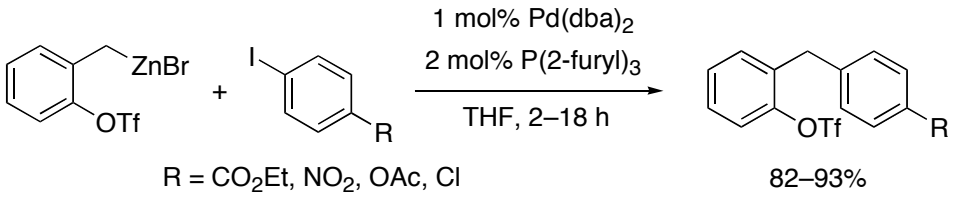
reported the palladium-catalyzed cross-coupling reaction of 2-indolylzinc chloride with functionalized benzyl bromide (Scheme 3).[6] The reaction proceeded even in a pilot plant run.

Scheme 3.



On the other hand, in the palladium-catalyzed benzylation of aryl halides, the scope of benzylmetals is narrow (Scheme 2, eq 2). Among benzylmetals, benzylzinc reagents are most convenient. Benzylzincs are available by treatment of benzylic bromides with zinc powder. Moreover, benzylzincs are compatible with many functional groups. Knochel *et al*. reported the efficient preparation of various polyfunctional aromatic compounds via palladium-catalyzed cross-coupling reaction using benzylzinc reagents (Scheme 4).[7]

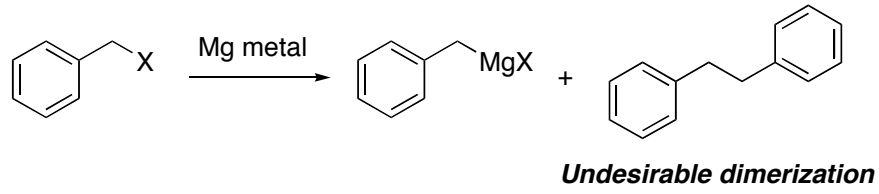
Scheme 4.



Benzylmagnesiums have sometimes been used as benzylmetal reagents since the original investigation of palladium-catalyzed benzylation.[8] However, the application of benzylmagnesium reagents is plagued with some problems. Although benzylmagnesiums are readily available by treatment of benzyl halides with Mg metal, the reactions are not so efficient as the corresponding reaction with Zn metal, due to the formation of 1,2-diarylethanes as by-products (Scheme 5). Furthermore, cross-homo scrambling can be observed via

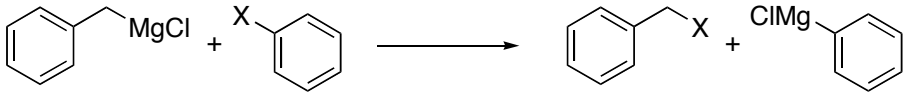
magnesium-halogen exchange (Scheme 6).

Scheme 5.



Undesirable dimerization

Scheme 6.

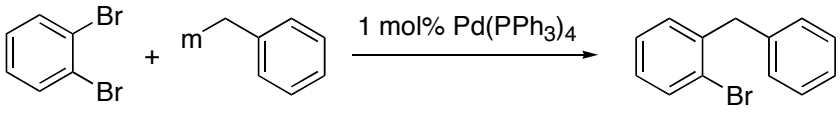


Halogen–magnesium exchange

Cross–homo scrambling

Finally, organomagnesium has naturally lower chemoselectivity, and strangely, often shows disappointing reactivity in palladium-catalyzed cross-coupling reactions. Kumada *et al.* reported a comparison of the reactivity of benzylmagnesium with that of benzylzinc in palladium-catalyzed benzylation of 1,2-dibromobenzene (Scheme 7).[9]

Scheme 7.



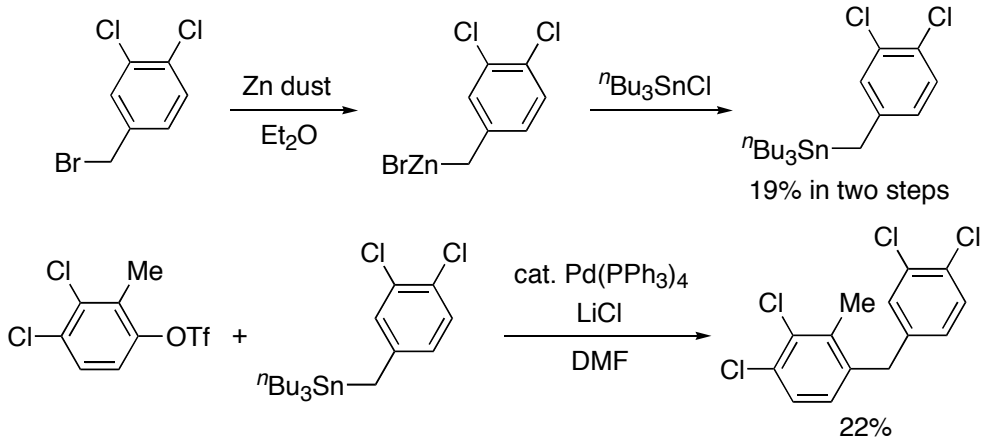
m = MgCl, Et_2O, reflux, 20 h 20%

m = ZnBr, THF, 50 ˚C, 16 h 68%

Benzylmetals containing less electropositive metals including Sn and B are rarely used. Benzylstannanes have found relatively few synthetic applications. This may be due to the difficulties in the synthesis of the benzylstannanes as well as to the lower reactivity of organostannanes. As a rare example, tributyl(3,4-dichlorophenylmethyl)stannane was prepared via the corresponding benzylzinc reagent only in 19% yield (Scheme 8).[10] Subsequent cross-coupling reaction of the benzylstannane with aryl triflate gave the desired diarylmethane

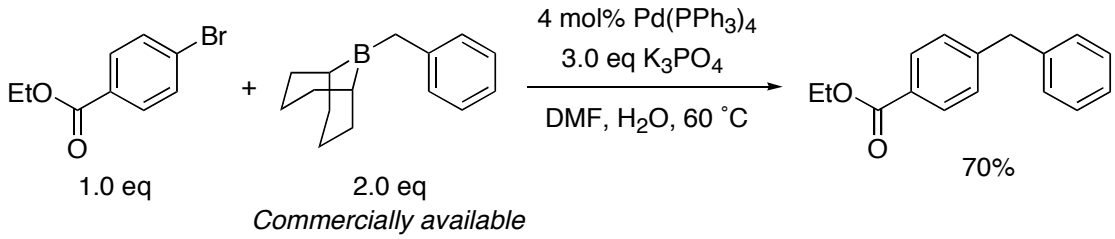
derivative in 22% yield.

Scheme 8.



Because organoboron compounds are generally synthesized via hydroboration, benzylboron compounds are less readily available and are uncommon coupling partners in Suzuki–Miyaura cross-coupling reaction. Flaherty *et al*. reported the palladium-catalyzed benzylation of aryl halides with commercially available benzylboron compounds (Scheme 9).[11]

Scheme 9.



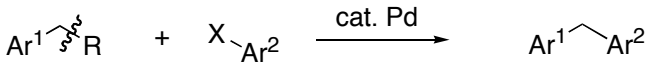
As described above, benzylzinc derivatives appear to be the most favorable benzylmetals in all respects for palladium-catalyzed benzylation. Although palladium-catalyzed cross-coupling reactions of benzylzincs display high reactivity and chemoselectivity, the need still exists for preparation of benzylzinc reagents by treatment of benzyl halides with a stoichiometric amount of Zn powder. Furthermore, synthesis of benzyl halides often requires several steps.

An alternative attractive route for the palladium-catalyzed benzylation of aryl halides is the use of stable organic compounds bearing no metallic atom as nucleophilic partners (Scheme 10). This method prevents the obligation to prepare and use the activated sensitive compounds such as

benzylzinc reagents. Instead, nucleophilic intermediates are generated in situ.

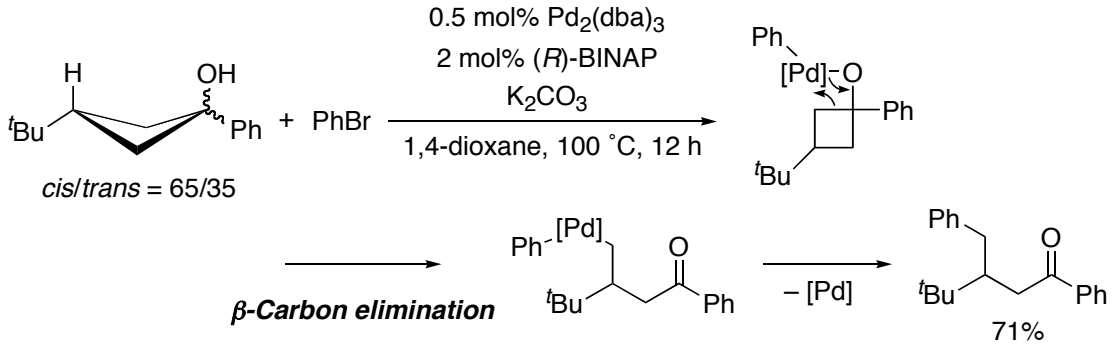
Scheme 10.

Use of stable organic compounds



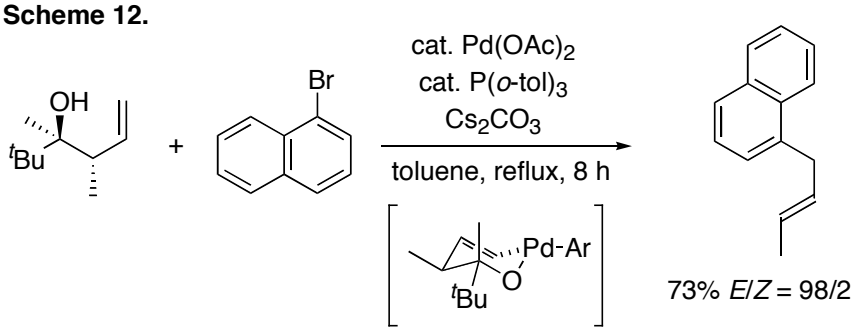
Carbon-carbon bond cleavage is one of the approaches. In particular, β-carbon elimination of heteroatom-coordinated palladium species is a unique process to produce organopalladium intermediates for successive reactions. Uemura *et al*. described palladium-catalyzed arylation of *tert*-cyclobutanols with aryl bromides (Scheme 11).[12] The reaction proceeds via β-carbon elimination of arylpalladium alkoxides by relief of the ring strain and the following reductive elimination.

Scheme 11.



Oshima *et al*. reported palladium-catalyzed allylation of aryl halides with homoallyl alcohols as the allyl sources via retro-allylation, which involves unstrained carbon-carbon bond cleavage (Scheme 12).[13] The retro-allylation reaction would proceed in a concerted fashion via a conformationally regulated six-membered cyclic transition state.

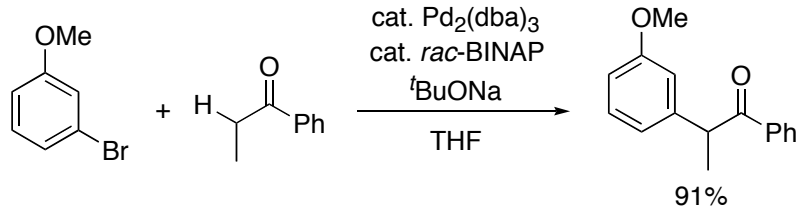
Scheme 12.



Six-membered transition state

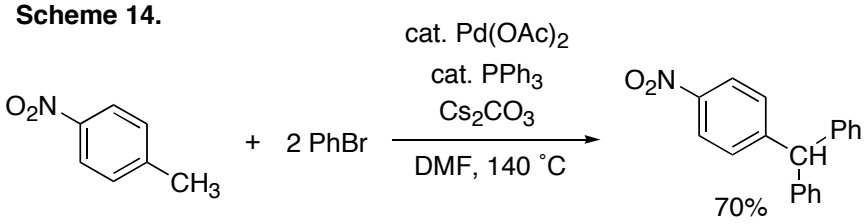
Direct metalation of a carbon-hydrogen bond is another method to use stable organic compounds as coupling partners in cross-coupling reaction. Recently, transformation of a carbon-hydrogen bond attracts increasing attention in the light of not only scientific interest but also the utility in organic synthesis.[14] Among them, palladium-catalyzed direct arylation at sp^3-hybridized carbons having acidic hydrogens has been emerging as one of the recent remarkable advances. In 1997, Miura[15], Buchwald[16], and Hartwig[17] independently reported direct arylation with aryl halides at the α-position of a carbonyl group (Scheme 13).

Scheme 13.



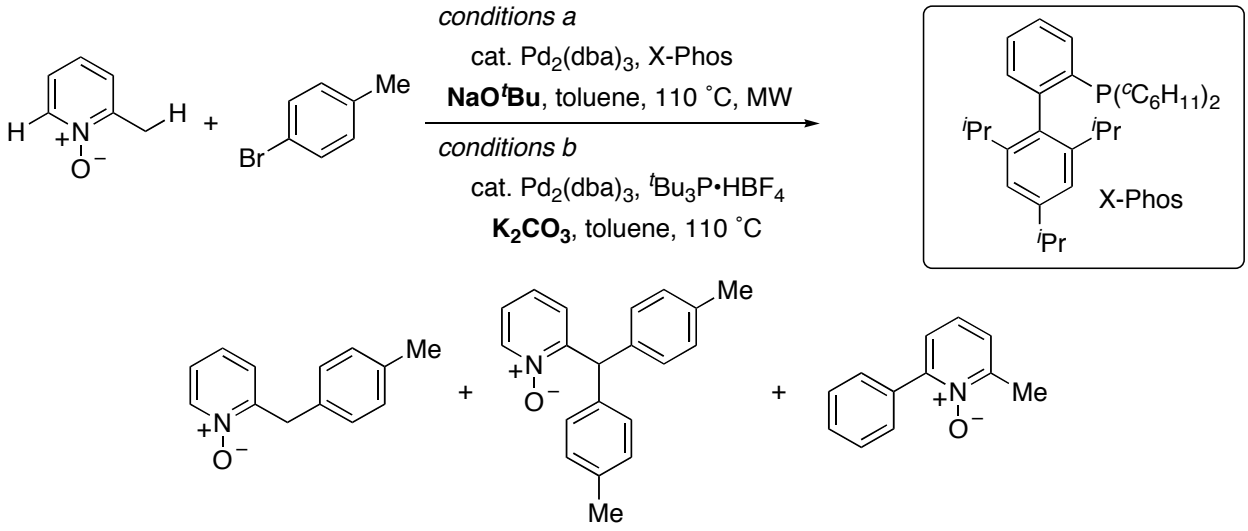
Since then, the direct arylation has opened the door to the carbon-carbon bond formation with aryl halides at sp^3-hybridized carbons bearing acidic hydrogens. In recent years, the scope of the arylation has been expanded to include a variety of substrates such as ketones,[18] aldehydes,[19] malonates,[18b] esters,[20] nitriles,[21] and amides.[20a,22] Nomura and Miura described palladium-catalyzed direct arylation of 4-alkylnitrobenzenes with aryl bromides at the benzylic position to give diarylated products (Scheme 14).[23] This is the first example of benzylic direct arylation.

Scheme 14.



Very recently, Fagnou *et al*. reported direct arylation of azine *N*-oxide substrates under palladium catalysis in the presence of base (Scheme 15).[24] They demonstrated direct arylation at the benzylic sp^3-hybridized carbon with NaO^{t}Bu and at the sp^2 2-carbon with K_2CO_3.

Scheme 15.



conditions a	85%	4%	0%
conditions b	0%	0%	56%

2. Overview of this thesis

The author focused on the strategy to prepare the organopalladium intermediates from stable organic substrates and found some new benzylic arylation reactions with aryl halides under palladium catalysis. In Chapter 1, palladium-catalyzed 2-pyridylmethyl transfer from

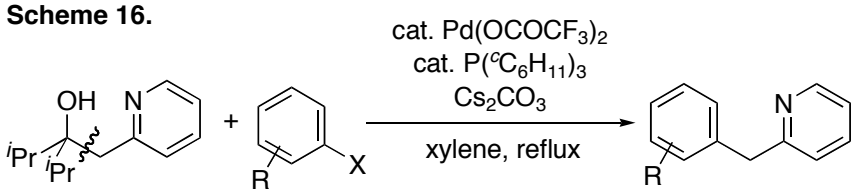
2-(2-pyridyl)ethanol derivatives to aryl halides via cleavage of unstrained sp^3C–sp^3C bonds are described. In Chapter 2–4, direct benzylic arylations with aryl halides in the presence of palladium catalysis are disclosed.

2.1. Palladium-Catalyzed 2-Pyridylmethyl Transfer from 2-(2-Pyridyl)ethanol Derivatives to Organic Halides by Chelation-Assisted Cleavage of Unstrained sp^3C–sp^3C Bonds (Chapter 1)

Transition-metal-catalyzed cleavage of carbon-carbon bonds is not only scientifically challenging but also potentially useful in organic synthesis. Among them, the cleavage of unstrained carbon-carbon bonds ranks as one of the most difficult processes due to the lack of sufficient strain energy as a driving force. Assistance by chelation is promising for the metal-mediated cleavage of such unstrained carbon-carbon bonds. However, it is always sp^3C–sp^2C[25] or sp^2C–sp^2C[26] bonds that are cleaved.

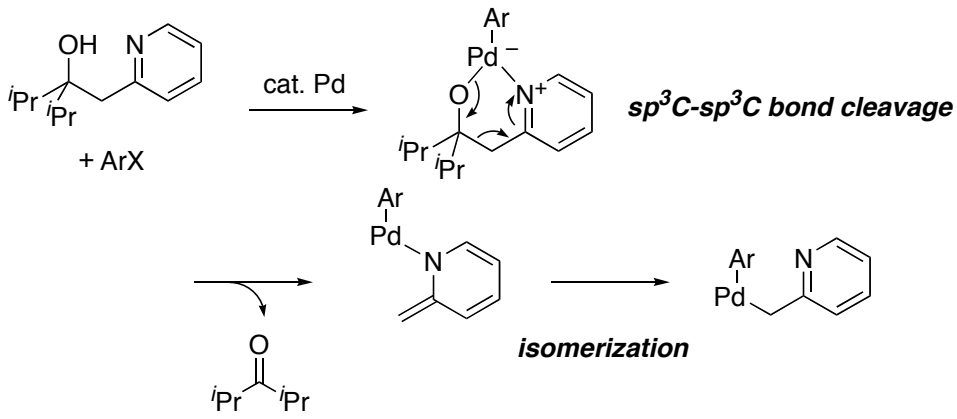
In Chapter 1, the author describes the 2-pyridylmethylation of various aryl and alkenyl halides with 2-(2-pyridyl)ethanol derivatives as a pyridylmethyl source in the presence of a palladium catalyst and a cesium base (Scheme 16).

Scheme 16.



He hypothesized the chelation–assisted cleavage of the sp^3C–sp^3C bond from arylpalladium alkoxides and sequential isomerization as the key steps (Scheme 17).

Scheme 17.

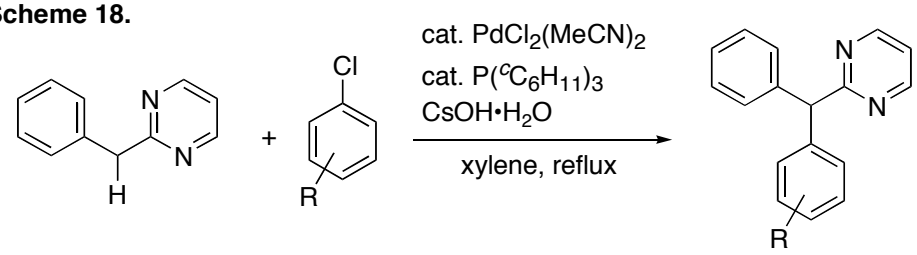


2.2 Direct Benzylic Arylations with Aryl Halides under Palladium Catalysis (Chapters 2–4)

Transition-metal-catalyzed cross-coupling reaction is one of the remarkable advances among the most important reactions in organic synthesis. Recent progress in this area has allowed for direct use of organic compounds bearing no metallic atoms as nucleophilic coupling partners. Among them, direct conversion of sp^2C–H bonds into sp^2C–sp^2C bonds of biaryls is widely investigated.[27–29] On the other hand, examples of direct arylation of sp^3C–H bonds are relatively less pronounced.[15–22,30–37]

In Chapter 2, the author describes the direct benzylic arylation of the aryl(azaaryl)methanes with aryl halides to give triarylmethanes under palladium catalysis in the presence of cesium hydroxide as a base (Scheme 18).

Scheme 18.

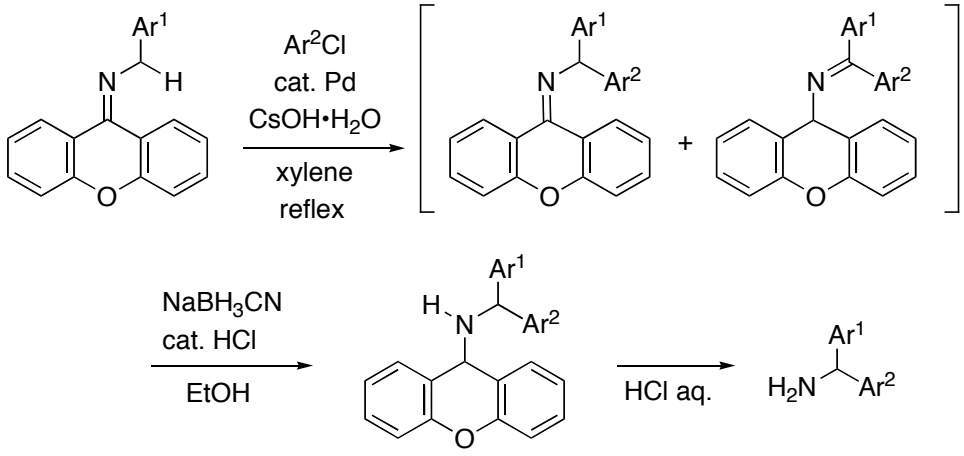


He proposes a reaction mechanism that includes deprotonation at the benzylic position

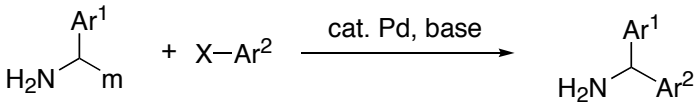
followed by transmetalation, and suggests that the acidity of the protons to be substituted by an aryl group is probably a decisive factor for the success of the reaction.

In Chapter 3, the author describes the palladium-catalyzed direct arylation of *N*-benzylxanthone imines at the benzylic carbon (Scheme 19). The product is readily transformed to benzhydrylamine. Taking into consideration that the starting imine is readily available from benzylic amine, the overall transformation represents a formal cross-coupling reaction of aryl halide with α-aminobenzyl metal (Scheme 20).

Scheme 19.



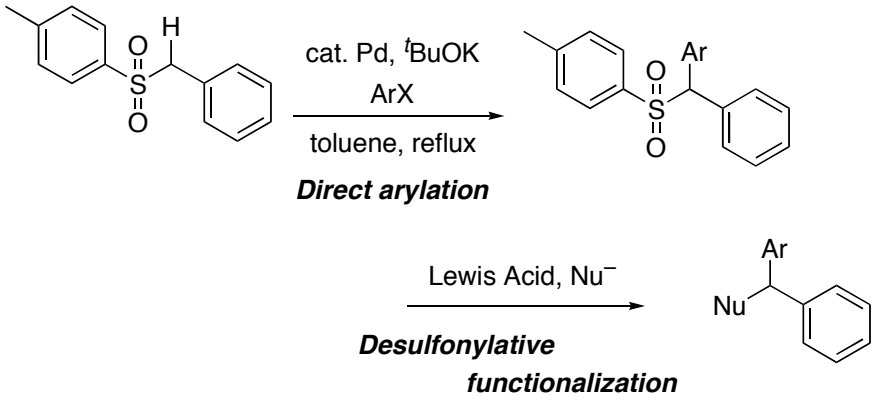
Scheme 20.



***α*-aminobenzylmetal**

In Chapter 4, the author shows palladium-catalyzed direct arylation at the α-position of sulfones. Treatment of benzyl sulfones, readily prepared from benzyl halide and sodium arenesulfinate, with aryl halides under palladium catalysis affords the corresponding diarylmethyl sulfones (Scheme 21). The product can be transformed further via desulfonylative functionalization with nucleophiles under acidic conditions. Thus, the reaction provides a facile route to diarylmethane derivatives.

Scheme 21.


H
O
S
O
cat. Pd, tBuOK
ArX
toluene, reflux
Direct arylation
Ar
O
S
O
Lewis Acid, Nu−
Ar
Nu
Desulfonylative
functionalization

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Chapter 1

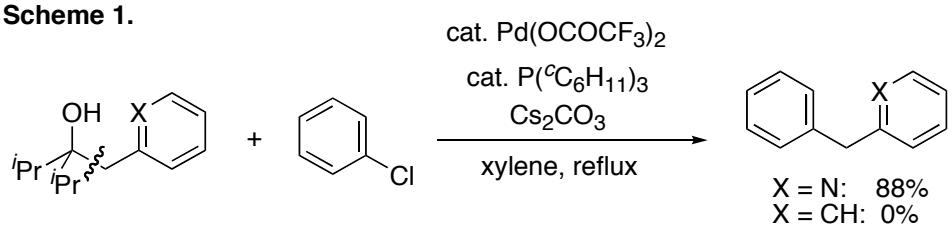
Palladium-Catalyzed 2-Pyridylmethyl Transfer from 2-(2-Pyridyl)ethanol Derivatives to Organic Halides by Chelation-Assisted Cleavage of Unstrained sp^3C–sp^3C Bonds

Treatment of 2-(2-pyridyl)ethanol derivatives with aryl chlorides in the presence of a palladium catalyst results in the transfer of the pyridylmethyl moiety of the alcohol to yield the corresponding (2-pyridylmethyl)arene. The reaction proceeds by chelation-assisted cleavage of an sp^3C–sp^3C bond followed by formation of a carbon–carbon bond.

Introduction

Transition-metal-catalyzed cleavage of carbon-carbon bonds is not only scientifically challenging but also potentially useful in organic synthesis.[1] Among the bond-breaking reactions, the cleavage of unstrained carbon-carbon bonds ranks as one of the most difficult processes due to the lack of sufficient strain energy as a driving force. Assistance by chelation is promising for the metal-mediated cleavage of such unstrained carbon-carbon bonds.[1d,1f,2] However, it is always sp^3C–sp^2C[1d, 1f, 2b, 2c] or sp^2C–sp^2C[2d] bonds that are cleaved. About the chelation-assisted cleavage of sp^3C–sp^3C bonds under catalytic conditions, little is known[3] because of the kinetics as well as thermodynamic stability of their bonds.[1a–1d] In Chapter 1, the author demonstrates 2-pyridylmethylation of aryl halides with 2-(2-pyridyl)ethanols via sp^3C–sp^3C bond cleavage (Scheme 1).

Scheme 1.

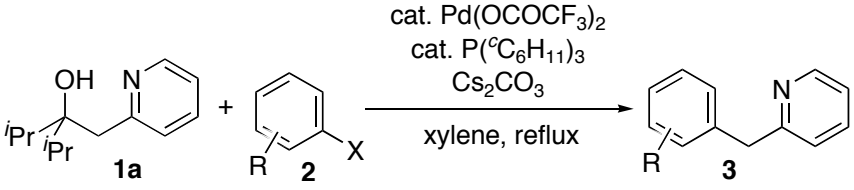


Results and Discussion

Treatment of chlorobenzene (**2a**) with pyridyl alcohol **1a** in the presence of cesium carbonate and a palladium catalyst in refluxing xylene provided 2-benzylpyridine (**3a**) in good yield (Table 1, entry 1). A variety of aryl chlorides underwent the reaction and the presence of either an electron-withdrawing or electron-donating group on the aromatic rings did not hinder the reaction (entries 2–5). Aryl chloride **2f** having a methyl group at the 2-position also participated in the reaction (entry 6). It is worth noting that the reaction of 4-chlorostyrene (**2g**) provided the desired product **3g** selectively (entry 7), even though **2g** can competitively undergo repetitious Mizoroki-Heck reactions which lead to oligo(4-phenylenevinylene) via

self-oligomerization.[4] The synthesis of di(2-pyridyl)methane (**3h**) was also successful (entry 8). The yield of **3a** was slightly lower when the reaction of **2a** was performed at a lower temperature (entry 9). Aryl bromide and iodide also underwent the pyridylmethylation (entries 10 and 11). Triphenylphosphine functioned as well as tricyclohexylphosphine as the ligand in the reaction of iodobenzene, affording **3a** in 80% yield in refluxing toluene (entry 12). The choice of palladium salt is crucial. Palladium (II) trifluoroacetate proved to be the best precursor. The use of $Pd(OAc)_2$, $Pd(acac)_2$, $PdCl_2$, $PdCl_2(CH_3CN)_2$, $[PdCl(\pi\text{-allyl})]_2$, $Pd(PPh_3)_4$ (with no additional ligand), and $Pd_2(dba)_3$ resulted in significantly lower yields of 73%, 33%, 15%, 14%, 20%, 26%, and 73%, respectively, relative to that obtained with iodobenzene in the presence of palladium(II) trifluoroacetate and $P(^cC_6H_{11})_3$ (entry 11). The author has no clear reason for the difference. Unfortunately, the reactions of alkyl chlorides failed to yield the corresponding products, and **1a** was completely recovered. The reactions of benzyl chloride and allyl chloride afforded complex mixtures.

Table 1. Palladium-Catalyzed 2-Pyridylmethyl Transfer to Aryl Halides **2** from Alcohol **1a**[a]

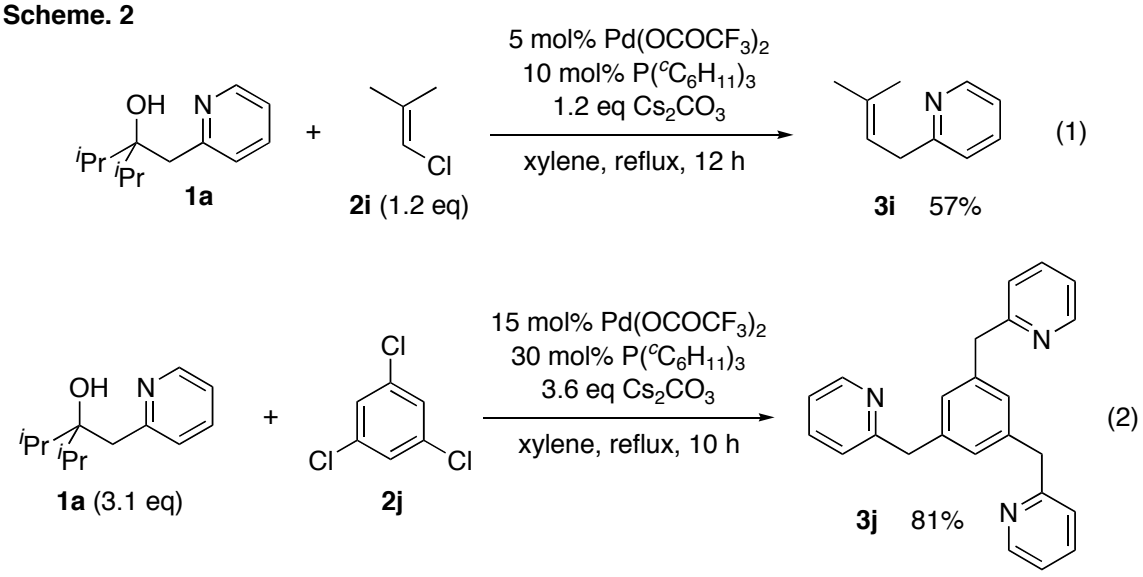


entry	R	X	**2**	**3**	yield[b] (%)
1	H	Cl	**2a**	**3a**	88
2	4-CF_3	Cl	**2b**	**3b**	89
3	4-CO_2Et	Cl	**2c**	**3c**	80
4	4-CN	Cl	**2d**	**3d**	70
5	4-OMe	Cl	**2e**	**3e**	90
6	2-Me	Cl	**2f**	**3f**	79
7	4-CH_2=CH	Cl	**2g**	**3g**	81
8	2-chloropyridine	Cl	**2h**	**3h**	50 (63)
9	H	Cl	**2a**	**3a**	85[c]
10	H	Br	**2a-Br**	**3a**	80[c]
11	H	I	**2a-I**	**3a**	88[c]
12	H	I	**2a-I**	**3a**	80[c,d]

[a] A mixture of **1a** (0.80 mmol), **2** (1.2 eq), $Pd(OCOCF_3)_2$ (5 mol%), $P(^cC_6H_{11})_3$ (10 mol%), and Cs_2CO_3 (1.2 eq) was boiled in xylene (0.50 M) for 1.5–10 h.
[b] Isolated yield. A yield determined by ^{1}H NMR is in parentheses.
[c] Performed in refluxing toluene. [d] PPh_3 was used instead of $P(^cC_6H_{11})_3$.

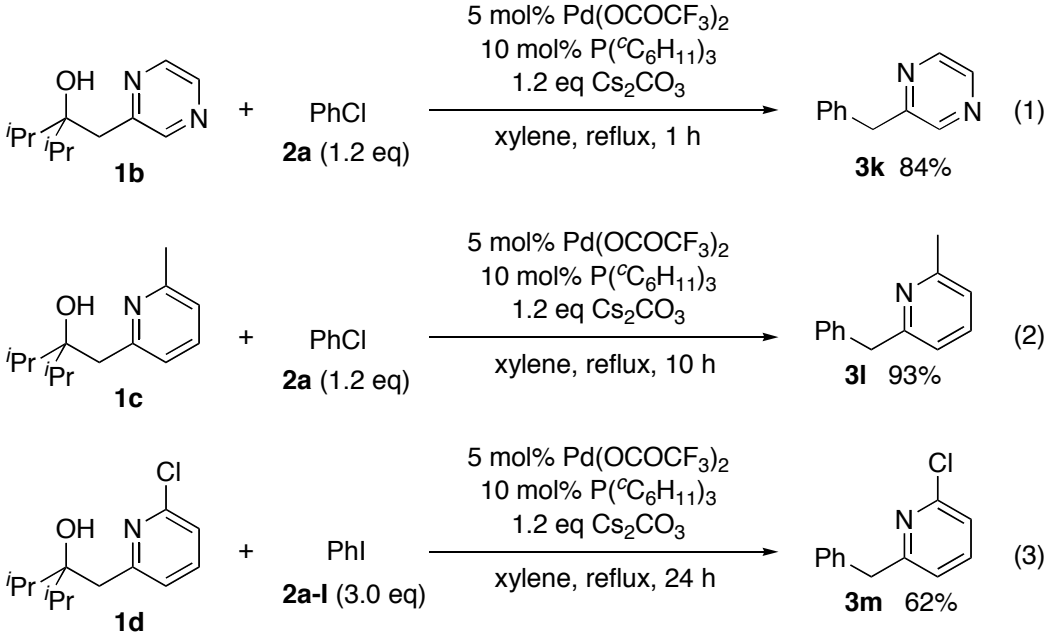
The reaction of alkenyl chloride **2i** yielded 2-prenylpyridine (**3i**) in reasonable yield (Scheme 2, eq 1). The high efficiency of the 2-pyridylmethyl transfer resulted in the reaction of 1,3,5-trichlorobenzene (**2j**) provided a new scaffold **3j** which is potentially applicable to supramolecular chemistry (eq 2).

Scheme. 2



Pyrazinyl alcohol **1b** transferred the pyrazinylmethyl moiety efficiently under the same reaction conditions (Scheme 3, eq 1). Disubstituted pyridines such as **3l** and **3m** were readily synthesized (eqs 2 and 3).[5]

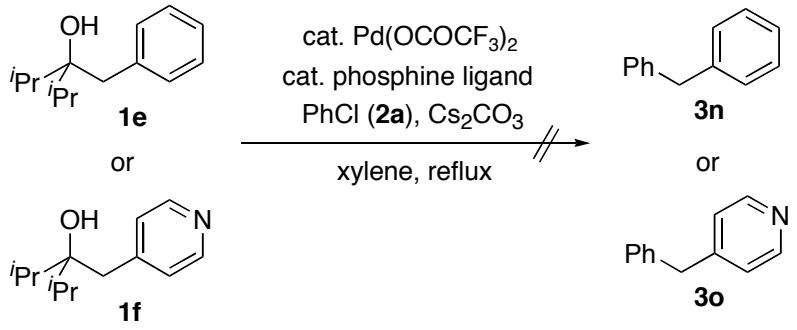
Scheme 3.



Notably, a number of attempts for benzyl group transfer reactions with **1e** and related

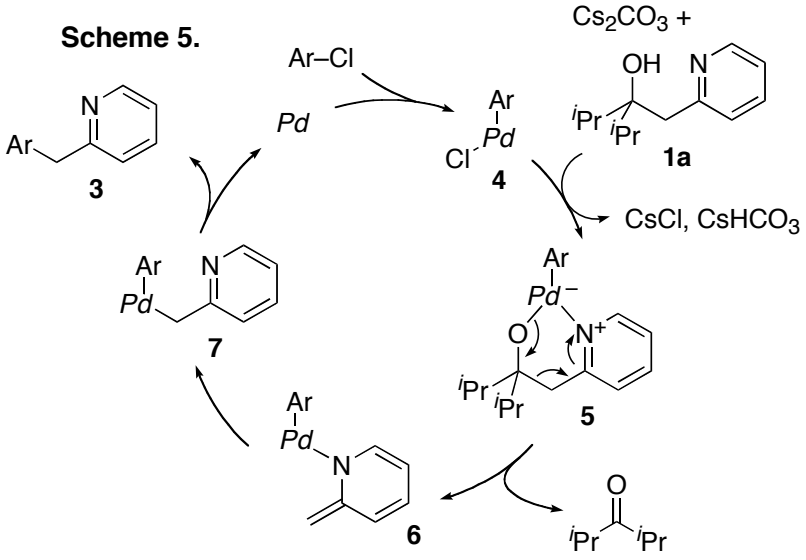
2-phenylethanols resulted in recovery of the starting alcohols (Scheme 4). Furthermore, alcohol **1f**, the 4-pyridyl analogue of **1a**, also resisted bond cleavage. These results clearly suggest that the coordination of the basic nitrogen atom is essential for the success of the transfer reactions, and that the hydroxy group by itself is not sufficient to induce cleavage of the sp^3C–sp^3C bond.[6]

Scheme 4.



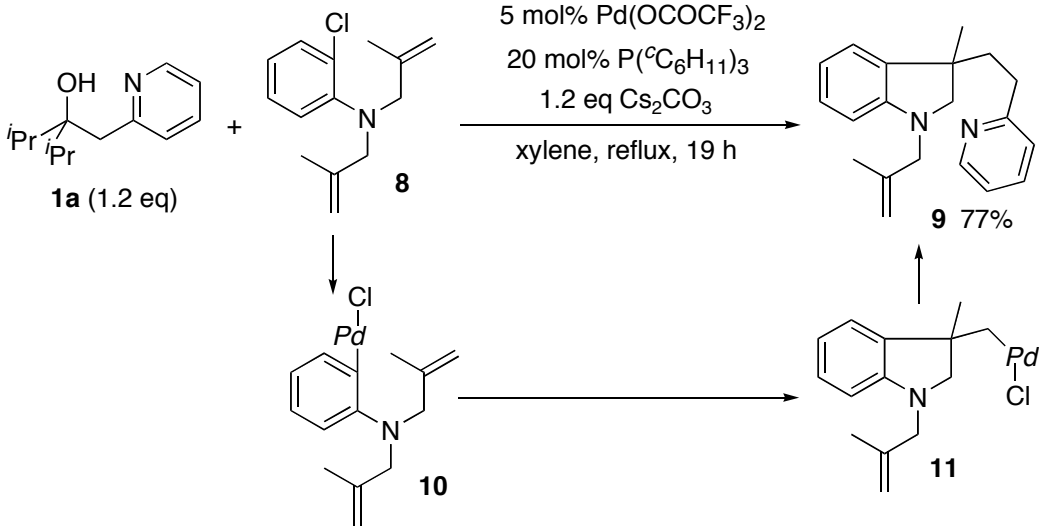
The author tentatively postulates that the reaction mechanism is as follows (Scheme 5). After the oxidative addition,[7] ligand exchange takes place to afford arylpalladium alkoxide **5** through intramolecular coordination of the basic nitrogen atom to the palladium center. With the aid of the coordination, the intermediate **5** is likely to undergo cleavage of the sp^3C–sp^3C bond to yield palladium amide **6**.[8,9] The amide **6** would immediately isomerize to aryl(2-pyridylmethyl)palladium **7** to recover aromaticity. Reductive elimination then regenerates the initial low-valent palladium species in addition to the product **3**.

Scheme 5.



Following cleavage of the sp^3C–sp^3C bond, formation not only of sp^2C–sp^3C bond but also of sp^3C–sp^3C bond proceeded smoothly. The reaction of **8** with **1a** furnished pyridylethyl-substituted dihydroindole **9** in good yield (Scheme 6). The reaction involves the conversion of the initial oxidative adduct **10** having an sp^2C–Pd bond into a dihydroindolylmethylpalladium intermediate **11** having an sp^3C–Pd bond by intramolecular carbopalladation.

Scheme 6.



Conclusion

Pyridine and related azaarenes are interesting cores of biologically active molecules and functional materials. The author has found a new method to install such azaarenes by taking advantage of chelation-assisted cleavage of an sp^3C–sp^3C bond.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were taken on a Varian Unity INOVA 500 spectrometer and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and xylene were purchased from Wako Pure Chemical Co. and stored over slices of sodium. Triphenylphosphine and cesium carbonate were purchased from Wako Pure Chemical Co. Tricyclohexylphosphine was purchased from Strem. Palladium (II) trifluoroacetate was from Aldrich Chemicals. All reactions were carried out under argon atmosphere. Preparations of pyridyl alcohols **1a**, **1c**, **1d**, and **1f** and pyrazinyl alcohol **1b** are shown below. Alcohol **1e** was prepared by the benzylation of diisopropyl ketone with benzylmagnesium chloride.

Experimental Procedure

Synthesis of Pyridylethanols (1a, 1c, 1d)

Synthesis of 2-pyridylethanol **1a** is representative. Butyllithium (1.6 M in hexane, 13 mL, 20 mmol) was slowly added to a solution of 2-picoline (2.0 mL, 20 mmol) in tetrahydrofuran (20 mL) at –30 °C and the reaction mixture was stirred for 30 min. Diisopropyl ketone (3.4 mL, 24 mmol) was then added, the reaction mixture was stirred for 2 h at ambient temperature. Water (30 mL) was added, and the product was extracted with ethyl acetate (20 mL × 3). The

combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane:ethyl acetate = 3:1) gave the pyridyl alcohol **1a** (3.5 g, 17 mmol) in 85% yield.

Synthesis of 2,4-dimethyl-3-(pyrazinyl)methyl-3-pentanol (1b)

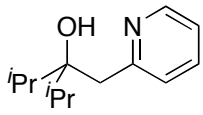
Butyllithium (1.7 M in hexane, 1.8 mL, 3.1 mmol) was slowly added to a solution of diisopropylamine (0.44 mL, 3.2 mmol) in tetrahydrofuran (3.0 mL), and the mixture was stirred for 10 min at 0 °C. After the mixture was cooled to –30 °C, 2-methylpyrazine (0.28 mL, 3.0 mmol) was added and the mixture was stirred for 30 min. Diisopropyl ketone (0.51 mL, 3.6 mmol) was then added, and the reaction mixture was stirred for 2 h at ambient temperature. Water (10 mL) was added, and the product was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane:ethyl acetate = 3:1) gave the pyrazinyl alcohol **1b** (0.40 g, 1.9 mmol) in 64% yield. Alcohol **1f** was prepared in a similar fashion.

Typical Procedure for Palladium-catalyzed 2-Pyridylmethyl Transfer to Aryl Halides

Cesium carbonate (0.32 g, 0.97 mmol) was placed in a 30-mL two-necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was heated with a hair dryer in vacuo for 2 min. The flask was then filled with argon by using the standard Schlenk technique. Palladium (II) trifluoroacetate (13.4 mg, 0.040 mmol), tricyclohexylphosphine (0.50 M in toluene, 0.16 mL, 0.080 mmol), xylene (1.6 mL), pyridyl alcohol **1a** (0.17 g, 0.81 mmol), and chlorobenzene (**2a**, 0.11 g, 0.97 mmol) were sequentially added at room temperature. The resulting mixture was heated at reflux for 6 h. After the mixture was cooled to room temperature, water (10 mL) was added. The product was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane:ethyl acetate = 5:1) gave 2-benzylpyridine (**3a**, 0.12 g, 0.71 mmol) in 88% yield.

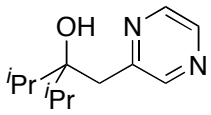
Characterization Data for Compounds

2,4-Dimethyl-3-(2-pyridylmethyl)-3-pentanol (1a)



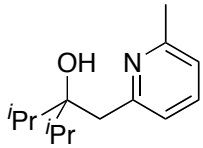
IR (neat) 3328, 2963, 2878, 1596, 1569, 1440, 1029, 1011, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 7.0 Hz, 6H), 0.90 (d, *J* = 7.0 Hz, 6H), 1.92 (sep, *J* = 7.0 Hz, 2H), 2.91 (s, 2H), 6.37 (bs, 1H), 7.11–7.14 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.60 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 8.44 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.3, 35.3, 38.1, 78.2, 121.1, 124.7, 136.9, 147.9, 161.9. Found: C, 75.55; H, 10.03; N, 6.96%. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76%.

2,4-Dimethyl-3-pyrazinylmethyl-3-pentanol (1b)



IR (neat) 3419, 2963, 2880, 1527, 1475, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, *J* = 7.0 Hz, 6H), 0.92 (d, *J* = 7.0 Hz, 6H), 1.94 (sep, *J* = 7.0 Hz, 2H), 2.97 (s, 2H), 4.89 (bs, 1H), 8.44–8.46 (m, 2H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 18.3, 35.3, 36.1, 78.6, 142.5, 142.7, 146.2, 157.3. Found: C, 69.37; H, 9.90; N, 13.40%. Calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45%.

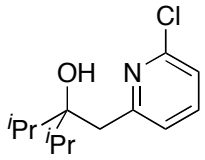
2,4-Dimethyl-3-[2-(6-methyl)pyridyl]methyl-3-pentanol (1c)



IR (neat) 3329, 1962, 1579, 1460, 1033, 1010, 792 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 7.0 Hz, 6H), 0.91 (d, *J* = 7.0 Hz, 6H), 1.91 (sep, *J* = 7.0 Hz, 2H), 2.50 (s, 3H), 2.86 (s, 2H), 6.83 (bs, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 7.48 (dd, *J* = 7.5, 7.5 Hz, 1H); ^{13}C NMR

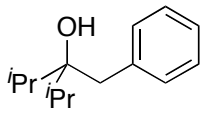
($CDCl_3$) δ 18.2, 18.4, 24.4, 35.3, 38.1, 78.2, 120.7, 121.5, 137.2, 156.9, 161.2.

3-[2-(6-Chloro)pyridyl]methyl-2,4-dimethyl-3-pentanol (1d)



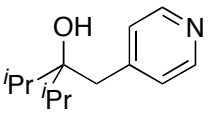
IR (neat) 3418, 2963, 1586, 1559, 1440, 1167, 1137, 1030, 1010, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 7.0 Hz, 6H), 0.92 (d, *J* = 7.0 Hz, 6H), 1.92 (sep, *J* = 7.0 Hz, 2H), 2.91 (s, 2H), 5.10 (s, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 18.3, 35.3, 38.8, 78.3, 121.8, 123.2, 139.3, 150.1, 162.6. Found: C, 64.59; H, 8.34; N, 5.93%. Calcd for $C_{13}H_{20}ClNO$: C, 64.74; H, 8.34; N, 5.79%.

3-Benzyl-2,4-dimethyl-3-pentanol (1e)[10]



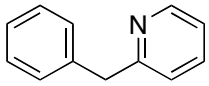
IR (neat) 3502, 2963, 1603, 1496, 1453, 1001, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 6H), 1.01 (s, 6H), 1.16 (bs, 1H), 1.93 (sep, *J* = 7.0 Hz, 2H), 2.84 (s, 2H), 7.20–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.4, 34.6, 39.2, 77.5, 126.3, 128.3, 131.1, 138.5. Found: C, 81.41; H, 11.01%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.50%.

2,4-Dimethyl-3-(4-pyridylmethyl)-3-pentanol (1f)



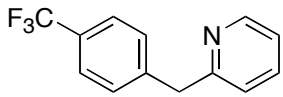
IR (neat) 3336, 2971, 1602, 1456, 1378, 1313, 1025, 997 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, *J* = 7.0 Hz, 6H), 0.99 (d, *J* = 7.0 Hz, 6H), 1.93 (sep, *J* = 7.0 Hz, 2H), 2.82 (s, 2H), 7.26 (d, *J* = 6.0 Hz, 2H), 8.47 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.2, 34.8, 39.0, 78.0, 126.5, 148.3, 149.5.

2-Benzylpyridine (3a)[11]



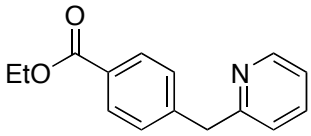
^{1}H NMR ($CDCl_3$) δ 4.15 (s, 2H), 7.08 (dd, *J* = 5.0, 5.0 Hz, 2H), 7.19–7.22 (m, 1H), 7.24–7.30 (m, 4H), 7.54 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 8.53 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.8, 121.3, 123.2, 126.5, 128.7, 129.2, 136.6, 139.5, 149.4, 161.0.

2-[(4-Trifluoromethylphenyl)methyl]pyridine (3b)



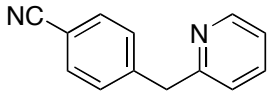
IR (neat) 1619, 1590, 1570, 1436, 1419, 1326, 1165, 1109, 1068, 1019, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.20 (s, 2H), 7.12–7.15 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.60 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H), 8.55–8.58 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 44.5, 121.8, 123.3, 124.5 (q, $J_{C–F}$ = 257 Hz), 125.6 (q, $J_{C–F}$ = 3 Hz), 129.0 (q, $J_{C–F}$ = 20 Hz), 129.5, 136.9, 143.7, 149.7, 160.0. Found: C, 65.63; H, 4.37; N, 6.02%. Calcd for $C_{13}H_{10}F_3N$: C, 65.82; H, 4.25; N, 5.90%.

Ethyl 4-(2-pyridyl)methylbenzoate (3c)



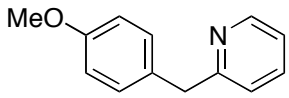
IR (neat) 2982, 1717, 1278, 1102, 1022, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, *J* = 7.0 Hz, 3H), 4.21 (s, 2H), 4.35 (q, *J* = 7.0 Hz, 2H), 7.10–7.15 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.59 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 7.99 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 2H), 8.55 (dd, *J* = 4.5, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 44.7, 60.9, 121.6, 123.3, 128.7, 129.1, 129.9, 136.8, 144.8, 149.6, 160.1, 166.6. Found: C, 74.52; H, 6.37; N, 5.82%. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81%.

4-(2-Pyridyl)methylbenzonitrile (3d)



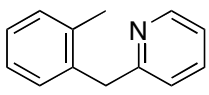
IR (neat) 3052, 2228, 1609, 1588, 1473, 1436, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.20 (s, 2H), 7.14–7.18 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.63 (ddd, *J* = 9.5, 9.5, 2.0 Hz, 1H), 8.56 (ddd, *J* = 5.0, 1.0, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.6, 110.3, 119.0, 121.9, 123.4, 129.9, 132.4, 137.0, 145.1, 149.7, 159.2. Found: C, 80.59; H, 5.39; N, 14.29%. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42%.

2-[(4-Methoxyphenyl)methyl]pyridine (3e)



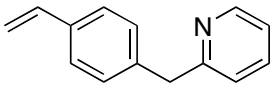
IR (neat) 2932, 2835, 1611, 1589, 1511, 1436, 1248, 1178, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 4.10 (s, 2H), 6.84–6.86 (m, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.08–7.11 (m, 1H), 7.17–7.19 (m, 2H), 7.56 (ddd, *J* = 7.5, 2.0, 2.0 Hz, 1H), 8.53–8.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 43.9, 55.4, 114.1, 121.3, 123.1, 130.2, 131.7, 136.7, 149.4, 158.3, 161.5. Found: C, 78.53; H, 6.77; N, 6.76%. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03%.

2-[(2-Methylphenyl)methyl]pyridine (3f)



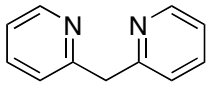
IR (neat) 3011, 2921, 1591, 1568, 1473, 1433, 1049, 994, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 4.18 (s, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.10 (ddd, *J* = 8.0, 4.5, 0.5 Hz, 1H), 7.17–7.18 (m, 4H), 7.54 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H), 8.55–8.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 42.6, 121.3, 122.9, 126.3, 127.0, 130.4, 130.6, 136.7, 137.0, 137.7, 149.4, 160.8. Found: C, 85.12; H, 7.28; N, 7.48%. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64%.

2-[(4-Ethenylphenyl)methyl]pyridine (3g)



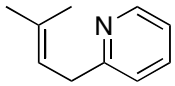
IR (neat) 3084, 3007, 2923, 1588, 1511, 1473, 1435, 994, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (s, 2H), 5.20 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.71 (dd, *J* = 17.5, 1.0 Hz, 1H), 6.69 (dd, *J* = 17.5, 11.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.57 (ddd, *J* = 8.5, 8.5, 2.0 Hz, 1H), 8.54–8.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 44.6, 113.5, 121.4, 123.2, 126.6, 129.4, 135.9, 136.7, 136.7, 139.3, 149.5, 161.0. Found: C, 86.11; H, 6.70; N, 7.00%. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17%.

2-(2-Pyridylmethyl)pyridine (3h)[12]



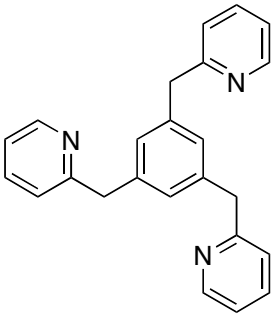
^1H NMR ($CDCl_3$) δ 4.35 (s, 2H), 7.14 (dd, *J* = 8.0, 5.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.62 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H), 8.55–8.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 47.3, 121.7, 123.8, 136.8, 149.5, 159.5.

2-(3-Methyl-2-butenyl)pyridine (3i)



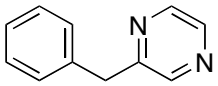
IR (neat) 2969, 2915, 1589, 1569, 1474, 1435, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.77 (s, 3H), 3.54 (d, *J* = 7.5 Hz, 2H), 5.41–5.44 (m, 1H), 7.09 (dd, *J* = 4.5, 2.0 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.59 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H), 8.51–8.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 26.0, 37.3, 121.1, 121.4, 122.6, 133.9, 136.6, 149.4, 161.7. Found: C, 81.62; H, 9.20%. Calcd for $C_{10}H_{13}N$: C, 81.59; H, 8.90%.

1,3,5-Tri[(2-pyridyl)methyl]benzene (3j)



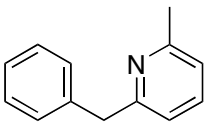
IR (neat) 3008, 2923, 1590, 1569, 1475, 1435, 1050, 995, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (s, 6H), 7.03 (s, 3H), 7.09–7.11 (m, 6H), 7.55 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 3H), 8.52 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 44.7, 121.4, 123.4, 128.2, 136.7, 140.1, 149.4, 161.0. HRMS (DI-EI$^+$) (*m*/*z*) Observed: 351.1743 (Δ = +2.1 ppm). Calcd for $C_{24}H_{21}N_3$ [M^+]: 351.1735.

Benzylpyrazine (3k)



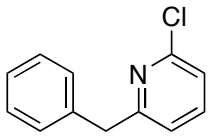
IR (neat) 3030, 1496, 1403, 1057, 1018, 748, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.18 (s, 2H), 7.23–7.34 (m, 5H), 8.41 (d, *J* = 2.5 Hz, 1H), 8.47 (s, 1H), 8.50–8.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 42.2, 127.0, 129.0, 129.2, 138.3, 142.6, 144.3, 145.0, 156.7. Found: C, 77.65; H, 5.95; N, 16.21%. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46%.

2-Benzyl-6-methylpyridine (3l)



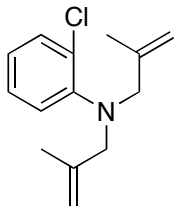
IR (neat) 3026, 2924, 1591, 1577, 1452, 1031, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3H), 4.14 (s, 2H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 7.20–7.23 (m, 1H), 7.25–7.32 (m, 4H), 7.45 (dd, *J* = 7.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7, 44.9, 120.1, 120.9, 126.5, 128.7, 129.4, 136.9, 139.8, 158.0, 160.5.

2-Benzyl-6-chloropyridine (3m)



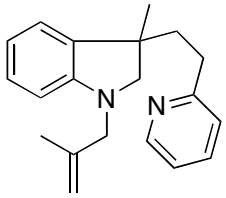
IR (neat) 1583, 1437, 1134, 780, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (s, 2H), 6.98 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.16 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.23–7.27 (m, 3H), 7.30–7.33 (m, 2H), 7.52 (dd, *J* = 7.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.4, 109.9, 121.6, 121.9, 126.8, 128.8, 129.4, 138.8, 139.2, 162.3.

2-Chloro-*N*,*N*-di(2-methyl-2-propenyl)aniline (8)



IR (neat) 3073, 2971, 2821, 1652, 1588, 1480, 1442, 1120, 1040, 898, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 6H), 3.57 (s, 4H), 4.84 (s, 2H), 4.93 (s, 2H), 6.93 (ddd, *J* = 7.5, 1.5 Hz, 1H), 7.07 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.15 (ddd, *J* = 7.5, 1.5 Hz, 1H), 7.35 (ddd, *J* = 7.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 58.8, 113.3, 123.5, 123.7, 126.9, 130.0, 130.8, 142.9, 148.1. Found: C, 71.21; H, 7.64; N, 5.98%. Calcd for $C_{14}H_{18}ClN$: C, 71.32; H, 7.70; N, 5.94%.

3-Methyl-1-(2-methyl-2-propenyl)-3-[2-(2-pyridyl)ethyl]-2,3-dihydroindole (9)



IR (neat) 2919, 2818, 1606, 1590, 1489, 1436, 1023, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.78 (s, 3H), 1.98 (dt, *J* = 12.5, 5.0 Hz, 1H), 2.07 (dt, *J* = 12.5, 5.0 Hz, 1H), 2.66 (dt, *J* = 12.5, 5.0 Hz, 1H), 2.85 (dt, *J* = 12.5, 5.0 Hz, 1H), 3.08 (d, *J* = 9.0 Hz, 1H), 3.34 (d, *J* = 9.0 Hz, 1H), 3.54 (d, *J* = 15.0 Hz, 1H), 3.64 (d, *J* = 15.0 Hz, 1H), 4.88 (s, 1H), 4.96 (s, 1H), 6.48 (d, *J* = 8.0 Hz,

1H), 6.67 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.03–7.08 (m, 4H), 7.55 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 8.50 (dd, *J* = 5.5, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 26.3, 34.1, 41.1, 43.7, 55.6, 65.7, 106.9, 112.2, 117.5, 121.1, 122.6, 122.9, 127.8, 136.5, 137.1, 142.4, 149.4, 151.9, 162.5. Found: C, 82.19; H, 8.42; N, 9.69%. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58%.

References and Notes

(1) For reviews: (a) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*, S. Murai, Ed.; Springer: Berlin, 1999; pp. 97–129. (b) Bishop III, K. C. *Chem. Rev.* **1976**, *76*, 461–486. (c) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245–269. (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870–883. (e) Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, *34*, 1462–1467. (f) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610–618. (g) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201–216. (h) Catellani, M. *Synlett* **2003**, 298–313. (i) Jennings, P. W.; Johnson, L. L.; *Chem. Rev.* **1994**, *94*, 2241–2290.

(2) (a) Kaneda, K.; Azuma, H.; Wayaku, M.; Teranishi, S. *Chem. Lett.* **1974**, 215–216. (b) Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054–3056. (c) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880–881. (d) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 8645–8646.

(3) (a) Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem.* **1997**, *109*, 2449–2451; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2352–2354. (b) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658–8659.

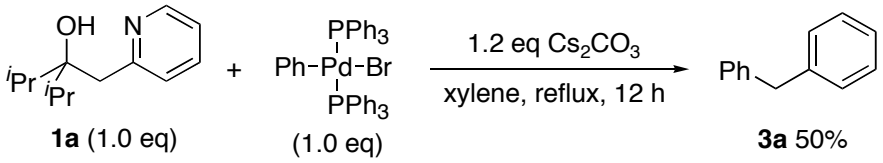
(4) Heitz, W.; Brugging, W.; Freund, L.; Gailberger, M.; Greiner, A.; Jung, H.; Kampschulte, U.; Niessner, N.; Osan, F.; Schmidt, H. W.; Wicker, M. *Makromol. Chem.* **1988**, *189*, 119–127.

(5) A pyridyl alcohol, C(OH)(^{i}Pr)$_2$CHMe(2-pyridyl) did undergo similar carbon–carbon bond cleavage, but unfortunately the author only obtained vinylpyridine and other byproducts.

(6) Examples of catalytic sp^3C–sp^3C bond cleavage with the aid of coordination of a single oxygen atom: (a) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587–5588. (b) Shukla, P.; Cheng, C. H. *Org. Lett.* **2006**, *8*, 2867–2869. (c) Hayashi, S.; Hirano, K. ; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211. (d) Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 2515–2517. (e) Yanagisawa, A.; Aoki, T.; Arai, T. *Synlett*

2006, 2071–2074.

(7) The author prepared a palladium complex, $PdBr(Ph)(PPh_3)_2$, and performed the stoichiometric reaction of the arylpalladium complex with **1a** in the presence of 1.2 equimolar amounts of cesium carbonate in boiling xylene for 12 h. The reaction afforded **3a** in 50% yield.



(8) X-ray structures of similar metal amides were reported: (a) Pieper, U.; Stalke, D. *Organometallics* **1993**, *12*, 1201–1206. (b) Leung, W.-P.; Lee, H. K.; Weng, L.-H.; Luo, B.-S. Zhou, Z.-Y.; Mak, T. C. W. *Organometallics* **1996**, *15*, 1785–1792. (c) Andrews, P. C.; Armstrong, D. R.; Raston, C. L.; Roberts, B. A.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **2001**, 996–1006. (d) Thomas, D.; Baumann, W.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *Organometallics* **1998**, *17*, 2096–2102.

(9) Alternatively, a β-carbon elimination process would produce **7**: (a) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407–10408. (b) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910–1913. (c) Ooi, T.; Miura, T.; Maruoka, K. *J. Am. Chem. Soc.* **1998**, *120*, 10790–10791. (d) Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* **2003**, *5*, 2997–2999.

(10) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

(11) Flaherty, A.; Trunkfield, A.; Barton, W. *Org. Lett.* **2005**, *7*, 4975–4978.

(12) Dyker, G.; Muth, O. *Eur. J. Org. Chem.* **2004**, 4319–4322.

Chapter 2

Palladium-Catalyzed Direct Arylation of Aryl(azaaryl)methanes with Aryl Halides Providing Triarylmethanes

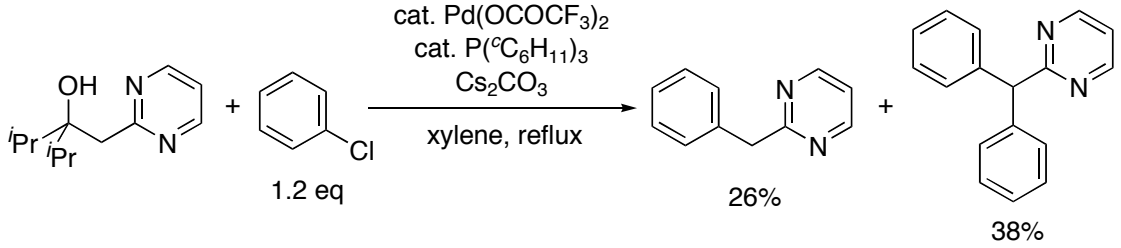
Direct arylation of aryl(azaaryl)methanes with aryl halides takes place at the benzylic position in the presence of a hydroxide base under palladium catalysis to yield triarylmethanes.

Introduction

Transition-metal-catalyzed cross-coupling reactions are among the most important reactions in organic synthesis.[1] The conventional cross-coupling procedure requires preparation of organometallic reagents in advance of the reaction. Recent progress in this area has allowed for direct use of organic compounds bearing no metallic atoms as nucleophilic coupling partners. Among them, direct conversion of sp^2C–H bonds into sp^2C–sp^2C bonds of biaryls is widely investigated.[2–5] On the other hand, examples of direct arylation of sp^3C–H bonds are relatively less pronounced.[6–14]

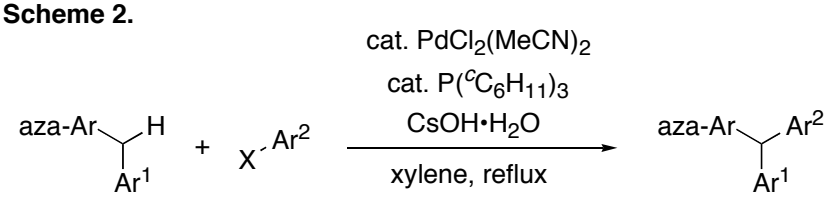
During the course of the author's studies on palladium-catalyzed 2-pyridylmethylation of aryl halides (Chapter 1), he serendipitously found triarylmethane as a by-product, which means the direct arylation at the benzylic sp^3-hybridized bond occurred (Scheme 1).

Scheme 1.



In Chapter 2, the author reports a new repertoire of direct arylation of sp^3C–H bonds, direct arylation of aryl(azaaryl)methanes providing triarylmethanes under palladium catalysis in the presence of cesium hydroxide as a base (Scheme 2).

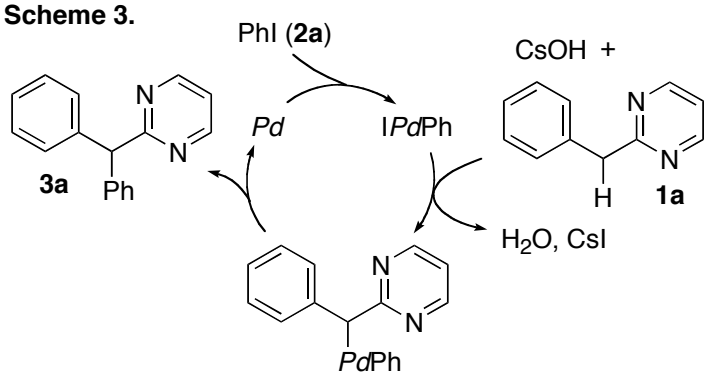
Scheme 2.



Results and Discussion

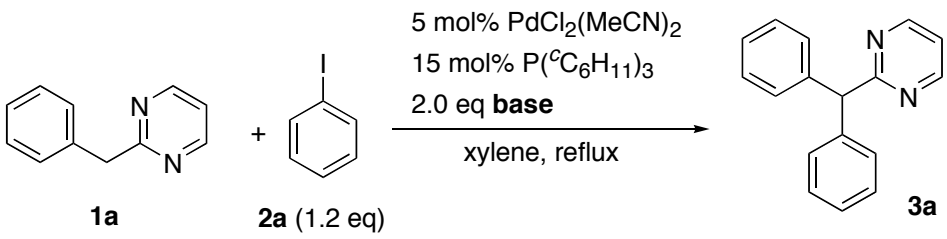
The author focused on aryl(azaaryl)methanes as substrates to achieve this project. On the basis of the structural similarity between imines and azaarenes as well as the fact that direct α-arylation of carbonyl compounds proceeds efficiently,[6] it would be feasible that aryl(azaaryl)methanes undergo direct arylation at the benzylic position. This was indeed the case, and treatment of iodobenzene (**2a**) with 2-benzylpyrimidine (**1a**) in the presence of cesium hydroxide under $PdCl_2$/tricyclohexylphosphine ($P(^cC_6H_{11})_3$) catalysis in refluxing xylene provided 2-(diphenylmethyl)pyrimidine (**3a**) in high yield (Table 1, entry 1). A plausible reaction mechanism includes oxidative addition, deprotonation of **1a** with cesium hydroxide, transmetalation of phenyl(2-pyrimidyl)methylcesium with an arylpalladium iodide (or hydroxide) intermediate, and reductive elimination (Scheme 3).

Scheme 3.



2-Benzylpyrimidine (**1a**) was chosen as a model reactant, and the effect of bases was examined (Table 1). A number of bases were screened, and cesium and potassium hydroxide proved to be outstandingly effective for the direct phenylation reaction (entries 1 and 2). The use of sodium hydroxide showed moderate efficiency (entry 3), while cesium carbonate showed almost no activity (entry 4). Interestingly, treatment of substrates with 1.2 eq of cesium hydroxide gave the product **3a** in 18% yield (entry 5). Hence, more than 2 eq of base is needed for the reaction.

Table 1. Optimization of Pd-Catalyzed Phenylation of 2-Benzylpyrimidine (**1a**) by Using Various Bases[a]



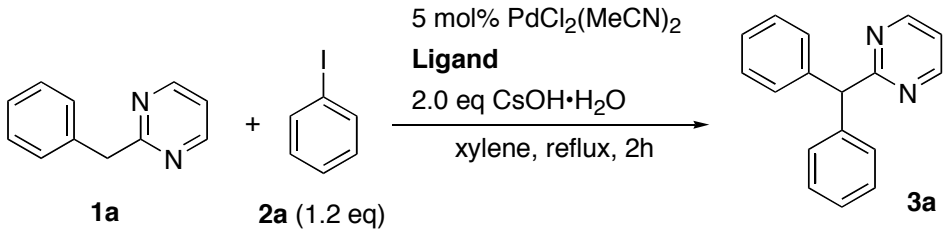
1a **2a** (1.2 eq) **3a**

entry	base	time (h)	**3a** (%)[b]	**1a** (%)[b]
1	$CsOH•H_2O$	2	87	<1
2	KOH	3	76	<1
3	NaOH	6	65	22
4	Cs_2CO_3	3	6	84
5	$CsOH•H_2O$[c]	11	18	54

[a] A mixture of **1a** (0.50 mmol), iodobenzene (**2a**, 0.60 mmol), $PdCl_2(MeCN)_2$ (0.025 mmol), $P(^cC_6H_{11})_3$ (0.075 mmol), and base (1.0 mmol) was boiled in xylene (1.0 mL).
[b] ^1H NMR yields. [c] 1.2 eq of base was used.

With cesium hydroxide as the optimal base, he screened various ligands (Table 2). PMe_3, P^tBu_3, and P(*o*-tol)$_3$ showed no activity (entry 4) or only slight activity (entries 2 and 5) while PPh_3 led to the formation of desired product in moderate yield (entry 3). Bidentate phosphine ligands such as DPPE, DPPP, and DPPF had similar activities (entries 6–8). $P(^cC_6H_{11})_3$ and *rac*-BINAP showed high efficiency compared to other ligands (entries 1 and 9).

Table 2. Optimization of Pd-Catalyzed Phenylation of 2-Benzylpyrimidine (**1a**) by Using Various Ligands[a]



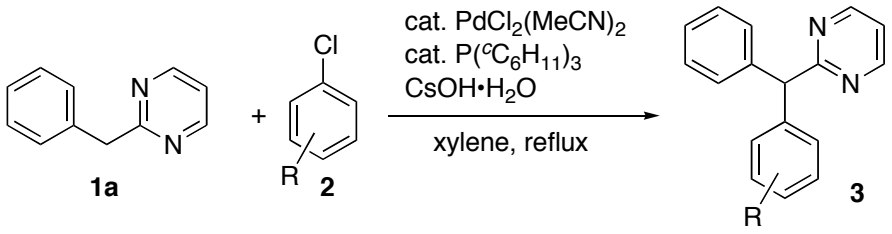
entry	Ligand	**3a** (%)[b]	**1a** (%)[b]
1	15 mol% P(^{c}C$_6$H$_{11}$)$_3$	87	<1
2	15 mol% P^{t}Bu$_3$	5	84
3	15 mol% PPh$_3$	41	39
4	15 mol% PMe$_3$	<1	91
5	15 mol% P(*o*-tol)$_3$	2	62
6	7.5 mol% DPPE	63	25
7	7.5 mol% DPPP	43	40
8	7.5 mol% DPPF	35	49
9	7.5 mol% *rac*-BINAP	86	4

[a] A mixture of **1a** (0.50 mmol), iodobenzene (0.60 mmol), $PdCl_2(MeCN)_2$ (0.025 mmol), ligand, and cesium hydroxide (1.0 mmol) was boiled in xylene (1.0 mL).
[b] ^{1}H NMR yields.

With the optimal reaction conditions in hand, he surveyed the scope and limitation of the reaction (Table 3). Bromobenzene (**2b**) and chlorobenzene (**2c**) reacted smoothly (entries 1 and 2). Aryl chloride **2e** having a methyl group at the 2-position participated in the reaction similarly (entry 4). Electron-rich 4-chloroanisole (**2f**) reacted with the aid of P(^{c}C$_6$H$_{11}$)$_3$ to yield the corresponding triarylmethane in excellent yield (entry 5). The reaction of 4-chloro-*N*,*N*-dimethylaniline (**2g**) required prolonged reaction time and an excess of the base to proceed to completion (entry 6). The reaction of 4-chlorostyrene (**2h**) provided the desired

product **3h** (entry 7), although **2h** can alternatively undergo self-contained Mizoroki-Heck reactions which lead to oligo(4-phenylenevinylene).[15] Unfortunately, attempted reactions of electron-deficient **2i** resulted in incomplete conversion. The highest yield was obtained when di(*tert*-butyl)(2-biphenylyl)phosphine was used as a ligand (entry 8). The reaction of **2i** would proceed via [4-(*tert*-butoxycarbonyl)phenyl][phenyl(pyrimidyl)methyl]palladium, which would suffer from slow reductive elimination because of the electron-withdrawing nature of the carbonyl group. In addition, cleavage of the ester bond was observed.

Table 3. Pd-Catalyzed Arylation of 2-Benzylpyrimidine (**1a**)[a]



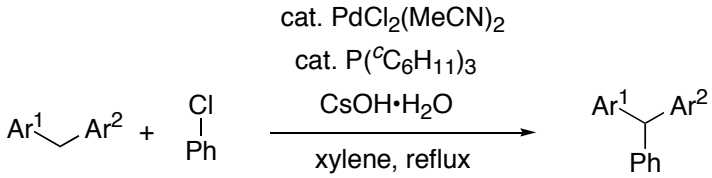
entry	R	2	time (h)	3	yield (%)
1	bromobenzene	**2b**	2	**3a**	94
2	H	**2c**	3	**3a**	86
3	(1-Naphthyl)	**2d**	2	**3d**	96
4	2-Me	**2e**	2	**3e**	94
5	4-OMe	**2f**	8	**3f**	86
6	4-NMe_2	**2g**	18	**3g**	63[b]
7	4-$CH{=}CH_2$	**2h**	5	**3h**	62
8	4-$CO_2{}^t$Bu	**2i**	24	**3i**	29[c]

[a] A mixture of **1a** (0.50 mmol), **2** (0.60 mmol), $PdCl_2(MeCN)_2$ (0.025 mmol), $P(^cC_6H_{11})_3$ (0.075 mmol), and $CsOH{\bullet}H_2O$ (1.0 mmol) was boiled in xylene (1.0 mL).
[b] $CsOH{\bullet}H_2O$ (1.5 mmol) was used.
[c] Di(*tert*-butyl)(2-biphenylyl)phosphine was used as a ligand. 30% of **1a** was recovered. *tert*-Butyl benzoate (4%) and **2i** (6%) were detected. The yields are based on ^{1}H NMR.

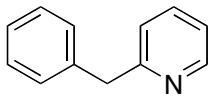
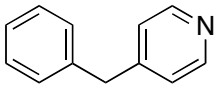
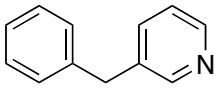
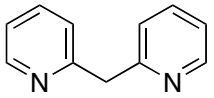
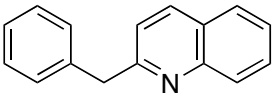
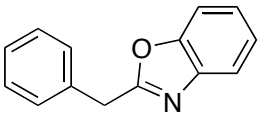
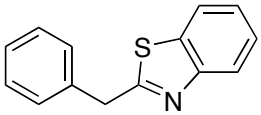
Other aryl(azaaryl)methanes were subjected to the arylation reaction (Table 4). The

reaction of 2- or 4-benzylpyridine proceeded smoothly (entries 1 and 2). It is worth noting that the author could obtain tetraarylmethane, triphenyl(4-pyridyl)methane, in 8% yield in the reaction of **1c**. Further optimization of the reaction conditions will allow us to prepare tetraarylmethane through a cross-coupling methodology.[16] Unfortunately, 3-benzylpyridine (**1d**) resisted the reaction (entry 3). Di(2-pyridyl)methane (**1e**) and 2-benzylquinoline (**1f**) readily reacted to proceed to completion within 6 h (entries 4 and 5). The reactions of 2-benzylbenzoxazole (**1g**) and -benzothiazole (**1h**) were successful by using KOH[17] as a base, albeit with prolonged reaction times (entries 6 and 7). The reactions of 2-picoline and of diphenylmethane resulted in no conversion. The acidity of the protons to be substituted by an aryl group is probably a decisive factor for the success of the reaction. The pK_a values of the acidic protons of **1b**, **1c**, **1d**, diphenylmethane, and water in DMSO were reported to be 28.2, 26.7, 30.2, 32.2, and 32, respectively.[18] A hydroxide ion would fail to deprotonate **1d** and diphenylmethane under the reaction conditions. An attempted reaction of 4-benzylbenzonitrile resulted in hydrolysis of the nitrile group to yield 4-benzylbenzoic acid (83%).

Table 4. Pd-Catalyzed Phenylation of Aryl(azaaryl)methanes[a]



1 **2a** **4**

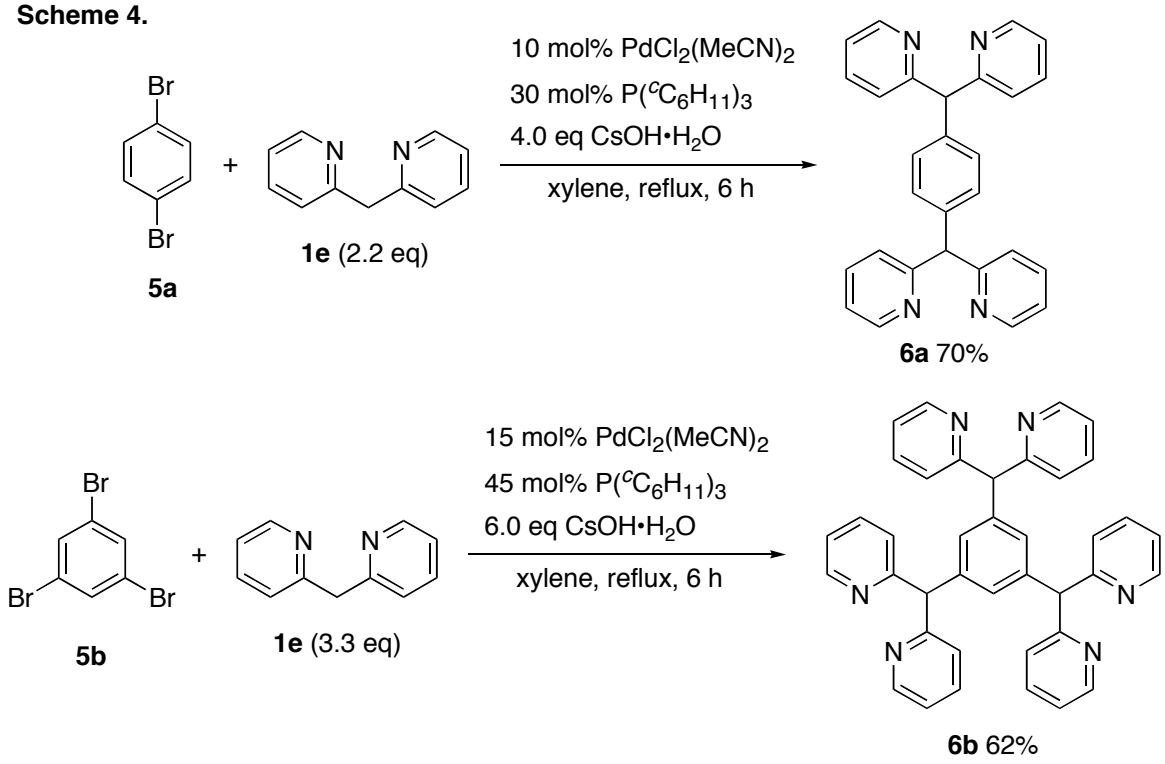
entry	**1**		time (h)	**4**	yield (%)
1		**1b**	18	**4a**	87
2		**1c**	14	**4b**	92[b]
3		**1d**	6	**4c**	<1
4		**1e**	6	**4d**	91
5		**1f**	3	**4e**	91[c]
6		**1g**	19	**4f**	71[c]
7		**1h**	17	**4g**	82[c]

[a] A mixture of **1** (0.50 mmol), chlorobenzene (**2a**, 0.60 mmol), $PdCl_2(MeCN)_2$ (0.025 mmol), $P(^cC_6H_{11})_3$ (0.075 mmol), and $CsOH•H_2O$ (1.0 mmol) was boiled in xylene (1.0 mL).
[b] Triphenyl(4-pyridyl)methane (8%) was obtained.
[c] Iodobenzene and KOH were used instead of chlorobenzene and $CsOH•H_2O$, respectively.

The present method is concise and reliable enough to offer a straightforward route to highly azaarylated structures in one pot. The reactions of 1,4-dibromobenzene (**5a**) and 1,3,5-tribromobenzene (**5b**) with **1e** afforded new multicoordinating molecular structures **6a** and **6b** (Scheme 4). They are potentially useful in constructing supramolecular architecture not only

as they are[19] but also as their anionic forms upon deprotonation of the methyne protons.[20]

Scheme 4.



Conclusion

Azaarenes can find many applications in various fields of chemical science. The author has found a new method to synthesize triarylmethanes[21] having at least one azaaryl group through the palladium-catalyzed direct benzylic arylation of aryl(azaaryl)methanes.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were taken on a Varian Unity INOVA 500 spectrometer and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Xylene was purchased from Wako Pure Chemical Co. and stored over slices of sodium. Di(acetonitrile)dichloropalladium and cesium hydroxide monohydrate were purchased from Aldrich. Tricyclohexylphosphine was purchased from Strem. All reactions were carried out under argon atmosphere. Preparations of aryl(azaaryl)methanes **1** are shown below. **1e**[22] and **1f**[23] were prepared according to the method in the literature.

Experimental Procedure

Synthesis of 2-Benzylpyrimidine (1a)

Benzylmagnesium chloride (0.76 M in THF, 28 mL, 21 mmol) was slowly added to a solution of 2-chloropyrimidine (2.2 g, 19 mmol), nickel acetylacetonate (250 mg, 1.0 mmol), and triphenylphosphine (1.0 g, 4.0 mmol) in THF (40 mL) at 0 °C. The reaction mixture was stirred for 2 h at 20 ˚C. Water (60 mL) was added, and the product was extracted with ethyl acetate (40 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification (hexane:ethyl acetate = 1:1) afforded 2-benzylpyrimidine (**1a**, 2.4 g, 13 mmol) in 70% yield.

Synthesis of 2-Benzylbenzothiazole (1h)

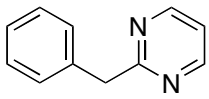
Phenylacetyl chloride (1.3 mL, 12 mmol) was added to a solution of 2-aminothiophenol (1.1 mL, 10 mmol) and magnesium sulfate (5.0 g) in toluene (20 mL) at 0 °C. The resulting mixture was heated at reflux for 6 h. $NaHCO_3$ aq. was added, and the product was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane:ethyl acetate = 2:1) provided 2-benzylbenzothiazole (**1h**, 2.1 g, 9.3 mmol) in 93% yield. 2-Benzylbenzoxazole (**1g**) was prepared in similar fashion.

Typical Procedure for Palladium-catalyzed Direct Arylation of Aryl(azaaryl)methanes 1

Cesium hydroxide monohydrate (0.17 g, 1.0 mmol) and di(acetonitrile)dichloropalladium (6.5 mg, 0.025 mmol) were placed in a 30-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.5 M in toluene, 0.15 mL, 0.075 mmol), xylene (1.0 mL), 2-benzylpyrimidine (**1a**, 85 mg, 0.50 mmol), and chlorobenzene (**2a**, 68 mg, 0.60 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 3 h. After the mixture was cooled to room temperature, water (10 mL) was added. The product was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Purification on silica gel (hexane:ethyl acetate = 1:1) afforded 2-(diphenylmethyl)pyrimidine (**3a**, 0.11 g, 0.43 mmol) in 86% yield.

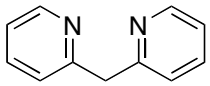
Characterization Data for Compounds

2-Benzylpyrimidine (1a)



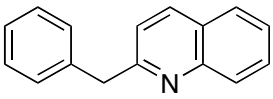
IR (neat) 3032, 1561, 1496, 1419, 746, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.30 (s, 2H), 7.12 (dd, *J* = 5.0, 5.0 Hz, 1H), 7.21–7.24 (m, 1H), 7.29–7.32 (m, 2H), 7.36–7.37 (m, 2H), 8.68 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 46.2, 118.8, 126.8, 128.7, 129.3, 138.3, 157.5, 170.2. Found: C, 77.87; H, 6.02; N, 16.37%. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46%.

2-(2-Pyridylmethyl)pyridine (1e)[22]



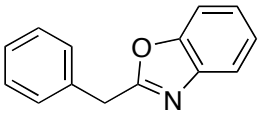
^1H NMR ($CDCl_3$) δ 4.35 (s, 2H), 7.14 (dd, *J* = 8.0, 5.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.62 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H), 8.55–8.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 47.3, 121.7, 123.8, 136.8, 149.5, 159.5.

2-Benzylquinoline (1f)[23]



IR (nujol) 1618, 1598, 1505, 1453, 1425, 747, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.35 (s, 2H), 7.21–7.25 (m, 2H), 7.28–7.32 (m, 4H), 7.49 (ddd, *J* = 7.0, 7.0, 1.0 Hz, 1H), 7.70 (ddd, *J* = 7.0, 7.0, 1.0 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 45.7, 121.7, 126.1, 126.7, 126.9, 127.7, 128.8, 129.2, 129.4, 129.6, 136.7, 139.4, 148.0, 161.4.

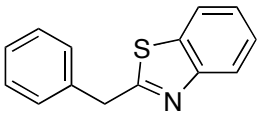
2-Benzylbenzoxazole (1g)



IR (neat) 3032, 1570, 1455, 1242, 1141, 1003, 842, 746, 721, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.27 (s, 2H), 7.25–7.31 (m, 3H), 7.33–7.39 (m, 4H), 7.39–7.47 (m, 1H), 7.67–7.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 35.5, 110.6, 120.0, 124.4, 124.9, 127.5, 129.0, 129.2, 135.0, 141.5, 151.2, 165.4.

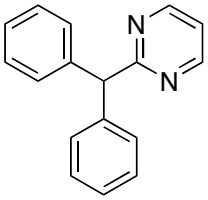
Found: C, 80.38; H, 5.48; N, 6.69%. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69%.

2-Benzylbenzothiazole (1h)[24]



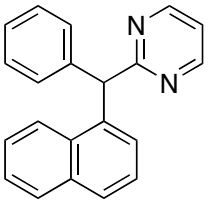
IR (nujol) 1517, 1495, 1454, 1437, 759, 730, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.44 (s, 2H), 7.28–7.38 (m, 6H), 7.45 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.8, 121.7, 123.0, 125.0, 126.1, 127.5, 129.0, 129.3, 135.8, 137.4, 153.4, 171.3.

2-(Diphenylmethyl)pyrimidine (3a)



IR (nujol) 2925, 2855, 1560, 1452, 1415, 1377, 704, 624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (s, 1H), 7.11 (t, *J* = 5.0 Hz, 1H), 7.20–7.24 (m, 2H), 7.28–7.33 (m, 8H), 8.71 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 60.7, 118.9, 126.9, 128.5, 129.3, 141.9, 157.5, 171.9. Found: C, 82.87; H, 6.03; N, 11.33%. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37%. m.p.: 65–68 °C.

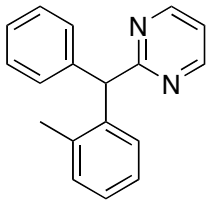
2-[(1-Naphthyl)phenylmethyl]pyrimidine (3d)



IR (nujol) 2925, 1559, 1418, 801, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56 (s, 1H), 7.13 (t, *J* = 5.0 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 7.24–7.27 (m, 1H), 7.29–7.34 (m, 4H), 7.38–7.45 (m, 3H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.84–7.86 (m, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 8.73 (d, *J* = 5.0 Hz, 2H); ^{13}C

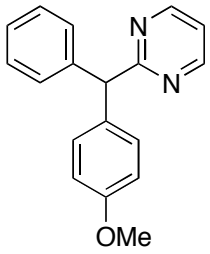
NMR ($CDCl_3$) δ 57.2, 118.8, 124.1, 125.6, 125.6, 126.4, 127.0, 127.2, 127.8, 128.7, 129.0, 129.8, 132.1, 134.2, 138.2, 141.4, 157.6, 172.3. Found: C, 85.03; H, 5.64; N, 9.43%. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45%. m.p.: 124–126 °C.

2-[(2-Methylphenyl)phenylmethyl]pyrimidine (3e)



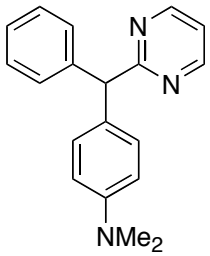
IR (nujol) 2925, 2855, 1559, 1562, 1413, 1378, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 5.98 (s, 1H), 7.06–7.08 (m, 1H), 7.10–7.18 (m, 4H), 7.20–7.24 (m, 3H), 7.28–7.31 (m, 2H), 8.71 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.2, 57.4, 118.7, 126.1, 126.8, 126.9, 128.5, 129.1, 129.6, 130.6, 136.7, 140.3, 141.3, 157.5, 172.0. Found: C, 83.17; H, 6.22; N, 10.72%. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76%. m.p.: 96–98 °C.

2-[(4-Methoxylphenyl)phenylmethyl]pyrimidine (3f)



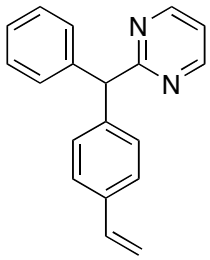
IR (nujol) 3031, 2933, 1562, 1511, 1414, 1250, 1178, 1033, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 5.74 (s, 1H), 6.84–6.86 (m, 2H), 7.14 (dd, *J* = 5.0, 5.0 Hz, 1H), 7.23–7.25 (m, 3H), 7.29–7.30 (m, 4H), 8.73 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.4, 60.0, 114.0, 118.9, 126.8, 128.5, 129.2, 130.4, 134.1, 142.3, 157.5, 158.5, 172.2.

2-[(4-Dimethylaminophenyl)phenylmethyl]pyrimidine (3g)



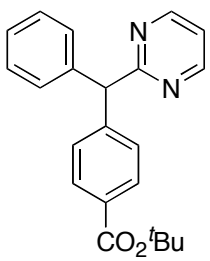
IR (nujol) 2925, 2855, 1561, 1523, 1452, 1417, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.91 (s, 6H), 5.70 (s, 1H), 6.67–6.70 (m, 2H), 7.12 (t, *J* = 4.5 Hz, 1H), 7.19–7.20 (m, 3H), 7.28–7.30 (m, 4H), 8.72 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 40.8, 60.0, 112.8, 118.7, 126.6, 128.4, 129.3, 129.9, 130.0, 142.7, 149.6, 157.4, 172.6. Found: C, 78.74; H, 6.68; N, 14.47%. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52%. m.p.: 124–126 °C.

2-[(4-Ethenylphenyl)phenylmethyl]pyrimidine (3h)



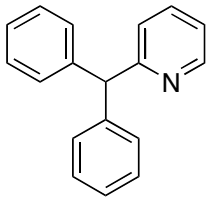
IR (neat) 3032, 1569, 1561, 1510, 1495, 1416, 909, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.70 (dd, *J* = 12.5, 1.0 Hz, 1H), 5.78 (s, 1H), 6.68 (dd, *J* = 12.5, 11.0 Hz, 1H), 7.15 (t, *J* = 5.0 Hz, 1H), 7.21–7.25 (m, 1H), 7.27–7.31 (m, 6H), 7.34–7.36 (m, 2H), 8.74 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 60.5, 113.8, 118.9, 126.4, 126.9, 128.6, 129.3, 129.5, 136.3, 136.7, 141.6, 141.9, 157.5, 171.9. Found: C, 83.91; H, 5.79; N, 10.20%. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29%. m.p.: 68–70 °C.

***tert*-Butyl 4-[phenyl(2-pyrimidyl)methyl]benzoate (3i)**



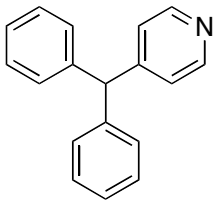
IR (nujol) 1711, 1562, 1413, 1294, 1166, 1121, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 9H), 5.83 (s, 1H), 7.16 (t, *J* = 5.0 Hz, 1H), 7.22–7.32 (m, 5H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 8.73 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.4, 60.7, 81.0, 119.1, 127.1, 128.7, 129.3, 129.3, 129.7, 130.7, 141.4, 146.6, 157.6, 165.8, 171.4.

2-(Diphenylmethyl)pyridine (4a)



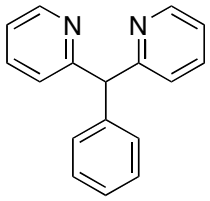
IR (nujol) 2924, 2855, 1585, 1466, 1430, 1377, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.70 (s, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 7.13 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H), 7.16–7.18 (m, 4H), 7.20–7.24 (m, 2H), 7.28–7.31 (m, 4H), 7.60 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H), 8.60 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 59.6, 121.6, 123.9, 126.7, 128.6, 129.5, 136.6, 142.9, 149.8, 163.4. Found: C, 88.21; H, 6.27; N, 5.55%. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71%. m.p.: 68–70 °C.

4-(Diphenylmethyl)pyridine (4b)[25]



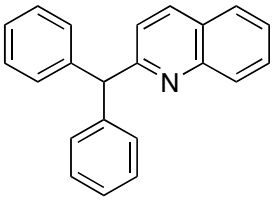
IR (nujol) 2925, 1591, 1448, 1416, 1378, 1031, 700, 607 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.50 (s, 1H), 7.03–7.04 (m, 2H), 7.09–7.11 (m, 4H), 7.23–7.27 (m, 2H), 7.29–7.33 (m, 4H), 8.50–8.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.4, 124.8, 127.0, 128.8, 129.5, 142.3, 150.0, 152.9. Found: C, 88.32; H, 6.40; N, 5.65%. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71%. m.p.: 74–75 °C.

2-[Phenyl(2-pyridyl)methyl]pyridine (4d)



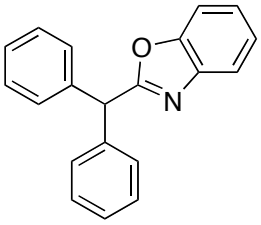
IR (nujol) 2925, 2855, 1586, 1464, 1431 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.82 (s, 1H), 7.13 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 2H), 7.23–7.31 (m, 7H), 7.62 (ddd, *J* = 8.0, 8.0, 3.0 Hz, 2H), 8.59 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 61.9, 121.7, 124.2, 126.9, 128.7, 129.5, 136.6, 141.9, 149.6, 162.3. Found: C, 83.02; H, 5.94; N, 11.30%. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37%. m.p.: 95–97 °C.

2-Diphenylmethylquinoline (4e)



IR (nujol) 2925, 2855, 1494, 1450, 824, 757, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.92 (s, 1H), 7.21–7.25 (m, 6H), 7.28–7.32 (m, 5H), 7.51 (ddd, *J* = 7.0, 7.0, 1.5 Hz, 1H), 7.69 (ddd, *J* = 7.0, 7.0, 1.5 Hz, 1H), 7.78 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 60.3, 122.1, 126.4, 126.7, 127.0, 127.6, 128.5, 128.6, 129.6, 129.6, 136.5, 142.8, 148.1, 163.3. Found: C, 89.22; H, 5.74; N, 4.59%. Calcd for $C_{22}H_{17}N$: C, 89.46; H, 5.80; N, 4.74%. m.p.: 120–122 °C.

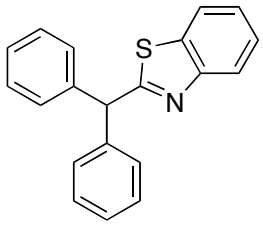
2-(Diphenylmethyl)benzoxazole (4f)[26]



IR (nujol) 1602, 1564, 1496, 1455, 1243, 1141, 1003, 909, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.77 (s, 1H), 7.25–7.35 (m, 12H), 7.45–7.47 (m, 1H), 7.72–7.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 51.7,

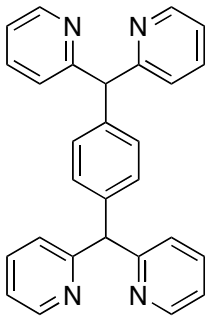
110.8, 120.4, 124.4, 125.0, 127.6, 128.9, 128.9, 139.4, 141.4, 151.1, 166.8.

2-(Diphenylmethyl)benzothiazole (4g)[27]



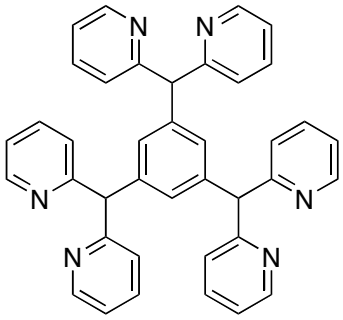
IR (nujol) 3061, 3027, 1599, 1494, 1313, 1140, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 (s, 1H), 7.27–7.37 (m, 11H), 7.46 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0, 121.7, 123.4, 125.1, 126.2, 127.5, 128.9, 129.3, 135.8, 141.5, 153.6, 174.4.

1,4-Bis[di(2-pyridyl)methyl]benzene (6a)



IR (nujol) 2925, 2855, 1587, 1467, 1433 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (s, 2H), 7.12 (dd, *J* = 7.5, 5.0 Hz, 4H), 7.21 (s, 4H), 7.24 (d, *J* = 7.5 Hz, 4H), 7.60 (dd, *J* = 7.5, 7.5 Hz, 4H), 8.56 (d, *J* = 5.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 61.6, 121.7, 124.3, 129.6, 136.6, 140.3, 149.6, 162.3. Found: C, 81.00; H, 5.23; N, 13.26%. Calcd for $C_{28}H_{22}N_4$: C, 81.13; H, 5.35; N, 13.52%.

1,3,5-Tris[di(2-pyridyl)methyl]benzene (6b)



IR (nujol) 2924, 2855, 1585, 1465, 1432 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.70 (s, 3H), 7.01 (s, 3H), 7.07 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 6H), 7.10 (d, *J* = 8.0 Hz, 6H), 7.53 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 6H), 8.47 (d, *J* = 5.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 61.8, 121.6, 124.2, 129.1, 136.5, 142.0, 149.4, 162.2.

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Chapter 3

Palladium-Catalyzed Benzylic Arylation of *N*-Benzylxanthone Imine

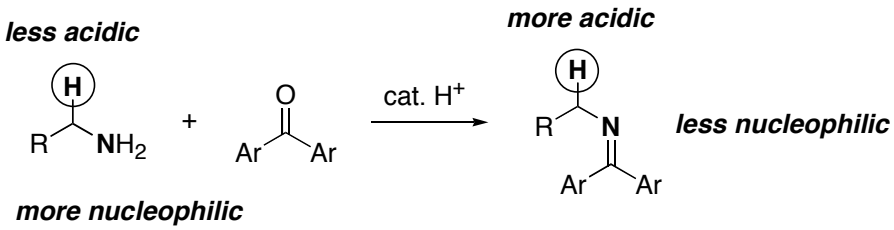
The direct benzylic arylation of *N*-benzylxanthone imine with aryl chloride proceeds under palladium catalysis, yielding the corresponding coupling product. The product is readily transformed to benzhydrylamine. Taking into consideration that the imine is readily available from benzylic amine, the overall transformation represents a formal cross-coupling reaction of aryl halide with α-aminobenzyl metal.

Introduction

Transition-metal-catalyzed direct arylation at sp^3-hybridized carbons having acidic hydrogens has been emerging as one of the recent remarkable advances in cross-coupling reaction.[1–5] In light of the importance of this transformation, further progress should be made.

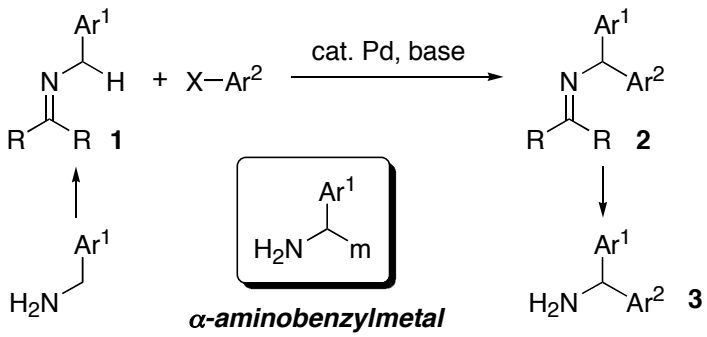
Generally, transition-metal-catalyzed functionalization of an amine at the α-position of an amino group is quite difficult, due to the nucleophilicity of the amino group to deactivate the catalyst and low acidity of the α-protons. On the contrary, the corresponding imine derived from the amines and diarylketones has highly acidic α-protons and less nucleophilicity of the nitrogen atom (Scheme 1).

Scheme 1.



The author thus envisioned a new application of the direct arylation, specifically, intermolecular benzylic arylation of *N*-benzyl imines (Scheme 2). Imine **1**, readily prepared from benzylamine and ketone, has benzylic hydrogens of satisfactory acidity for deprotonation.[6] Palladium-catalyzed arylation of **1** with aryl halide would afford **2**. Hydrolysis of **2** should finally yield **3**. The overall transformation represents a formal cross-coupling reaction of aryl halide with an α-aminobenzyl metal.

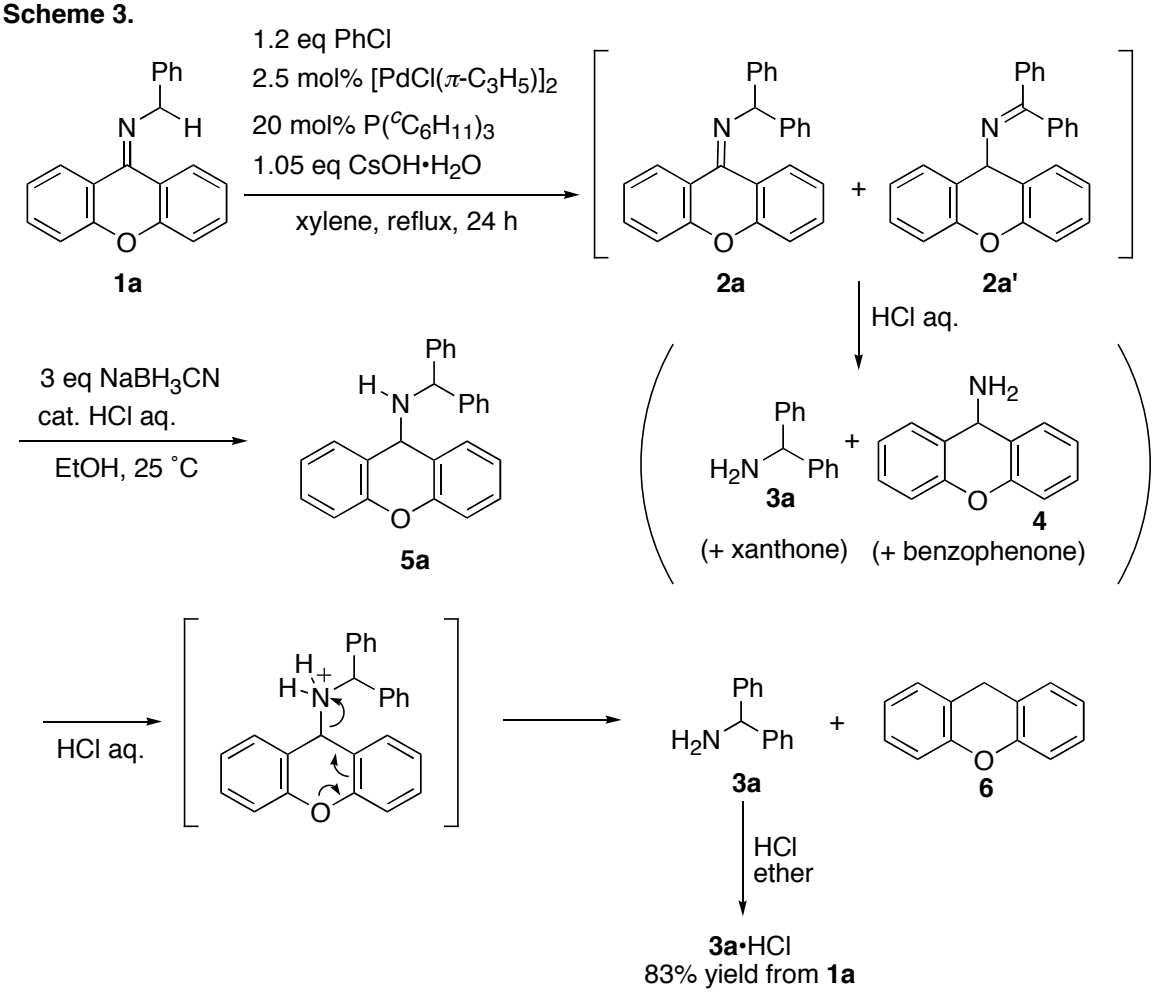
Scheme 2.



Results and Discussion

Treatment of *N*-benzylxanthone imine (**1a**) with chlorobenzene in the presence of cesium hydroxide and a palladium catalyst afforded the corresponding coupling product **2a** and its isomer **2a'** in a ratio of 7:3 (Scheme 3). Facile deprotonation of initially formed **2a** at the benzylic position took place in situ, which led to the formation of a mixture of **2a** and **2a'**. Hydrolysis of the mixture of **2a** and **2a'** afforded a mixture of desired **3a** and undesired amine **4**. Hence, the mixture of imines **2a** and **2a'** was reduced with sodium cyanoborohydride to afford the corresponding amine **5a**. Then hydrolysis of **5a** under acidic conditions provided benzhydrylamine (**3a**) and xanthene (**6**), which was formed through the reduction of xanthenyl cation with the remaining sodium cyanoborohydride in the same pot. No xanthenyl alcohol, which could be generated by the nucleophilic attack of hydroxide to the cation, was observed. Oxygen-bridged xanthone is a suitable precursor of *N*-benzyl imine **1** because the exclusive formation of highly delocalized and thus stable 9-xanthenyl cation allowed the regioselective hydrolysis of **5a**, producing the desired amine **3a**. After acid/base extraction in a separatory funnel, the product **3a** was isolated as its hydrochloride salt **3a**•HCl in 83% overall yield. Notably, each step was high yielding, and no chromatographic purification was needed during the process.

Scheme 3.

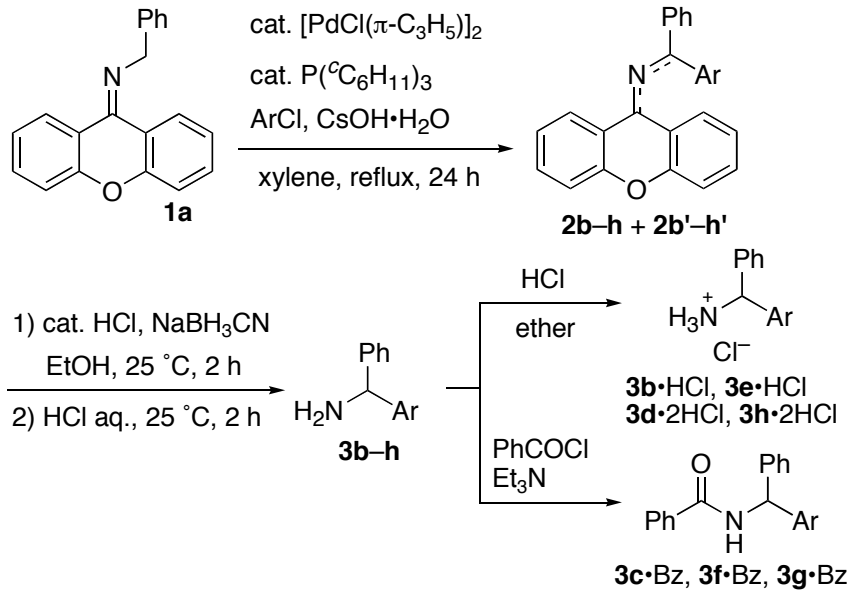


Bromobenzene reacted with **1a** as smoothly as chlorobenzene to yield **3a•**HCl in 80% yield. On the other hand, the use of iodobenzene resulted in the formation of a complex mixture. When other trialkylphosphines, such as PMe_3, $P(^cC_5H_9)_3$, P^nBu_3, and P^tBu_3, were used instead of $P(^cC_6H_{11})_3$, the reaction was sluggish (30–50% combined yields of **2a** and **2a'**) and a mixture of unidentified byproducts was obtained. Use of triarylphosphines in the arylation of **1a** with bromobenzene also led to low combined yields of **2a** and **2a'** (30–50%), along with byproducts and recovered **1a** (10–30%). The 1:4 molar ratio of Pd/$P(^cC_6H_{11})_3$ led to the highest catalytic activity. The combined yield of **2a** and **2a'** was less than 20% when a Pd/$P(^cC_6H_{11})_3$ ratio was 1:3. As the precursor of the catalyst, other palladium complexes, such as $Pd(acac)_2$, $PdCl_2(PhCN)_2$, and $Pd(OAc)_2$, showed comparable yet slightly lower catalytic activity. A temperature as high as 140 °C was essential: a similar reaction in refluxing toluene failed to

afford **2a** and **2a'**. The choice of base is quite important, and the use of KOH, ^{t}BuOK, and Cs_2CO_3 gave only traces of **2a** and **2a'**.

A variety of aryl chlorides participated in the reaction (Table 1). Both electron-rich and electron-deficient aryl chlorides (entries 1–3 and 6) reacted smoothly to yield the corresponding benzhydrylamine derivatives in good yields. 2-Chlorotoluene underwent the reaction similarly, irrespective of the steric hindrance of the 2-methyl group (entry 4). The reaction of 4-chlorostyrene provided the desired product **3f•**Bz in moderate yield (entry 5), although the aryl chloride can alternatively undergo self-contained Mizoroki-Heck reaction, forming oligo(4-phenylenevinylene).[7] Installation of heteroarene at the benzylic position was satisfactory (entry 7). Not only *N*-benzyl imine **1a** but also other *N*-arylmethyl imines **1b–d** were arylated (Scheme 4). However, **1e** having an electron-donating group suffered from very low conversion, probably due to the slower deprotonation.

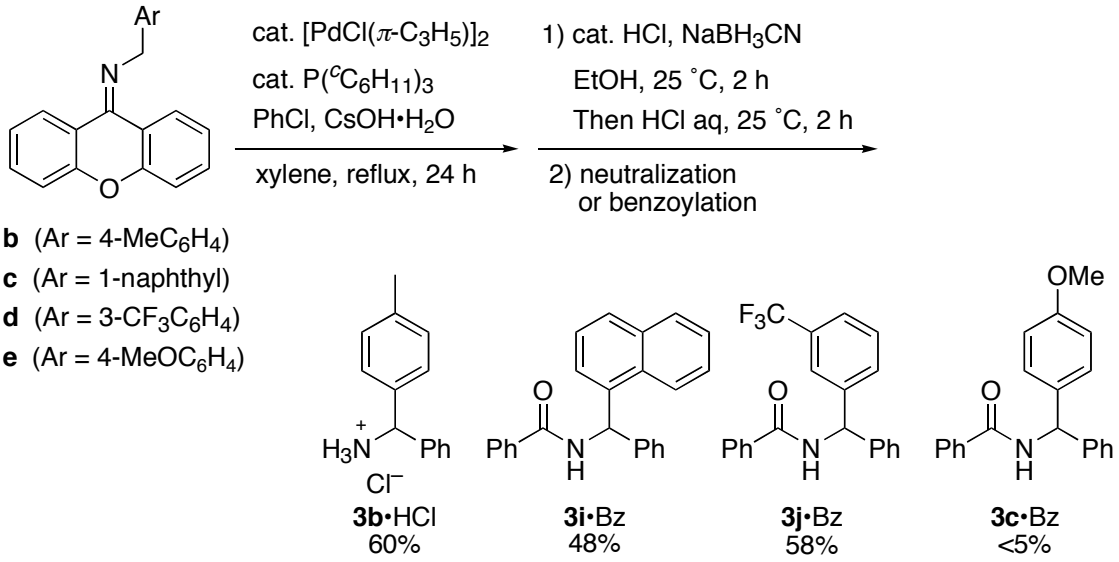
Table 1. Arylation of **1a** and Isolation of Benzhydrylamine Derivatives[a]



entry	ArCl	product	overall yield (%)
1	4-MeC_6H_4Cl	**3b**•HCl	73
2	4-$MeOC_6H_4Cl$	**3c**•Bz[b]	75
3	4-$Me_2NC_6H_4Cl$	**3d**•2HCl	82
4	2-MeC_6H_4Cl	**3e**•HCl	73
5[c]	4-CH_2=CHC_6H_4Cl	**3f**•Bz[b]	47
6	4-$Me_2NC(=O)C_6H_4Cl$	**3g**•Bz[b]	71
7	2-chloropyridine	**3h**•2HCl	80

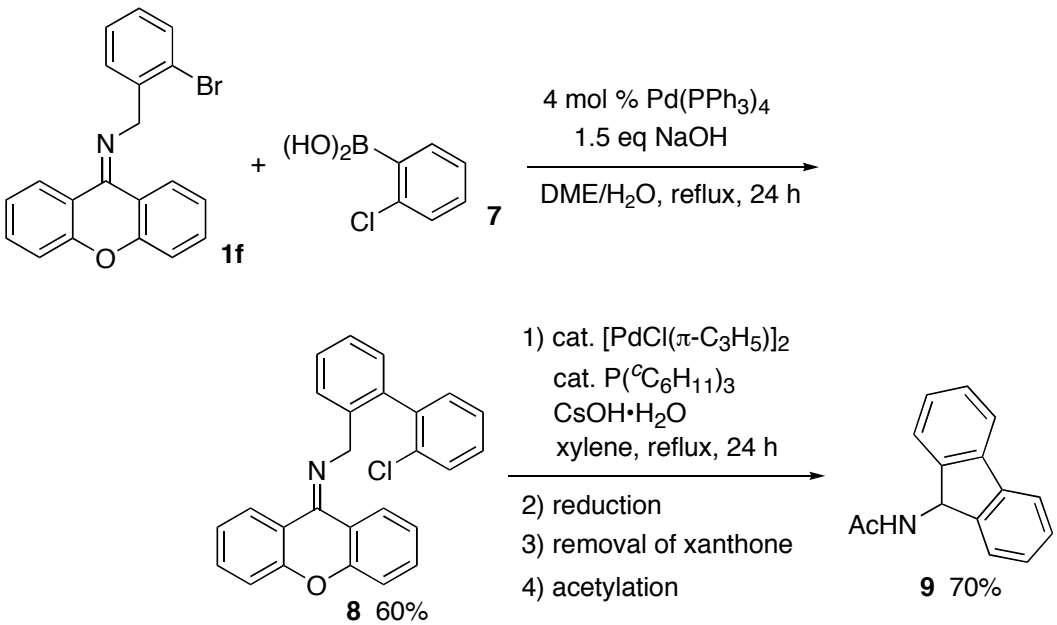
[a] The reaction conditions are the same as shown in Scheme 3.
[b] Instead of treatment with HCl, **3c**, **3f**, and **3g** were benzoylated for chromatographic isolation.
[c] Formic acid was used instead of hydrochloric acid for the removal of the xanthenyl group.

Scheme 4.



The Suzuki-Miyaura cross-coupling reaction of **1f** with arylboronic acid **7** afforded biaryl **8** in high yield (Scheme 5). The intramolecular benzylic arylation of **8** created fluorenylamine skeleton, eventually leading to the formation of **9**. The transformation from **1f** and **7** to **9** thus offers a new route to 9-fluorenylamine derivatives.

Scheme 5.



Conclusion

By converting benzylamine to *N*-benzylxanthone imine, metalation at the benzylic position becomes facile. The present method provides a new concept for transition-metal-catalyzed functionalization of aminated carbons.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were taken on a Varian Unity INOVA 500 spectrometer and were recorded in $CDCl_3$ [using tetramethylsilane (for ^{1}H, δ = 0.00 ppm) and $CDCl_3$ (for ^{13}C, δ = 77.2 ppm) as an internal standard] or DMSO-d_6 [using DMSO (for ^{1}H, δ = 2.50 ppm) and DMSO-d_6 (for ^{13}C, δ = 39.7 ppm) as an internal standard]. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and xylene were purchased from Wako Pure Chemical Co. and stored over slices of sodium. Cesium hydroxide monohydrate was purchased from Nacalai Tesque. Tricyclohexylphosphine was purchased from Strem. Allylpalladium(II) chloride dimer was obtained from Aldrich Chemicals. All reactions were carried out under argon atmosphere. Preparations of xanthone imines (**1a**–**1f**) are shown below.

Experimental Procedure

Synthesis of *N*-Benzylxanthone Imine (**1a**)

A solution of titanium(IV) chloride (4.1 mL, 37.5 mmol) in toluene (50 mL) was slowly added to a solution of xanthone (9.8 g, 50 mmol) and benzylamine (24.6 mL, 225 mmol) in toluene (150 mL) at 0 °C. The resulting mixture was stirred for 30 min at ambient temperature, and then for 6 h at reflux. Diethyl ether (200 mL) was added, and the reaction mixture was passed through a pad of Celite and precipitate was washed with diethyl ether (40 mL × 3). The solvent was removed under reduced pressure. *N*-Benzylxanthone imine (**1a**) was recrystallized

from hexane/toluene as a white solid (13.1 g, 46 mmol) in 92% yield. Imines **1b–1f** were prepared in a similar fashion.

Typical Procedure for Synthesis of Benzhydrylamine Hydrochlorides

Synthesis of benzhydrylamine hydrochloride (**3a•**HCl) is representative. Cesium hydroxide monohydrate (0.18 g, 1.05 mmol) and allylpalladium (II) chloride dimer (9.1 mg, 0.025 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.50 M in toluene, 0.40 mL, 0.20 mmol), xylene (2.0 mL), *N*-benzylxanthone imine (**1a**, 285 mg, 1.0 mmol), and chlorobenzene (0.12 mL, 1.2 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with chloroform (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue included a mixture of imines **2a** and **2a'** (7:3), which was used for the next step without further purification.

A drop of hydrochloric acid (12 M) was added to a solution of the crude mixture of **2a** and **2a'** and sodium cyanoborohydride (189 mg, 3.0 mmol) in ethanol (5 mL). The resulting mixture was stirred at 25 ˚C for 2 h. Hydrochloric acid (12 M, 5 mL) and water (1 mL) were then added, and the resulting mixture was stirred at 25 ˚C for 2 h. The reaction was quenched with water (10 mL), and diethyl ether (10 mL) was then added. The product was extracted with hydrochloric acid (1 M, 5 mL × 3). The combined aqueous layer was neutralized with sodium hydroxide and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. The residue containing amine **3a** was used for the next step without further purification.

Hydrogen chloride in ether (1.0 M, 2.0 mL, 2.0 mmol) was added to a solution of the crude amine **3a** in methanol (5 mL). After the mixture was stirred for 2 h at room temperature, the solvent was removed in vacuo. Anhydrous ether (20 mL) was added to the resulting mixture.

Insoluble materials were collected by filtration to yield benzhydrylamine hydrochloride (**3a**•HCl) (183 mg, 0.83 mmol, 83% overall yield).

Procedure for Synthesis of Benzhydrylbenzamide 3f

Cesium hydroxide monohydrate (0.18 g, 1.05 mmol) and allylpalladium (II) chloride dimer (9.1 mg, 0.025 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.50 M in toluene, 0.40 mL, 0.20 mmol), xylene (2.0 mL), *N*-benzylxanthone imine (**1a**, 285 mg, 1.0 mmol), and *p*-chlorostyrene (0.14 mL, 1.2 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with chloroform (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue included a mixture of imines **2f** and **2f'**, which was used for the next step without further purification.

A drop of formic acid was added to a solution of the crude mixture of **2f** and **2f'** and sodium cyanoborohydride (189 mg, 3.0 mmol) in ethanol (5 mL). The resulting mixture was stirred at 80 ˚C for 2 h. Formic acid (5 mL) and water (1 mL) were then added, and the resulting mixture was stirred at 80 ˚C for 2 h. The reaction was quenched with water (10 mL), and diethyl ether (10 mL) was then added. The product was extracted with hydrochloric acid (1 M, 5 mL × 3). The combined aqueous layer was neutralized with sodium hydroxide and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue containing amine **3f** was used for the next step without further purification.

Benzoyl chloride (0.12 mL, 1.0 mmol) was added to a solution of the crude amine **3f** and triethylamine (0.28 mL, 2.0 mmol) in dichloromethane (5 mL). After the mixture was stirred for 2 h at room temperature, the reaction was quenched with water (10 mL). The product was extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium

sulfate and concentrated in vacuo. Silica gel column purification (hexane/ethyl acetate = 5:1) provided *N*-benzhydrylbenzamide **3f•**Bz (146 mg, 0.47 mmol) in 47% overall yield.

Procedure for Suzuki-Miyaura Cross-Coupling Reaction of Imine 1f with Arylboronic acid 7

Sodium hydroxide (30 mg, 0.75 mmol), tetrakis(triphenylphosphine)palladium (0) (11.6 mg, 0.01 mmol), arylboronic acid **7** (152 mg, 1.0 mmol), and imine **1f** (182 mg, 0.50 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Dimethoxyethane (3.0 mL) and water (0.5 mL) were sequentially added at ambient temperature. The resulting mixture was heated at 100 ˚C for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Chromatographic purification through a short silica gel column (hexane/ethyl acetate = 1:1) provided crude product. The yield of the imine **8** (60%) was determined by ^{1}H NMR measurement with 1,1,2,2-tetrachloroethane as an internal standard. The residue was used for the next step without further purification.

Synthesis of *N*-(9-Fluorenyl)acetamide (9)

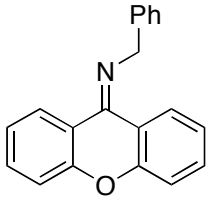
Cesium hydroxide monohydrate (0.88 g, 0.53 mmol) and allylpalladium (II) chloride dimer (4.6 mg, 0.013 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.50 M in toluene, 0.20 ml, 0.10 mmol), xylene (2.5 mL), and crude imine described above were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with chloroform (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was used for the next step without further purification.

A drop of hydrochloric acid (12 M) was added to a solution of the crude imine described above and sodium cyanoborohydride (90 mg, 1.5 mmol) in ethanol (2.5 mL). The resulting mixture was stirred at 25 ˚C for 2 h. Hydrochloric acid (12 M, 2.5 mL) and water (0.5 mL) were then added, and the resulting mixture was stirred at 25 ˚C for 2 h. The reaction was quenched with water (5 mL), and diethyl ether (5 mL) was then added. The product was extracted with hydrochloric acid (1 M, 3 mL × 3). The combined aqueous layer was neutralized with sodium hydroxide and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue containing 9-fluorenylamine was used for the next step without further purification.

Acetyl chloride (0.11 mL, 1.5 mmol) was added to a solution of the crude amine and triethylamine (0.21 mL, 1.5 mmol) in dichloromethane (5 mL). After the mixture was stirred for 2 h at room temperature, the reaction was quenched with water (10 mL). The product was extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane/ethyl acetate = 5:1) provided *N*-(9-fluorenyl)acetamide (**9**, 47 mg, 0.21 mmol) in 70% isolated yield starting from **8**.

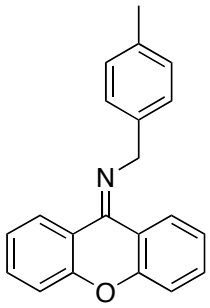
Characterization Data

***N*-Benzylxanthone Imine (1a)**



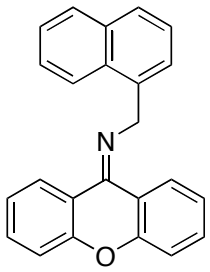
IR (nujol) 1602, 1247, 1124, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.25 (s, 2H), 7.20–7.29 (m, 4H), 7.37–7.41 (m, 3H), 7.46 (ddd, *J* = 7.0, 1.5, 1.5 Hz, 1H), 7.50–7.52 (m, 3H), 7.96 (dd, *J* = 7.0, 1.5 Hz, 1H), 8.31 (dd, *J* = 7.0, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.7, 116.5, 118.4, 118.9, 122.4, 123.8, 126.0, 126.6, 127.4, 127.4, 128.4, 128.4, 128.8, 130.9, 131.6, 141.6, 152.7, 155.0. Found: C, 84.46; H, 5.32; N, 4.84%. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91%. m.p.: 98–100 ˚C.

***N*-(4-Methylphenylmethyl)xanthone Imine (1b)**



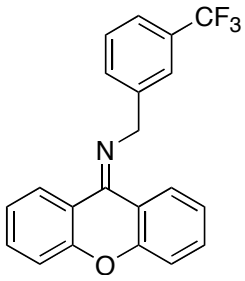
IR (nujol) 1609, 1558, 1507, 1457, 1249, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 5.20 (s, 2H), 7.18–7.25 (m, 5H), 7.37–7.40 (m, 3H), 7.44 (ddd, *J* = 8.0, 8.0, 1.5Hz, 1H), 7.49 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.30 (dd, *J* = 7.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 56.6, 116.7, 118.5, 119.1, 122.5, 124.0, 125.2, 126.2, 127.5, 129.0, 129.3, 131.1, 131.7, 136.3, 138.7, 150.9, 152.9, 155.1. m.p.: 118–121 ˚C.

***N*-(1-Naphthylmethyl)xanthone Imine (1c)**



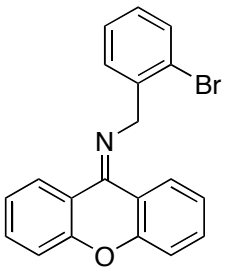
IR (nujol) 1607, 1558, 1456, 1248, 779, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.67 (s, 2H), 7.16 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.22–7.28 (m, 2H), 7.41–7.57 (m, 6H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.90–7.95 (m, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.7, 116.8, 118.6, 119.0, 122.8, 123.7, 124.1, 124.8, 125.2, 125.8, 125.9, 126.1, 126.3, 127.6, 128.9, 129.0, 131.2, 131.7, 131.9, 134.1, 136.7, 151.7, 153.0, 155.2. Found: C, 85.70; H, 5.30; N, 4.21%. Calcd for $C_{24}H_{17}NO$: C, 85.94; H, 5.11; N, 4.18%. m.p.: 177–182 ˚C (decomposition.).

***N*-[(3-Trifluoromethylphenyl)methyl]xanthone Imine (1d)**



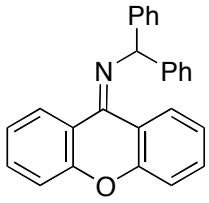
IR (nujol) 1616, 1456, 1329, 1130, 775, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.27 (s, 2H), 7.23–7.28 (m, 3H), 7.41 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.46–7.55 (m, 4H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.81 (s, 1H), 7.97 (dd, *J* = 8.5, 1.0 Hz, 1 H), 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.4, 116.8, 118.7, 122.6, 123.7 (q, $J_{C–F}$ = 3.9 Hz), 124.1, 124.5 (q, $J_{C–F}$ = 3.9 Hz), 124.5 (q, $J_{C–F}$ = 270.6 Hz), 125.5, 126.1, 128.9, 129.0, 130.8 (q, $J_{C–F}$ = 31.9 Hz), 131.0, 131.3, 132.0, 138.1, 143.0, 151.2, 152.9, 155.2. Found: C, 71.57; H, 4.17; N, 4.03%. Calcd for $C_{21}H_{14}F_3NO$: C, 71.38; H, 3.99; N, 3.96%. m.p.: 76–79 °C.

***N*-(2-Bromophenylmethyl)xanthone Imine (1f)**



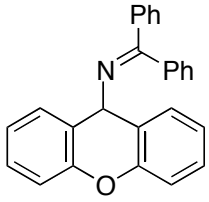
IR (nujol) 1745, 1613, 1455, 1334, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.25 (s, 2H), 7.16 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.24–7.29 (m, 3H), 7.36 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.49 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.54 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.60 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.79 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.97 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.35 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.9, 116.8, 118.6, 119.1, 122.8, 123.4, 124.1, 125.0, 126.2, 127.7, 128.3, 128.9, 129.3, 131.3, 132.0, 132.5, 134.7, 140.7, 152.9, 155.1. m.p.: 81–82 °C.

_N_-Benzhydrylxanthone Imine (2a)



IR (nujol) 1611, 1559, 1456, 1334, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.40 (s, 1H), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.23–7.32 (m, 4H), 7.35 (dd, *J* = 7.5, 7.5 Hz, 4H), 7.40–7.41 (m, 1H), 7.46–7.52 (m, 2H), 7.57 (d, *J* = 7.5 Hz, 4H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.48 (dd, *J* = 8.0, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 68.9, 109.9, 116.6, 118.5, 122.7, 124.0, 125.6, 126.3, 127.0, 127.5, 128.8, 128.8, 131.1, 131.7, 145.9, 150.2, 153.1, 155.3. Found: C, 86.42; H, 5.48; N, 3.89%. Calcd for $C_{26}H_{19}NO$: C, 86.40; H, 5.30; N, 3.88%. m.p.: 150–152 °C

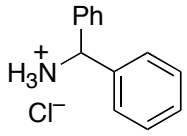
_N_-(9-Xanthenyl)benzophenone Imine (2a')



IR (nujol) 1648, 1576, 1454, 1259, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.72 (s, 1H), 7.08 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.13–7.17 (m, 4H), 7.25–7.28 (m, 2H), 7.33–7.36 (m, 2H), 7.39–7.41 (m, 3H), 7.45–7.51 (m, 3H), 7.73–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.8, 116.8, 123.3 (two signals merged), 128.0 (two signals merged), 128.3, 128.6, 129.0, 129.0, 129.3, 130.7, 136.5, 139.6, 151.5, 169.4. Found: C, 86.43; H, 5.60; N, 3.64%. Calcd for $C_{26}H_{19}NO$: C, 86.40; H, 5.30; N, 3.88%. m.p. 233–236 °C.

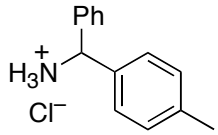
Amine hydrochlorides **3b•**HCl, **3e•**HCl were acylated with acid chlorides in the presence of triethylamine in dichloromethane in more than 90% yield to afford analytically pure materials.

Benzhydrylamine Hydrochloride (3a•HCl)



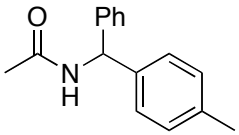
IR (nujol) 1684, 1653, 1558, 1521, 1457, 739, 701 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.63 (s, 1H), 7.34–7.37 (m, 2H), 7.41–7.44 (m, 4H), 7.53–7.54 (m, 4H), 9.14 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 57.0, 127.3, 128.3, 128.8, 138.3. Found: C, 70.79; H, 6.51; N, 6.43%. Calcd for $C_{13}H_{14}ClN$: C, 71.07; H, 6.42; N, 6.38%. m.p.: 297–304 ˚C.

_N_-(4-Methylphenyl)phenylmethylamine Hydrochloride (3b•HCl)



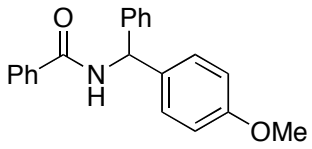
IR (nujol) 1684, 1653, 1558, 1517, 1507, 1456, 699 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.27 (s, 3H), 5.54 (s, 1H), 7.18 (d, J = 7.0 Hz, 2H), 7.31–7.44 (m, 5H), 7.51–7.55 (m, 2H), 9.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 56.9, 127.3, 128.1, 128.5, 128.7, 129.0, 129.2, 135.5, 125.7, 138.6. m.p.: 218–222 ˚C.

_N_-[(4-Methylphenyl)phenylmethyl]acetamide (3b•Ac)



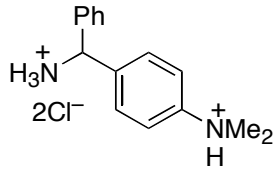
IR (nujol) 3303, 2853, 1653, 1539, 1456, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.33 (s, 3H), 6.02 (d, J = 7.5 Hz, 1H), 6.21 (d, J = 7.5 Hz, 1H), 7.10–7.15 (m, 4H), 7.22–7.27 (m, 3H), 7.31–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 23.6, 56.9, 127.5, 127.5, 127.6, 128.8, 129.5, 137.4, 138.8, 141.8, 169.2. Found: C, 80.41; H, 7.23; N, 5.85%. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. m.p.: 129–131 ˚C.

_N_-[(4-Methoxyphenyl)phenylmethyl]benzamide (3c•Bz)



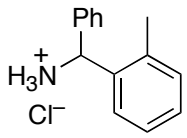
IR (nujol) 2855, 1558, 1507, 1457, 1247, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 6.40 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.87–6.89 (m, 2H), 7.20–7.23 (m, 2H), 7.25–7.36 (m, 5H), 7.42–7.45 (m, 2H), 7.49–7.52 (m, 1H), 7.81–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.5, 57.1, 114.3, 127.2, 127.5, 127.6, 128.8, 128.9, 128.9, 131.8, 133.8, 134.4, 141.8, 159.2, 166.6. Found: C, 79.61; H, 5.97; N, 4.52%. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41%. m.p.: 185–187 ˚C.

_N_-[4-(_N_,_N_-Dimethylamino)phenyl]phenylmethylamine Dihydrochloride (3d•2HCl)



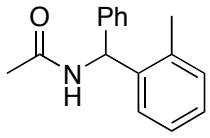
IR (nujol) 1684, 1653, 1558, 1508, 1457 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.03 (s, 6H), 5.64 (s, 1H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.59–7.60 (m, 2H), 7.65–7.68 (m, 5H), 9.37 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 43.9 (bs), 56.6, 124.8 (t□□□signals merged), 125.3 (three□signals merged), 127.4 (t□□□signals merged), 134.9. Found: C, 59.97; H, 6.56; N, 9.29%. Calcd for $C_{15}H_{20}Cl_2N_2$: C, 60.21; H, 6.74; N, 9.39%. m.p.: 214–216 ˚C (decomp.).

_N_-(2-Methylphenyl)phenylmethylamine Hydrochloride (3e•HCl)



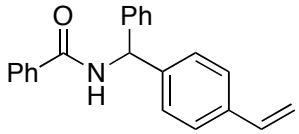
IR (nujol) 2855, 1684, 1653, 1558, 1508, 1457 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H), 5.69 (s, 1H), 7.22–7.47 (m, 8H), 7.69–7.70 (m, 1H), 9.19 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 19.2, 53.9, 126.2, 126.4, 128.2, 128.5, 128.7, 128.9, 130.8, 135.5, 136.2, 137.3. m.p.: 277–281 ˚C.

***N*-(2-Methylphenyl)phenylmethylacetamide (3e•Ac)**



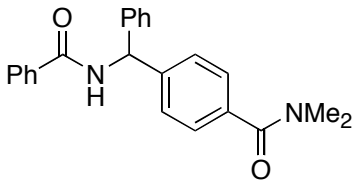
IR (nujol) 2855, 1539, 1507, 1457, 1451 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.29 (s, 3H), 5.97 (d, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 7.5 Hz, 1H), 7.09–7.11 (m, 1H), 7.16–7.21 (m, 5H), 7.24–7.27 (m, 1H), 7.29–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.7, 23.5, 54.2, 126.3, 126.8, 127.6, 127.6, 127.7, 128.8, 131.0, 136.5, 139.7, 141.2, 169.0. Found: C, 80.36; H, 7.14; N, 5.87%. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. m.p.: 147–155 °C.

***N*-[Phenyl(4-vinylphenyl)methyl]benzamide (3f•Bz)**



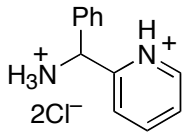
IR (nujol) 2842, 1636, 1558, 1539, 1457, 1374 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.24 (dd, *J* = 18.0, 1.0 Hz, 1H), 5.73 (dd, *J* = 18.0, 1.0 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 6.65–6.73 (m, 2H), 7.26–7.31 (m, 5H), 7.34–7.37 (m, 2H), 7.38–7.40 (m, 2H), 7.42–7.45 (m, 2H), 7.51 (ddd, *J* = 7.0, 7.0, 1.5 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 57.4, 114.4, 126.8, 127.2, 127.7, 127.8, 127.9, 128.8, 129.0, 131.9, 134.4, 136.5, 137.2, 141.2, 141.5, 166.6. Found: C, 84.09; H, 6.22; N, 4.39%. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47%. m.p.: 182–184 °C.

***N*-[{4-(*N*,*N*-Dimethylcarbamoyl)phenyl}phenylmethyl]benzamide (3g•Bz)**



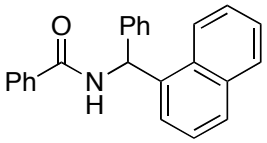
IR (nujol) 2930, 1733, 1267, 1090, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.94 (s, 3H), 3.05 (s, 3H), 6.48 (d, *J* = 7.5 Hz, 1H), 7.25–7.40 (m, 12H), 7.47 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 35.5, 39.7, 57.2, 127.2, 127.3, 127.4, 127.7, 128.5, 128.6, 128.7, 131.6, 134.0, 135.2, 141.0, 143.0, 166.6, 171.1.

Phenyl(2-pyridyl)methylamine Dihydrochloride (3h•2HCl)



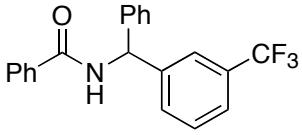
IR (nujol) 2597, 1684, 1653, 1558, 1507 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.82 (s, 1H), 7.21–7.78 (m, 7H), 8.00 (bs, 1H), 8.68 (bs, 1H), 9.39 (bs, 3H), 12.07 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 56.9, 123.2, 124.2, 127.9, 128.8, 128.9, 137.0, 139.5, 147.6, 155.6. m.p.: 230–234 °C (decomp.).

***N*-[(1-Naphthyl)phenylmethyl]benzamide (3i•Bz)**



IR (nujol) 2923, 2854, 1734, 1684, 1628, 1558, 1507, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.73 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.29–7.36 (m, 6H), 7.40–7.44 (m, 3H), 7.48–7.51 (m, 3H), 7.80–7.84 (m, 3H), 7.88–7.90 (m, 1H), 8.07–8.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 54.5, 123.9, 125.4, 125.8, 126.1, 126.9, 127.3, 127.7, 127.8, 128.8, 128.9, 128.9, 129.0, 131.5, 131.9, 134.3, 134.3, 137.2, 141.3, 166.5. Found: C, 85.57; H, 5.87; N, 4.21%. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15%. m.p. 166–169 °C.

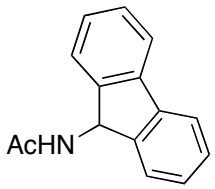
***N*-[(3-Trifluoromethylphenyl)phenylmethyl]benzamide (3j•Bz)**



IR (nujol) 3309, 2935, 1708, 1645, 1133, 667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.49 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 7.0 Hz, 2H), 7.32–7.40 (m, 3H), 7.44-7.57 (m, 7H), 7.83 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 57.5, 124.1 ($J_{C\text{-}F}$ = 4 Hz), 124.6 ($J_{C\text{-}F}$ = 4 Hz), 126.3 ($J_{C\text{-}F}$ = 263 Hz), 127.2, 127.8, 128.3, 128.9, 129.3, 129.3 ($J_{C\text{-}F}$ = 31 Hz), 129.4, 131.0, 132.1, 134.0, 140.8,

142.6, 166.8. Found: C, 70.95; H, 4.58%. Calcd for $C_{21}H_{16}F_3NO$: C, 70.89; H, 4.54%.

_N_-(9-Fluorenyl)acetamide (9)



IR (nujol) 3276, 1647, 1639, 1544, 761, 746, 728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 5.68 (d, J = 8.5 Hz, 1H), 6.24 (d, J = 8.5 Hz, 1H), 7.32 (ddd, J = 7.5, 7.5, 1.0 Hz, 2H), 7.41 (dd, J = 7.5, 7.5 Hz, 2H), 7.58 (dd, J = 7.5, 1.0 Hz, 2H), 7.69 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.7, 55.0, 120.2, 125.3, 128.0, 128.9, 140.8, 144.5, 170.9.

References and Notes

(1) α-Arylation of carbonyls: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383. (c) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (d) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465–475. (e) Satoh, T.; Inoh, J.; Kawamura, Y.; Kawamura Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239–2246. γ-Arylations of α,β-unsaturated carbonyl compounds: (f) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203–6206. (g) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581–7582.

(2) Intermolecular arylation at the activated benzylic or allylic positions: (a) Inoh, J.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673–4676. (b) Dyker, G.; Heiermann, J.; Miura, M.; Inoh, J.; Pivsa-Art, S.; Satoh, T.; Nomura, M. *Chem. Eur. J.* **2000**, *6*, 3426–3433. (c) Dyker, G.; Heiermann, J.; Miura, M. *Adv. Synth. Catal.* **2003**, *345*, 1127–1132. (d) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373–2375. (e) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641–1643. (f) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267.

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(6) The pK_a value of the benzylic protons of $Ph_2C{=}NCH_2Ph$ was reported to be 24.3 in dimethyl sulfoxide at 25 ˚C. See: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

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Chapter 4

Palladium-Catalyzed Benzylic Direct Arylation of Benzyl Sulfone

An effective palladium catalyst system for the direct arylation of benzyl sulfones with aryl halides has been developed. The catalytic reaction provides a facile route to diarylmethyl sulfones. The products can be transformed further via desulfonylative functionalization mediated by aluminum compounds.

Introduction

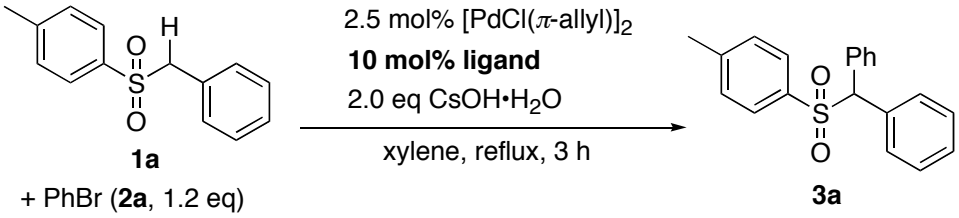
Transition-metal-catalyzed direct arylations at sp^3-hybridized carbons having acidic hydrogens have been attracting increasing attention in the modern cross-coupling reaction.[1–5] In light of the importance of this transformation, the author thus envisioned a new application of the direct arylation, specifically, intermolecular benzylic arylation of benzyl sulfones.[6] Benzyl sulfone **1**, readily prepared from benzyl halide and sodium arenesulfinate, has benzylic hydrogens of satisfactory acidity for deprotonation.[7] Palladium-catalyzed arylation of **1** with aryl halide **2** would afford diarylmethyl sulfone **3**.

Results and Discussion

Treatment of benzyl sulfone **1a** with bromobenzene (**2a**) in the presence of cesium hydroxide and catalytic amounts of π-allylpalladium (II) chloride dimer and tricyclohexylphosphine ($P(^cC_6H_{11})_3$) in refluxing xylene provided the corresponding arylated product **3a** in moderate yield (Table 1, entry 1). A plausible reaction mechanism includes deprotonation of **1a** with cesium hydroxide followed by transmetalation of α-tosylbenzylcesium with an arylpalladium bromide intermediate. Although the product should have the more acidic hydrogen,[8] he could not observe *p*-tolyl triphenylmethyl sulfone which could be derived from second arylation.[9]

The author first screened various ligands (Table 1). Although a number of phosphine ligands showed poor to moderate activity for the reaction, the use of $P(^cC_6H_{11})_3$ and P^tBu_3 resulted in high efficiency (entries 1 and 13). Other ligands such as triarylphosphines and bidentate phosphines were much less effective.

Table 1. Optimization of Reaction Conditioin for Direct Phenylation of Benzyl Sulfone **1a** by Using Various Ligands[a]



1a

+ PhBr (**2a**, 1.2 eq)

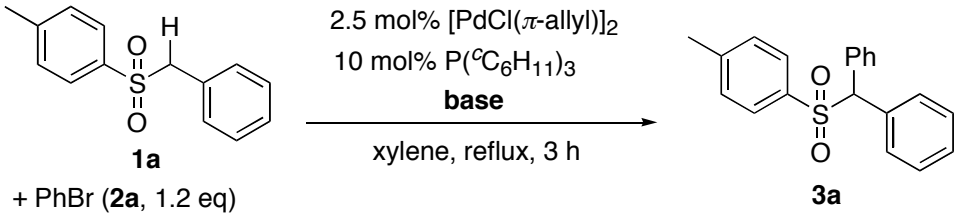
3a

entry	ligand	yield (%)[b]
1	$P(^cC_6H_{11})_3$	68
2	PPh_3	19
3	P(*o*-tol)$_3$	trace
4	P(*p*-MeOC_6H_4)$_3$	24
5	P(*p*-FC_6H_4)$_3$	35
6	dppe (2.5 mol%)	trace
7	*rac*-BINAP (2.5 mol%)	6
8	DPEphos (2.5 mol%)	8
9	Xantphos (2.5 mol%)	31
10	PMe_3	0
12	P^nBu_3	0
13	P^tBu_3 (2.5 mol%)	52

[a] A mixture of **1a** (0.50 mmol), **2a** (0.60 mmol), [PdCl(π-allyl)]$_2$ (0.013 mmol), ligand (0.050 mmol), and cesium hydroxide (1.0 mmol) was boiled in xylene (2.5 mL).
[b] ^{1}H NMR yields.

By using $P(^cC_6H_{11})_3$ as the optimal ligand, the effect of bases was examined (Table 2). Cesium carbonate showed no activity (entry 7) while alkali metal hydroxides and ^{t}BuOK acted as effective bases (entries 1–6 and 8). Finally, he found that the desired product **3a** was obtained in 90% yield in refluxing toluene (entry 9). The reaction at 80 ºC or lower temperature resulted in incomplete conversion even after 15 h (entries 10 and 11).

Table 2. Optimization of Reaction Conditions for Direct Phenylation of Benzyl Sulfone **1a** by Using Various Bases[a]



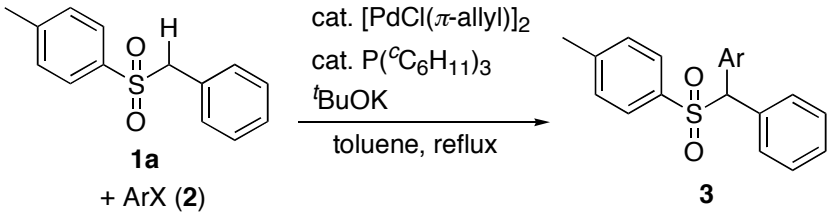
entry	base (eq)	yield (%)[b]
1	$CsOH•H_2O$ (1.2)	24
2	$CsOH•H_2O$ (2.0)	68
3	$CsOH•H_2O$ (3.0)	41
4	KOH (2.0)	50
5	KOH (3.0)	30
6	NaOH (2.0)	37
7	Cs_2CO_3 (2.0)	0
8	^{t}BuOK (2.0)	61
9	^{t}BuOK (2.0)[c]	90[d]
10	^{t}BuOK (2.0)[e]	39
11	^{t}BuOK (2.0)[f]	3

[a] A mixture of **1a** (0.50 mmol), **2a** (0.60 mmol), $[PdCl(\pi\text{-allyl})]_2$ (0.013 mmol), $P(^cC_6H_{11})_3$ (0.050 mmol), and base (1.0 mmol) was boiled in xylene (2.5 mL).
[b] ^{1}H NMR yields. [c] Toluene was used as a solvent. [d] Isolated yield.
[e] Performed in toluene at 80 ˚C for 15 h. [f] Performed in toluene at 50 ˚C for 15 h.

With the optimal conditions, the author performed the direct arylation of a variety of aryl halides (Table 3). Iodobenzene (**2b**) reacted smoothly (entry 2), although chlorobenzene (**2c**) gave **3a** in lower yield (entry 3). Aryl iodides having chloro- (entry 4), trifluoromethyl- (entry 5), and ester groups (entry 6) could be employed. Unfortunately, attempts on the reaction with electron-rich aryl iodides resulted in incomplete conversions. For such reactions, it was effective to use an *N*-heterocyclic carbene (NHC) precursor IPr•HCl[10] instead of tricyclohexylphosphine to obtain the corresponding product in high yield (entries 7–10). Sterically demanding aryl iodides **2k** and **2l** also participated in the reaction by using the NHC

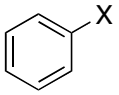
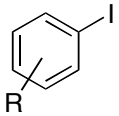
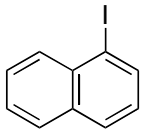
ligand (entries 11 and 12).

Table 3. Pd-Catalyzed Arylation of Benzyl Sulfone **1a**[a]

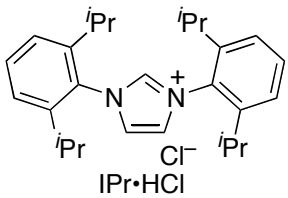


1a
+ ArX (**2**)

3

entry	ArX **2**			time (h)	**3**	yield (%)[b]
1		**2a**	X = Br	3	**3a**	90
2		**2b**	I	3	**3a**	99
3		**2c**	Cl	3	**3a**	31[c]
4		**2d**	R = *p*-Cl	2	**3d**	76
5		**2e**	*m*-CF_3	3	**3e**	75
6		**2f**	*p*-$CO_2{}^t$Bu	5	**3f**	75
7		**2g**	*p*-Me	2	**3g**	80[d]
8		**2h**	*p*-F	4	**3h**	64[d]
9		**2i**	*p*-MeO	7	**3i**	67[d]
10		**2j**	*m*-Me	2	**3j**	84[d]
11		**2k**	*o*-Me	5	**3k**	67[d]
12		**2l**		5	**3l**	69

[a] A mixture of **1a** (0.50 mmol), **2** (0.60 mmol), [PdCl(π-allyl)]$_2$ (0.013 mmol), P(^{c}C$_6$H$_{11}$)$_3$ (0.050 mmol), and ^{t}BuOK (1.0 mmol) was boiled in toluene (2.5 mL).
[b] Isolated yields. [c] The yield was determined by ^{1}H NMR analysis.
[d] IPr•HCl (0.030 mmol) was used as a ligand.

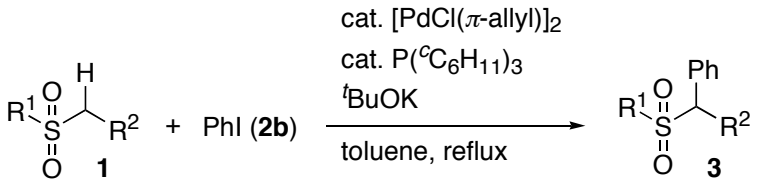


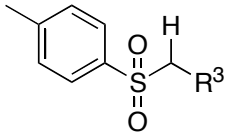
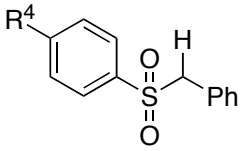
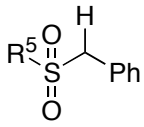
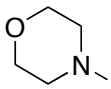
IPr•HCl

Other sulfones were subjected to the arylation reaction (Table 4). The reactions of *p*-substituted benzyl sulfones **1b**, **1c**, and 2-naphthylmethyl sulfone **1d** proceeded smoothly

(entries 1–3). The *p*-trifluoromethyl- and the *p*-methoxy groups of the arenesulfonyl moieties did not interfere with the arylation (entries 4 and 5). Benzylic sulfonamides **1g** and **1h** could be employed to afford the corresponding diarylmethanesulfonamides (entries 6 and 7).[11] Unfortunately, the reactions of 1-phenylethyl sulfone **1i** and benzyl methyl sulfone (**1j**) resulted in no conversions, because of the low acidity of the benzylic protons (Figure 1). The reaction of 2-biphenylylmethyl sulfone **1k** also afforded no arylated product, due to the steric hindrance.

Table 4. Pd-Catalyzed Phenylation of Other Sulfones[a]



entry	sulfone **1**			time (h)	**3**	yield (%)[b]
1		**1b**	R^3 = 4-FC_6H_4	3	**3o**	77[c]
2		**1c**	4-$MeOC_6H_4$	3	**3p**	73[c]
3		**1d**	2-naphthyl	4	**3q**	62
4		**1e**	R^4 = CF_3	1.5	**3r**	77
5		**1f**	OMe	2	**3s**	83
6		**1g**	R^5 = 	1	**3t**	75
7		**1h**	N(Me)Ph	1	**3u**	71

[a] A mixture of **1** (0.50 mmol), **2b** (0.60 mmol), [PdCl(π-allyl)]$_2$ (0.013 mmol), P(^{c}C$_6$H$_{11}$)$_3$ (0.050 mmol), and ^{t}BuOK (1.0 mmol) was boiled in toluene (2.5 mL). [b] Isolated yields. [c] IPr•HCl (0.030 mmol) was used as a ligand.

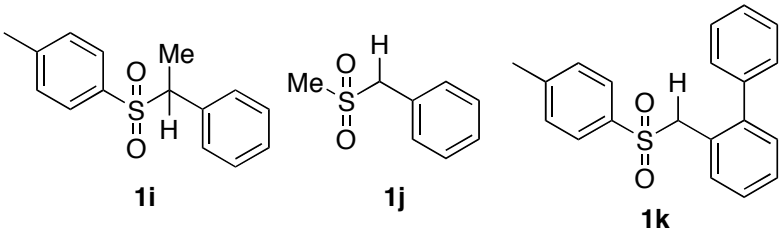
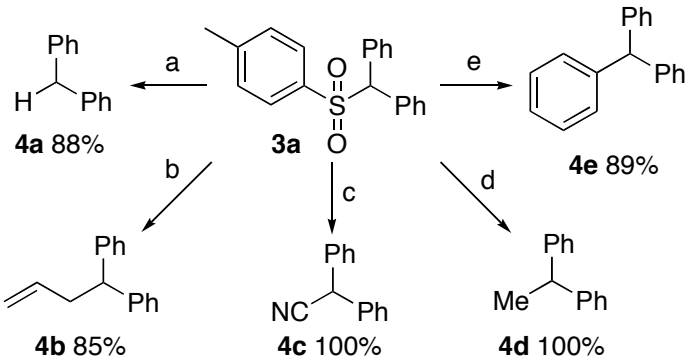


Figure 1. Other Sulfones

Finally, desulfonylative transformations of the product **3a** were investigated (Scheme 1). Treatment of diphenylmethyl sulfone **3a** with hydrosilane, allylsilane, or silyl cyanide in the presence of aluminum chloride provided the corresponding desulfonylative product in high yield.[12] Methylation of **3a** with trimethylaluminum proceeded smoothly.[13] Friedel–Crafts alkylation of benzene with diphenylmethyl sulfone **3a** was facile to yield triphenylmethane (**4e**).

Scheme 1. Desulfonylative Transformations of Diphenylmethyl Sulfone **3a** in the Presence of Aluminum Compounds[a]



[a] Conditions: a) $AlCl_3$ (1.5 eq), Et_3SiH (1.5 eq), CH_2Cl_2, 25 ºC, 1 h;
b) $AlCl_3$ (1.5 eq), $Me_3SiCH_2CH{=}CH_2$ (1.5 eq), CH_2Cl_2, 25 ºC, 1 h;
c) $AlCl_3$ (1.5 eq), Me_3SiCN (1.5 eq), CH_2Cl_2, 25 ºC, 1 h;
d) $AlMe_3$ (1.5 eq), CH_2Cl_2, 25 ºC, 2 h;
e) $AlCl_3$ (1.5 eq), C_6H_6, 25 ºC, 1 h.

Conclusion

The author has developed an effective palladium catalyst system for the direct arylation of

benzyl sulfones with aryl halides. The catalytic reaction provides a facile route to diarylmethane derivatives .

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were taken on a Varian Unity INOVA 500 spectrometer and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene was purchased from Wako Pure Chemical Co. and stored over slices of sodium. Tricyclohexylphosphine and imidazolinium salt IPr•HCl were purchased from Strem. Preparations of sulfones (**1a–1i**) are shown below. Preparations of sulfones **1j**[14] and **1k**[15] were carried out according to the literature. All reactions were carried out under argon atmosphere.

Synthesis of Benzyl Aryl Sulfones (1a–1d, 1i)

Synthesis of sulfone **1a** is representative. Benzyl chloride (4.6 mL, 40 mmol) was added to a suspension of sodium *p*-toluenesulfinate tetrahydrate (11.0 g, 44 mmol) and tetrabutylammonium bromide (0.64 g, 2.0 mmol) in 1,2-dimethoxyethane (40 mL) at room temperature. The resulting mixture was heated at reflux for 3 h. The mixture was poured into water, and insoluble materials were collected by filtration to yield benzyl *p*-tolyl sulfone (**1a**, 8.9 g, 36 mmol, 82%).

Synthesis of Benzyl Aryl Sulfones (1e and 1f)

Synthesis of sulfone **1e** is representative. A solution of butyllithium (1.6 M in hexane, 6.3

mL, 10 mmol) was slowly added to a solution of *p*-trifluoromethylbromobenzene (1.4 mL, 10 mmol) in tetrahydrofuran (50 mL) at –78 °C and the reaction mixture was stirred for 15 min at –78 °C. Sulfur (0.32 g, 10 mmol) was added to the reaction mixture. After the reaction mixture was stirred for 10 min at –78 °C, benzyl bromide (1.2 mL, 10 mmol) was slowly added. After being stirred for 1 h at room temperature, the reaction mixture was quenched with a saturated ammonium chloride solution. The product was extracted with ethyl acetate three times. The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. The residue containing benzyl 4-trifluoromethylphenyl sulfide was used for the next step without further purification.

Aqueous H_2O_2 (30%, 4.5 mL, 40 mmol) was slowly added to a solution of the crude sulfide and molybdenum dichloride dioxide (0.30 g, 1.5 mmol) in acetonitrile (10 mL). After being stirred for 18 h at room temperature, the resulting mixture was poured into aqueous sodium thiosulfate. Extraction with ethyl acetate followed by silica gel column purification furnished benzyl *p*-trifluoromethylphenyl sulfone (**1e**, 0.97 g, 3.2 mmol) in 32% yield in two steps.

Synthesis of Benzylic Sulfonamides (1g and 1h)

Synthesis of sulfonamide **1g** is representative. A solution of phenylmethanesulfonyl chloride (1.9 g, 10 mmol) in tetrahydrofuran (5 mL) was slowly added to a solution of morpholine (0.44 mL, 5.0 mmol) and diisopropylethylamine (2.1 mL, 12 mmol) in tetrahydrofuran (10 mL) at 0 °C. After the reaction mixture was stirred for 8 h at room temperature, the reaction mixture was quenched with a saturated ammonium chloride solution. Extraction with ethyl acetate followed by silica gel column purification furnished *N*-benzylsulfonylmorpholine (**1g**, 0.97 g, 4.0 mmol) in 80% yield.

Typical Procedure for Palladium-Catalyzed Direct Arylation of Aryl Benzyl Sulfones

Synthesis of sulfone **3a** is representative (Table 3, entry 2). ^{t}BuOK (449 mg, 4.0 mmol) and π-allylpalladium (II) chloride dimer (18 mg, 0.05 mmol) were placed in a 20-mL two-necked

reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.50 M in toluene, 0.40 mL, 0.20 mmol), toluene (10 mL), benzyl *p*-tolyl sulfone (**1a**, 493 mg, 2.0 mmol), and iodobenzene (**2a**, 0.27 mL, 2.4 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 2 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (10 mL) was added. The product was extracted with ethyl acetate three times. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane:ethyl acetate = 5:1) gave diphenylmethyl *p*-tolyl sulfone (**3a**, 637 mg, 1.97 mmol) in 99% yield.

Typical Procedure for Aluminum-Mediated Desulfonylative Transformations

Synthesis of 4a, 4b, and 4c

Synthesis of diphenylmethane (**4a**) is representative. Aluminum trichloride (40 mg, 0.3 mmol) was added to a solution of diphenylmethyl *p*-tolyl sulfone (**3a**, 65 mg, 0.20 mmol) and triethylsilane (48 μL, 0.30 mmol) in dichloromethane (2.0 mL). After being stirred for 1 h at room temperature, the reaction mixture was quenched with aqueous sodium hydroxide (1 M, 3 mL). The product was extracted with ethyl acetate three times. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification yielded diphenylmethane (**4a**, 30 mg, 0.18 mmol) in 88% yield.

Synthesis of 4d

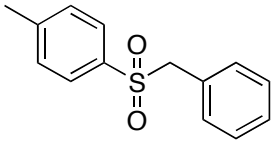
A solution of trimethylaluminum (1.0 M in toluene, 0.40 mL, 0.40 mmol) was added to a solution of diphenylmethyl *p*-tolyl sulfone (**3a**, 65 mg, 0.20 mmol) in dichloromethane (2.0 mL). After being stirred for 2 h at room temperature, the reaction mixture was quenched with aqueous sodium hydroxide (1 M, 3 mL). The product was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Chromatographic purification on silica gel gave 1,1-diphenylethane (**4d**, 26 mg, 0.20 mmol) in quantitative yield.

Synthesis of 4e

Aluminum trichloride (40 mg, 0.30 mmol) was added to a solution of diphenylmethyl *p*-tolyl sulfone (**3a**, 65 mg, 0.20 mmol) in benzene (2.0 mL). After being stirred for 1 h at room temperature, the reaction mixture was quenched with aqueous sodium hydroxide (1 M, 3 mL). Extractive work up followed by silica gel column purification afforded triphenylmethane (**4e**, 43 mg, 0.18 mmol) in 89% yield.

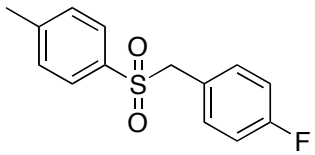
Characterization Data

Benzyl *p*-Tolyl Sulfone (1a)[13]



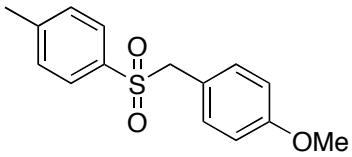
^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 4.29 (s, 2H), 7.08–7.10 (m, 2H), 7.22–7.28 (m, 4H), 7.30–7.33 (m, 1H), 7.49–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 63.1, 128.5, 128.7, 128.8, 128.9, 129.7, 131.0, 135.2, 144.8. Found: C, 68.51; H, 5.71%. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73%.

***p*-Fluorophenylmethyl *p*-Tolyl Sulfone (1b)**



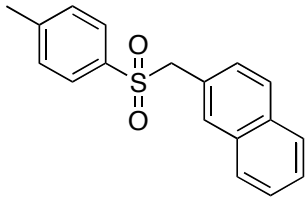
IR (nujol) 2923, 2854, 1460, 1377, 1126, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 4.26 (s, 2H), 6.94–6.98 (m, 2H), 7.06–7.08 (m, 2H), 7.25–7.27 (m, 2H), 7.50–7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 62.2, 115.8 (d, J_{C-F} = 21.5 Hz), 124.3 (d, J_{C-F} = 3.9 Hz), 129.3 (d, J_{C-F} = 127 Hz), 132.7 (J_{C-F} = 8.6 Hz), 134.9, 145.0, 162.2, 164.2. m.p.: 161–164 ˚C.

***p*-Methoxyphenylmethyl *p*-Tolyl Sulfone (1c)**[15]



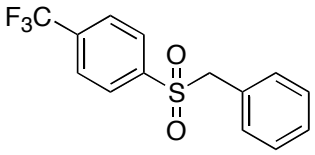
^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.79 (s, 3H), 4.23 (s, 2H), 6.79 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 55.4, 62.4, 114.2, 120.3, 128.8, 129.7, 132.2, 135.2, 144.8, 160.1.

2-Naphthylmethyl *p*-Tolyl Sulfone (1d)



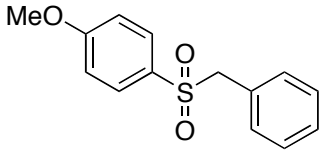
IR (nujol) 2923, 2854, 1654, 1507, 1465, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 4.45 (s, 2H), 7.19–7.22 (m, 3H), 7.46–7.52 (m, 4H), 7.56 (s, 1H), 7.72–7.75 (m, 2H), 7.81–7.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 63.3, 125.9, 126.6, 126.8, 127.9, 128.05, 128.14, 128.5, 128.8, 129.7, 130.7, 133.21, 133.25, 135.2, 144.9. m.p.: 135–137 °C.

Benzyl *p*-Trifluoromethylphenyl Sulfone (1e)



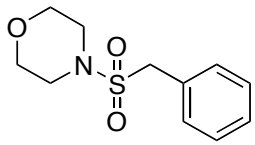
IR (nujol) 2922, 2854, 1655, 1457, 1378 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.35 (s, 2H), 7.08–7.10 (m, 2H), 7.26–7.30 (m, 2H), 7.35 (dddd, J = 7.0, 7.0, 2.0, 2.0 Hz, 1H), 7.70–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 63.0, 123.3 (q, $J_{C–F}$ = 272 Hz), 126.2 (q, $J_{C–F}$ = 3.8 Hz), 127.7, 129.0, 129.3, 129.5, 131.0, 135.6 (q, $J_{C–F}$ = 33.0 Hz), 141.5. Found: C, 55.73; H, 3.81%. Calcd for $C_{14}H_{11}F_3O_2S$: C, 55.99; H, 3.69%. m.p.: 163–165 °C.

Benzyl *p*-Methoxyphenyl Sulfone (1f)[16]



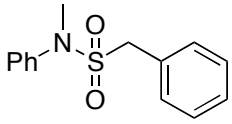
^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 4.28 (s, 2H), 6.88–6.91 (m, 2H), 7.08–7.10 (m, 2H), 7.25–7.29 (m, 2H), 7.30–7.34 (m, 1H), 7.51–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.8, 63.3, 109.9, 114.2, 128.68, 128.72, 128.8, 129.6, 131.0, 163.9.

_N_-Benzylsulfonylmorpholine (1g)[6d]



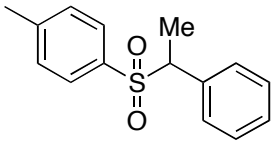
^{1}H NMR ($CDCl_3$) δ 3.10 (dd, J = 4.5, 4.5 Hz, 4H), 3.62 (dd, J = 4.5, 4.5 Hz, 4H), 4.24 (s, 2H), 7.39–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 46.3, 56.9, 66.9, 128.7, 129.0, 129.1, 130.9.

_N_-Benzylsulfonyl-_N_-methylaniline (1h)[6d]



^{1}H NMR ($CDCl_3$) δ 3.13 (s, 3H), 4.27 (s, 2H), 7.23–7.28 (m, 3H), 7.33–7.41 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 39.1, 56.5, 126.1, 127.0, 128.8, 128.93, 128.94, 129.4, 131.0, 141.6.

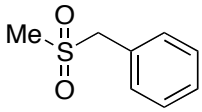
1-Phenylethyl _p_-Tolyl Sulfone (1i)



IR (nujol) 2923, 2854, 1654, 1645, 1457, 1373 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (d, J = 7.0 Hz, 3H), 2.40 (s, 3H), 4.21 (q, J = 7.0 Hz, 1H), 7.14–7.15 (m, 2H), 7.18–7.20 (m, 2H), 7.23–7.31 (m,

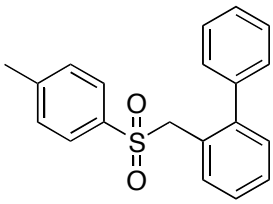
3H), 7.40–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 21.8, 66.2, 128.5, 128.9, 129.40, 129.44, 129.6, 134.07, 134.08, 144.6. m.p.: 114–117 °C.

Benzyl Methyl Sulfone (1j)[14]



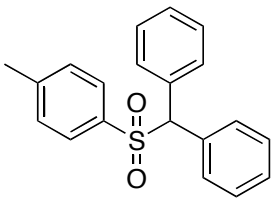
^{1}H NMR ($CDCl_3$) δ 2.75 (s, 3H), 4.25 (s, 2H), 7.42 (br, 5H); ^{13}C NMR ($CDCl_3$) δ 39.2, 61.5, 128.5, 129.3 (t□□ signals merged), 129.3, 130.7.

2-Biphenylylmethyl *p*-Tolyl Sulfone (1k)[15]



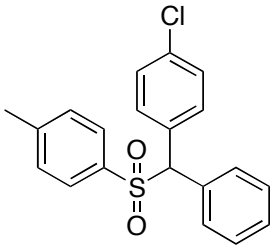
^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 4.39 (s, 2H), 6.84–6.86 (m, 2H), 7.12–7.14 (m, 3H), 7.23–7.29 (m, 5H), 7.35–7.37 (m, 2H), 7.60–7.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 59.1, 125.8, 127.3, 127.7, 128.2, 128.6, 128.7, 129.2, 129.6, 130.4, 131.7, 135.8, 139.9, 143.8, 144.6.

Diphenylmethyl *p*-Tolyl Sulfone (3a)



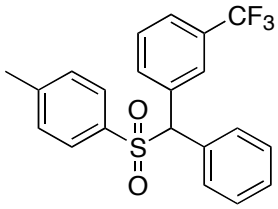
IR (nujol) 2925, 2854, 1457, 1377, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 5.26 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.30–7.33 (m, 6H), 7.49 (d, J = 8.0 Hz, 2H), 7.52–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.8, 76.7, 128.76, 128.85, 129.2, 129.4, 130.2, 133.3, 135.5, 144.6. Found: C, 74.20; H, 5.67%. Calcd for $C_{20}H_{18}O_2S$: C, 74.50; H, 5.63%. m.p.: 181–185 °C.

***p*-Chlorophenyl(phenyl)methyl *p*-Tolyl Sulfone (3d)**



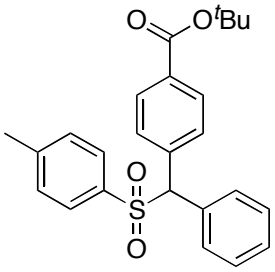
IR (nujol) 2924, 2854, 1655, 1457, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 5.24 (s, 1H), 7.17–7.18 (m, 2H), 7.29–7.32 (m, 5H), 7.47–7.50 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 21.8, 75.8, 129.0 (two signals merged), 129.1, 129.2, 129.6, 130.0, 131.4, 131.8, 132.9, 135.0, 135.2, 144.9. Found: C, 67.10; H, 4.90%. Calcd for $C_{20}H_{17}ClO_2S$: C, 67.31; H, 4.80%. m.p.: 131–135 °C.

(3-Trifluoromethylphenyl)phenylmethyl *p*-Tolyl Sulfone (3e)



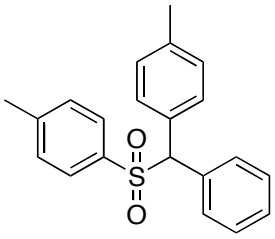
IR (nujol) 2923, 2854, 1692, 1654, 1465, 1451, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 5.33 (s, 1H), 7.15–7.17 (m, 2H), 7.32–7.33 (m, 3H), 7.45–7.52 (m, 5H), 7.56–7.57 (m, 1H), 7.66 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 76.0, 123.9 (q, $J_{C–F}$ = 271 Hz), 125.5 (q, $J_{C–F}$ = 4 Hz), 127.1 (q, $J_{C–F}$ = 4 Hz), 129.0, 129.08, 129.14, 129.4, 129.6, 130.0, 131.1 (q, $J_{C–F}$ = 32.5 Hz), 132.5, 133.3, 134.4, 134.9, 145.1. Found: C, 64.61; H, 4.53%. Calcd for $C_{21}H_{17}F_3O_2S$: C, 64.60; H, 4.39%. m.p.: 92–95 °C.

***tert*-Butyl *p*-[*p*-Tolylsulfonyl(phenyl)methyl]benzoate (3f)**



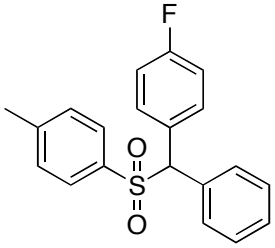
IR (nujol) 2923, 2854, 1654, 1507, 1457, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 9H), 2.39 (s, 3H), 5.31 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.31–7.32 (m, 3H), 7.49–7.51 (m, 4H), 7.59–7.60 (m, 2H), 7.92–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 28.3, 76.3, 81.5, 128.96, 128.97, 129.2, 129.6, 129.86, 129.94, 130.1, 132.3, 132.8, 135.3, 137.8, 144.9, 165.4. m.p.: 104–107 °C.

Phenyl(*p*-tolyl)methyl *p*-Tolyl Sulfone (3g)



IR (nujol) 2923, 2854, 1457, 1383, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.37 (s, 3H), 5.23 (s, 1H), 7.12–7.16 (m, 4H), 7.29–7.31 (m, 3H), 7.41–7.43 (m, 2H), 7.48–7.52 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.3, 22.0, 76.4, 128.7, 128.8, 129.2, 129.4, 129.6, 130.0, 130.1, 130.2, 133.5, 135.6, 138.7, 144.5. Found: C, 74.93; H, 6.05%. Calcd for $C_{21}H_{20}O_2S$: C, 74.97; H, 5.99%. m.p.: 145–148 °C.

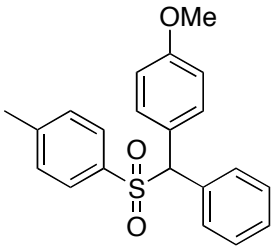
***p*-Fluorophenyl(phenyl)methyl *p*-Tolyl Sulfone (3h)**



IR (nujol) 2923, 2854, 1655, 1457, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 5.26 (s, 1H),

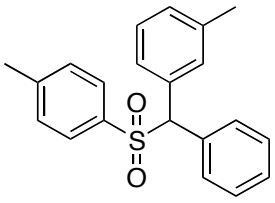
6.99–7.03 (m, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.30–7.33 (m, 3H), 7.47–7.53 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 21.8, 75.7, 115.8 (d, $J_{C–F}$ = 21.5 Hz), 128.88, 128.93, 129.1 (d, $J_{C–F}$ = 3.4 Hz), 129.2, 129.5, 130.0, 131.9 (d, $J_{C–F}$ = 8.1 Hz), 134.2 (d, $J_{C–F}$ = 269 Hz), 144.8, 162.0, 164.0. Found: C, 70.31; H, 5.20%. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03%. m.p.: 159–162 ˚C.

p-Methoxyphenyl(phenyl)methyl p-Tolyl Sulfone (3i)



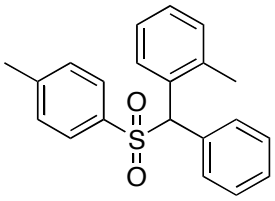
IR (nujol) 2923, 2854, 1457, 1377, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.78 (s, 3H), 5.22 (s, 1H), 6.84 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 7.29–7.43 (m, 3H), 7.43–7.46 (m, 2H), 7.48–7.53 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.8, 55.5, 76.0, 114.2, 125.1, 128.7, 128.8, 129.2, 129.4, 130.0, 131.4, 133.6, 135.6, 144.5, 159.9. Found: C, 71.56; H, 5.77%. Calcd for $C_{21}H_{20}O_3S$: C, 71.56; H, 5.72%. m.p.: 155–158 ˚C.

Phenyl(m-tolyl)methyl p-Tolyl Sulfone (3j)



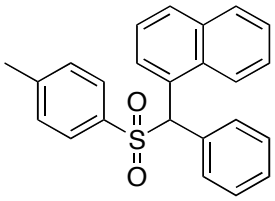
IR (nujol) 2923, 2854, 1655, 1457, 1379 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.38 (s, 3H), 5.26 (s, 1H), 7.13–7.18 (m, 3H), 7.23 (dd, J = 7.5, 7.5 Hz, 1H), 7.31–7.39 (m, 5H), 7.50–7.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 21.7, 76.6, 127.1, 128.7 (two signals merged), 128.8, 129.2, 129.4, 129.5, 130.1, 130.8, 133.1, 133.4, 135.5, 138.5, 144.5. Found: C, 74.96; H, 6.06%. Calcd for $C_{21}H_{20}O_2S$: C, 74.97; H, 5.99%. m.p.: 120–122 ˚C.

Phenyl(o-tolyl)methyl p-Tolyl Sulfone (3k)



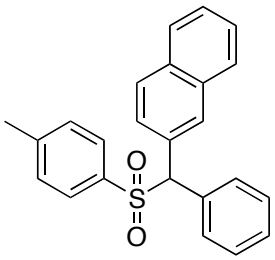
IR (nujol) 2923, 2854, 1655, 1457, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.38 (s, 3H), 5.57 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.15–7.21 (m, 3H), 7.28–7.31 (m, 4H), 7.47–7.51 (m, 4H), 8.16 (dd, *J* = 8.0, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 21.8, 71.5, 126.6, 128.6, 128.7, 128.8, 129.1 (two signals merged), 129.5, 130.5, 130.9, 132.2, 133.1, 135.9, 137.0, 144.6. Found: C, 74.73; H, 6.09%. Calcd for $C_{21}H_{20}O_2S$: C, 74.97; H, 5.99%. m.p.: 125–127 °C.

1-Naphthyl(phenyl)methyl *p*-Tolyl Sulfone (3l)



IR (neat) 3068, 2930, 2861, 2247, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 6.20 (s, 1H), 7.07 (d, *J* = 7.0 Hz, 2H), 7.22–7.26 (m, 3H), 7.35–7.39 (m, 2H), 7.48–7.56 (m, 5H), 7.76–7.81 (m, 3H), 8.48 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 70.9, 122.2, 125.4, 125.7, 126.8, 127.3, 128.3, 128.66, 128.72, 129.1, 129.2, 129.3, 129.4, 130.5, 131.6, 133.3, 134.1, 135.7, 144.6.

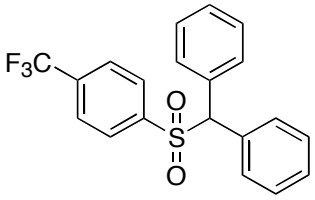
2-Naphthyl(phenyl)methyl *p*-Tolyl Sulfone (3m)



IR (nujol) 2923, 2854, 1654, 1465, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H), 5.45 (s, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.30–7.34 (m, 3H), 7.46–7.48 (m, 2H), 7.52 (d, *J* = 6.5 Hz, 2H), 7.57–7.59 (m, 2H), 7.66 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.79–7.80 (m, 3H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 76.7, 126.5, 126.8, 127.2, 127.7, 128.4, 128.6, 128.8, 128.9, 129.2, 129.5, 129.7,

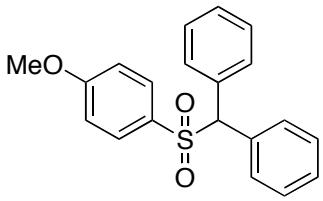
130.2, 130.8, 133.2, 133.3, 133.4, 135.5, 144.7. m.p.: 141–145 ˚C.

Diphenylmethyl *p*-Trifluoromethylphenyl Sulfone (3n)



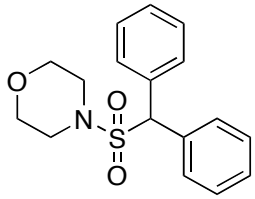
IR (nujol) 2922, 2954, 1462, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.31 (s, 1H), 7.31–7.34 (m, 6H), 7.53–7.55 (m, 4H), 7.61 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 76.7, 123.2 (q, $J_{C–F}$ = 272 Hz), 125.9 (q, $J_{C–F}$ = 4 Hz), 129.0, 129.2, 129.8, 130.1, 132.4, 135.2 (q, $J_{C–F}$ = 33 Hz), 142.0. Found: C, 63.73; H, 4.10%. Calcd for $C_{20}H_{15}F_3O_2S$: C, 63.82; H, 4.02%. m.p.: 130–133 ˚C.

***p*-Methoxyphenyl Diphenylmethyl Sulfone (3o)**



IR (nujol) 2910, 2852, 1472, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 5.26 (s, 1H), 6.80 (d, J = 7.0 Hz, 2H), 7.29–7.33 (m, 6H), 7.50–7.54 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 55.7, 76.8, 113.9, 128.7, 128.8, 129.9, 130.1, 131.3, 133.4, 163.7. Found: C, 70.91; H, 5.40%. Calcd for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36%. m.p.: 145–149 ˚C.

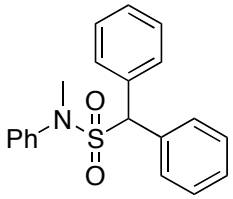
***N*-(Diphenylmethyl)sulfonylmorpholine (3p)**



IR (nujol) 2924, 2854, 1465, 1458, 1339 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (dd, J = 4.5, 4.5 Hz, 4H), 3.53 (dd, J = 4.5, 4.5 Hz, 4H), 5.29 (s, 1H), 7.33–7.41 (m, 6H), 7.63–7.65 (m, 4H); ^{13}C

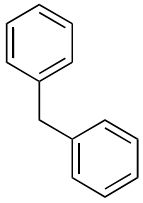
NMR ($CDCl_3$) δ 46.5, 66.9, 72.8, 128.9, 129.1, 129.7, 134.2. Found: C, 64.54; H, 6.02%. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03%. m.p.: 152–154 °C.

_N_-Methyl-_N_,1,1-triphenylmethanesulfonamide (3q)



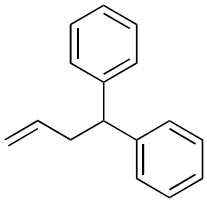
IR (nujol) 2923, 2854, 1654, 1457, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (s, 3H), 5.35 (s, 1H), 7.14–7.16 (m, 2H), 7.21–7.24 (m, 1H), 7.28–7.38 (m, 8H), 7.58–7.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 39.7, 72.2, 126.2, 126.9, 128.8, 128.9, 129.2, 129.9, 134.2, 141.6. Found: C, 71.22; H, 5.78%. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68%. m.p.: 115–117 °C.

Diphenylmethane (4a)[17]



^1H NMR ($CDCl_3$) δ 3.98 (s, 2H), 7.18–7.21 (m, 6H), 7.26–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 42.1, 126.3, 128.7, 129.1, 141.3.

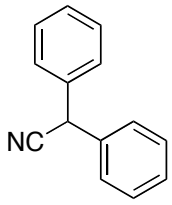
4,4-Diphenyl-1-butene (4b)[18]



^1H NMR ($CDCl_3$) δ 2.81 (dd, J = 7.5, 7.5 Hz, 2H), 4.00 (t, J = 7.5 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 5.02 (d, J = 17.0 Hz, 1H), 5.71 (ddt, J = 7.5, 10.5, 17.0 Hz, 1H), 7.16 (dd, J = 7.0, 7.0 Hz,

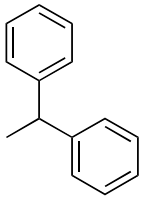
2H), 7.21–7.28 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 40.1, 51.4, 116.5, 126.4, 128.1, 128.6, 137.0, 144.7.

Diphenylacetonitrile (4c)[19]



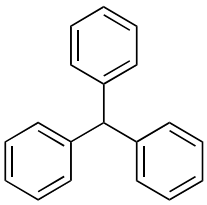
^{1}H NMR ($CDCl_3$) δ 5.13 (s, 1H), 7.30–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 42.8, 119.8, 127.9, 128.4, 129.4, 136.2.

1,1-Diphenylethane (4d)[20]



^{1}H NMR ($CDCl_3$) δ 1.64 (d, *J* = 7.0 Hz, 3H), 4.14 (q, *J* = 7.0 Hz, 1H), 7.15–7.19 (m, 2H), 7.21–7.24 (m, 4H), 7.25–7.29 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.0, 44.9, 126.2, 127.8, 128.5, 146.5.

Triphenylmethane (4e)[21]



^{1}H NMR ($CDCl_3$) δ 5.55 (s, 1H), 7.11–7.12 (m, 6H), 7.19–7.22 (m, 3H), 7.27–7.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 57.0, 126.5, 128.5, 129.6, 144.1.

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Chapter 1 Takashi Niwa, Hideki Yorimitsu, and Koichiro Oshima
Angew. Chem., Int. Ed. **2007**, *46*, 2643–2645.

Chapter 2 Takashi Niwa, Hideki Yorimitsu, and Koichiro Oshima
Org. Lett. **2007**, *9*, 2373–2375.

Chapter 3 Takashi Niwa, Hideki Yorimitsu, and Koichiro Oshima
Org. Lett. **2008**, *10*, 4689–4691.

Chapter 4 Takashi Niwa, Hideki Yorimitsu, and Koichiro Oshima
Tetrahedron accepted.

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