Studies on Catalytic Denitrative Transformations of Organic Nitro Compounds

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Contents

Abbreviations

Ac	acetyl
acac	acetylacetonato
AIBN	azobis(isobutyronitrile)
Anal.	elemental analysis
Å	ångström
aq.	aqueous solution
Ar	aryl
atm	atmospheric pressure
BDE	bond dissociation energy
BHT	2,6-di-*tert*-butyl-*p*-cresol
Bn	benzyl
br s	broad singlet (spectra)
Bz	benzoyl
calcd	calculated
cat.	catalyst
cod	1,5-cyclooctadiene
Cy	cyclohexyl
δ	chemical shift in parts per million (spectra)
Δ	delta, difference
º	degree
ºC	degrees Celsius
d	doublet (spectra)
dba	dibenzylideneacetone
DCM	dichloromethane
decomp.	decomposition
DFT	density functional theory
DG	directing group
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
ECP	effective core potential
EI	electron ionization
El	electrophile
Eq.	equation
ESI	electrospray ionization
Et	ethyl
eV	electron volt
EWG	electron withdrawing group
FG	functional group
FID	flame ionization detector
g	gram
G^{o}	standard Gibbs free energy
$G^{o‡}$	standard Gibbs free energy of transition state
GC	gas chromatography
h	hour(s)
Hal	halogen
HAT	hydrogen atom transfer
Het	hetero
HMDS	hexamethyldisilazide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz (s^{-1})
^{i}Pr	isopropyl
J	coupling constant (spectra)
K	Kelvin
kcal	kilocalorie(s)
KIE	kinetic isotope effect
kPa	kilopascal
λ	lambda, wavelength
LUMO	lowest unoccupied molecular orbital
m	meta
m	meter
m	multiplet (spectra)
M	molar (mole per liter)

Me	methyl
Mes	mesityl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mm	milimeter(s)
mmHg	millimeter of mercury
µm	micrometer(s)
mL	milliliter(s)
µL	microliter(s)
mmol	millimole(s)
µmol	micromole(s)
mol	mole
mol%	mole percent
MOM	methoxymethyl
mp.	melting point
MPLC	medium pressure liquid chromatography
Ms	mesyl
Mtl	metal
n	normal
^{n}Bu	normal butyl
nep	neopentylglycolato
NHC	*N*-heterocyclic carbene
nm	nanometer(s)
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
$\%V_{Bur}$	percent buried volume
Ph	phenyl
pin	pinacolato
ppm	parts per million (spectra)
PTLC	preparative thin layer chromatography
q	quartet (spectra)
quant.	quantitative
quint	quintet (spectra)
R^2	coefficient of determination
R_f	retention factor
rt	room temperature
s	singlet (spectra)
sept	septet (spectra)
SET	single-electron transfer
sex	sextet (spectra)
S_EAr	electrophilic aromatic substitution
S_NAr	nucleophilic aromatic substitution
S_N2'	bimolecular nucleophilic allylic substitution
SOMO	singly occupied molecular orbital
$S_{RN}1$	unimolecular radical nucleophilic substitution
t	triplet (spectra)
^{t}Bu	tertiary butyl
TES	triethylsilyl
Tf	triflyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
tol	tolyl
Ts	tosyl
UV	ultraviolet
V	volume
VNS	vicarious nucleophilic substitution
wt%	weight percent

Chapter 1

Introduction and General Summary

Organic synthesis has supported our modern life through the production of a variety of valuable organic compounds used as pharmaceuticals, agrochemicals, and materials. The development of new transformation reactions, which can make the synthetic process of such compounds more efficient, thus contributes to creating sustainable society. Especially, transition metal-catalyzed cross-coupling reactions have attracted much attention and found applications in a wide variety of scientific areas.[1] Conventional methods for the construction of carbon–carbon and carbon–heteroatom bonds usually rely on the use of aryl halides as carbon electrophiles to couple with diverse nucleophiles. However, the preparation of haloarenes is not only laborious and costly, but halogen-based cross-coupling reactions are also often accompanied by the emission of environmentally harmful byproducts. From a practical perspective, the inevitable sub-ppm contamination with halogen-containing waste may critically decline the performance of the resulting materials.[2] These shortcomings render other electrophiles attractive alternatives to take part in cross-coupling reactions as coupling partners. In this context, several functionalized arenes such as phenol derivatives, diazo compounds, ammonium salts, and others have been successfully used as starting materials.[3]

The author focused on the use of nitroarenes. Despite their facile preparation and functionalization, existing methods for denitrative conversion have seldom been utilized due to their difficulty and lack of practicality. Besides, not only aromatic but also aliphatic nitro compounds are under a similar situation: a nitro group enables fluent construction of complex tertiary alkyl skeletals, whose application in synthetic chemistry is not still matured. New methodologies for practical denitrative transformations would therefore endow nitro compounds with extra synthetic values. The uniqueness of organic nitro compounds should be now revisited.

1. Nitroarenes

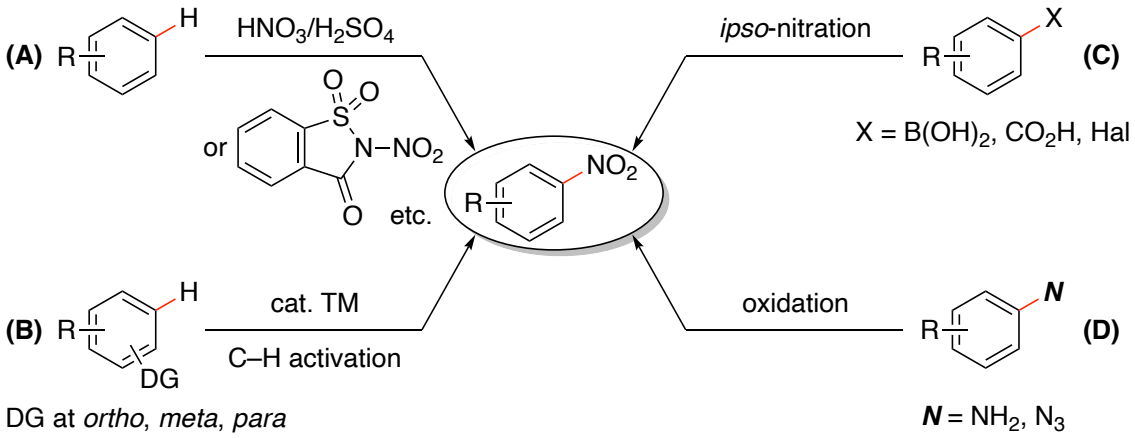
1-1. Preparation of nitroarenes

Nitroarenes are classically synthesized *via* electrophilic nitration of aromatic compounds both on industrial and laboratory scales (Scheme 1-1, A).[4] The use of mixed acid consisting of sulfuric acid and nitric acid has long been the fundamental method for this type of nitration. Although this would be highly reliable, alternative methods have been studied seeking for milder and more practical reaction conditions. Katayev recently reported bench-stable *N*-nitrosaccharin as an efficient and recyclable nitrating reagent, which can be used under mild and neutral conditions.[5]

The conversion of Ar–H to Ar–NO_2 can also be achieved *via* transition metal-catalyzed C–H activation (Scheme 1-1, B).[6] Various arenes can be nitrated at *ortho*, *meta*, and *para* positions of directing groups with excellent site-selectivity induced by the aid of the catalyst.

Ipso-nitration of pre-functionalized arenes is another practical method to obtain nitroarenes site-specifically (Scheme 1-1, C).[7] Aryl (pseudo-)halides,[7b,7c] carboxylic acids,[7d] and boronic acids[7e–7g] are efficiently transformed into the corresponding nitro aromatics, whereas the oxidation of aryl azides[8a] and anilines[8b] would be the most straightforward way (Scheme 1-1, D).

Scheme 1-1. Preparation of nitroarenes.

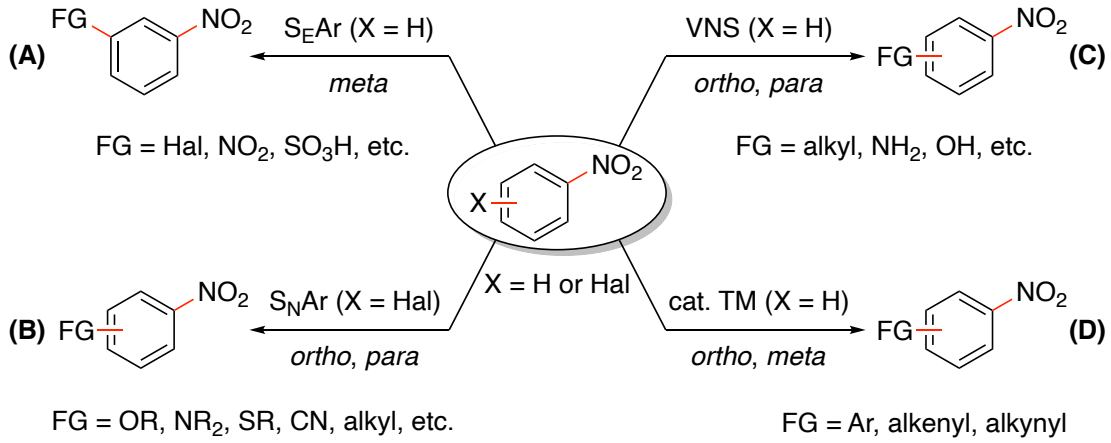


1-2. Modification of nitroarenes

Due to a highly electron-withdrawing character of nitro functionality, nitroarenes can be further functionalized in a site-selective manner. In addition to the conventional S_EAr reactions for *meta*-functionalization, *ortho* and *para* positions would be replaced by nucleophiles *via* S_NAr and VNS reactions (Scheme 1-2, A–C).[9]

Although a nitro group is usually reluctant to act as a directing group, there are some reports on transition metal-catalyzed and directed *ortho*- and *meta*-functionalization of nitroarenes (Scheme 1-2, D).[10] After Fagnou reported the pioneering Pd-catalyzed *ortho*-C–H arylation of nitroarenes with bromoarenes in 2008,[10b] site-selective arylation,[10c–10e] alkenylation,[10f] and alkynylation[10g,10h] have been achieved by Pd or Rh catalyst.

Scheme 1-2. Modification of nitroarenes.



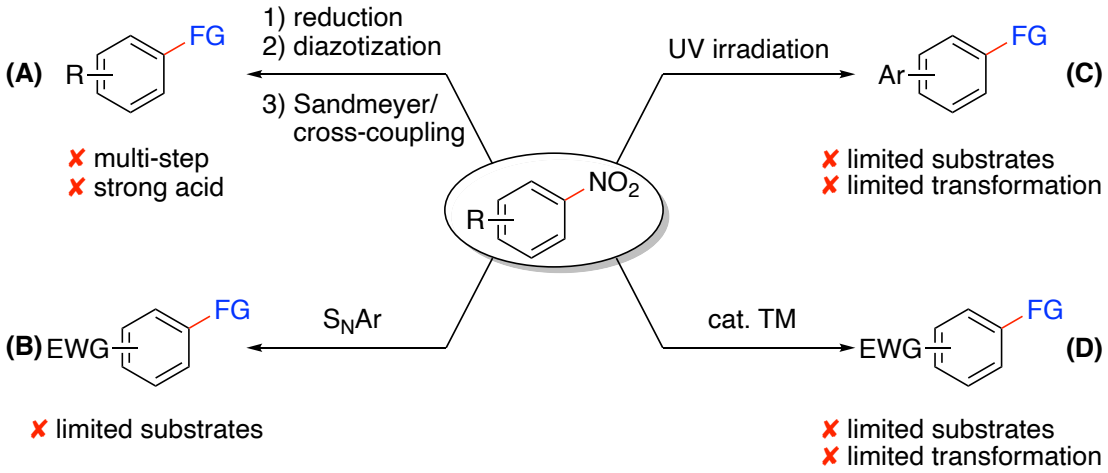
1-3. Denitrative transformation of nitroarenes

Nitroarenes with various substitution patterns could be thus prepared with ease. Though the substitution of the nitro group on aromatic rings by other functional groups accordingly offers an efficient approach to diverse molecules, such denitrative transformations are typically difficult because the facile reduction of nitro group often competes. This affords *N*-containing arenes such as nitroso compounds, hydroxylamines, and anilines, whose C–N bonds are also inert.[11] Hence, classical denitration of nitroarenes was performed by a three-step sequence composed of reduction to anilines, diazotization, and Sandmeyer/cross-coupling reactions, which severely lacks efficiency and functional group tolerance (Scheme 1-3, A).[3b,12] Denitrative S_NAr would be a powerful option, which is applicable only to nitroarenes bearing at least one additional electron-withdrawing group and carried out under harsh conditions to form high-energy Meisenheimer complexes (Scheme 1-3, B).[13] π-Extended nitroarenes such as nitronaphthalene, nitrobiphenyl, and nitroazulene are known to undergo UV-assisted C–NO_2 bond cleavage, whereas monocyclic nitroarenes are almost inert (Scheme 1-3, C).[14]

Recent progress in this transformation was brought by transition metal catalysis

(Scheme 1-3, D).[15] In 2011, Wu established the first Rh-catalyzed denitrative etherification of nitroarenes.[15a] Following this work, catalytic denitration was also achieved by Cu, Pd, and Ni catalysts, realizing etherification,[15b,15c,15d] thioetherification,[15e] and sulfonylation.[15f] These methods, however, suffer from limited substrate scope as well: highly electron-deficient nitroarenes were readily denitrated, while electron-donating substituents generally inhibited the reaction. This would assumingly be derived from Ar–NO_2 functionalizations in an S_NAr manner with transition metal catalysts acting as mere Lewis acids, though some reports insist on the involvement of oxidative addition of Ar–NO_2 bonds to the transition metal center.

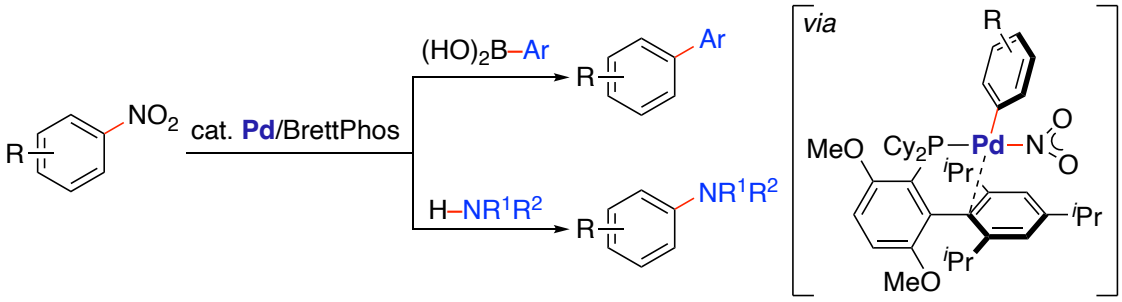
Scheme 1-3. Denitrative transformation of nitroarenes.



In 2017, the author's group reported the first Pd-catalyzed Suzuki–Miyaura cross-coupling of nitroarenes (Scheme 1-4).[16a] It was experimentally and theoretically illustrated that this reaction proceeds *via* the oxidative addition of Ar–NO_2 bonds to Pd(0) bearing BrettPhos as a supporting ligand. Owing to the generality of this elementary step, a wide range of nitroarenes is applicable. Using the same catalytic system, the Buchwald–

Hartwig amination was also demonstrated.[16b]

Scheme 1-4. Pd/BrettPhos-catalyzed Suzuki–Miyaura coupling and Buchwald–Hartwig amination of nitroarenes.



2. Nitroalkanes

2-1. Preparation of nitroalkanes

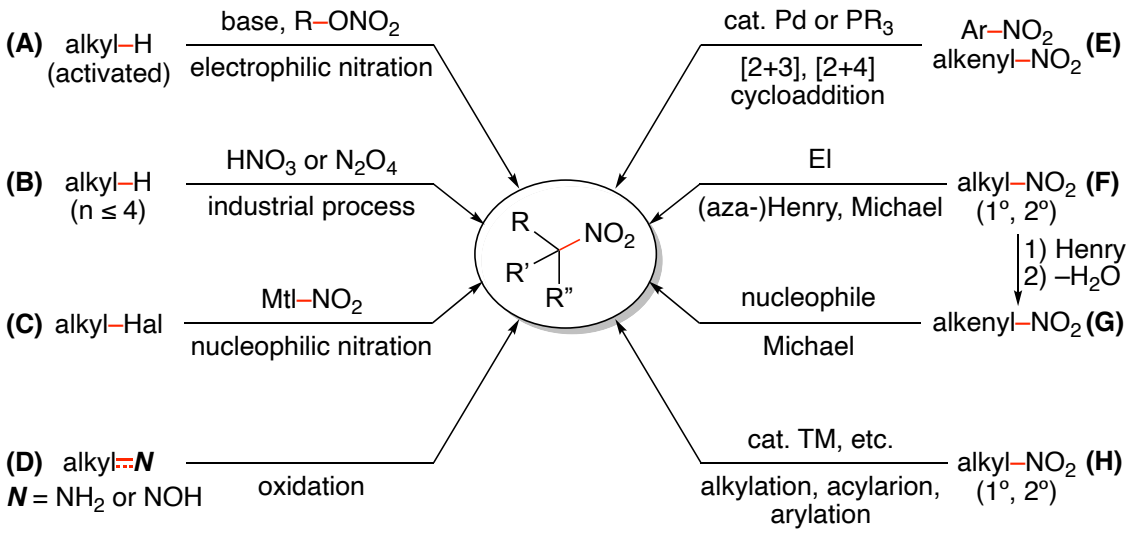
In contrast with facile C(sp^2)–H nitration, C(sp^3)–H nitration is usually difficult[17] unless the bond is located at an activated benzylic or α-carbonyl position, which can be electrophilically nitrated by alkyl nitrates (Scheme 1-5, A).[18] Industrially, on the other hand, lower nitroalkanes ($n \leq 4$) are massively synthesized by nitration of fossil fuels by nitric acid or nitrogen peroxide and are thus inexpensive (Scheme 1-5, B),[19] since they are largely consumed as engine fuels. Conventional methods to obtain higher nitroalkanes include nucleophilic substitution of haloalkanes by metal nitrites[20] and oxidation of amines or oximes[21] (Scheme 1-5, C and D). It is notable that recent prosperity of Pd- or phosphine-catalyzed [2+3]- or [2+4]-cycloaddition would afford complex nitroalkanes in a single step sometimes with enantioselectivity (Scheme 1-5, E).[22]

2-2. Modification of nitroalkanes

Primary and secondary nitroalkanes possess highly acidic α-proton because of

the strongly electron-withdrawing nitro group, which enables α-functionalization of nitroalkanes through deprotonation followed by the reaction with electrophiles under mild conditions. The representative examples are the Henry (nitroaldol) reactions with aldehydes or ketones,[23] the aza-Henry (nitro-Mannich) reaction with imines,[24] and the Michael addition across electron-deficient olefins[25] (Scheme 1-5, F). Furthermore, the Henry reaction delivers β-hydroxynitroalkanes, whose hydroxyl group would be easily replaced *via* a sequence of dehydration and the Michael addition, resulting in net α,β-difunctionalization of nitroalkanes (Scheme 1-5, G).[25b,26] Other electrophiles such as alkyl and acyl halides normally fail to functionalize the α-position of nitroalkanes due to competitive *O*-alkylation and *O*-acylation. Specific reagents and reaction conditions have been developed to avoid such side-reactions.[27] Besides, α-alkylation was competently performed under transition metal-catalyzed conditions.[28] α-Arylation has also been accomplished by several methods using aryl halides, aryl bismuth compounds, aryl iodanes, and so on (Scheme 1-5, H).[29]

Scheme 1-5. Preparation and modification of nitroalkanes.

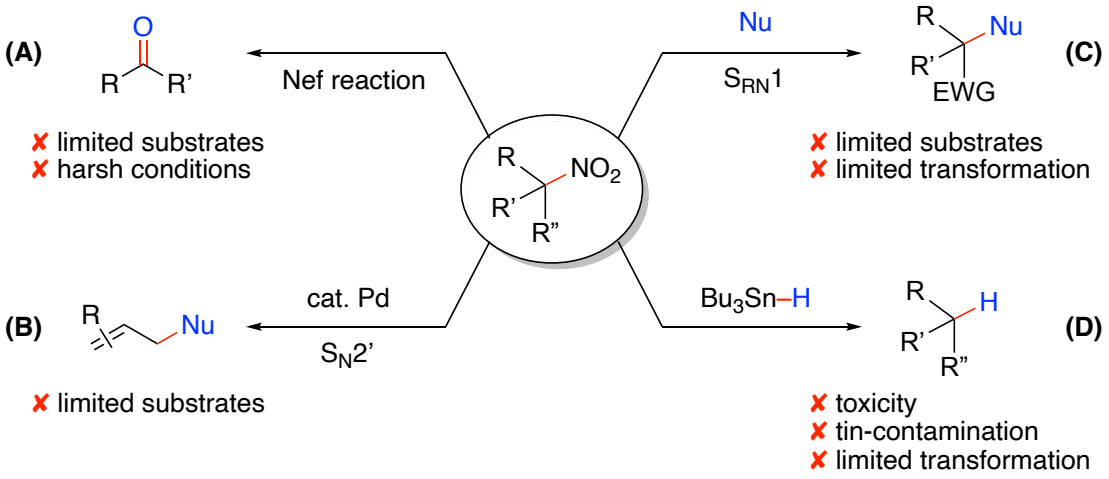


2-3. Denitrative transformation of nitroalkanes

Considering high acidity of nitrous acid, a NO_2 group is expected to be a good leaving group. A denitrative conversion of nitroalkanes is, however, not so easy as nucleophilic substitution of haloalkanes because of their inverse polarity: nitroalkanes have nucleophilic α-carbon while haloalkanes have electrophilic α-carbon. Substitution of a nitro functionality has been thus developed by using different strategies. The Nef reaction can transform primary and secondary nitroalkanes into carbonyl compounds (Scheme 1-6, A).[30] A Pd-catalyst was found to be effective to replace a nitro group by various nucleophiles, in which only allylic nitro compounds were applicable (Scheme 1-6, B).[31] Nitroalkanes bearing another electron-withdrawing group at the α-carbon can undergo the $S_{RN}1$ reaction with some nucleophiles (Scheme 1-6, C).[32]

Tin hydride, especially tributyltin hydride, has been utilized for the cleavage of C–NO_2 bonds in nitroalkanes to afford the corresponding alkyl radicals, which typically capture a hydrogen atom of tin hydride to form the parent alkanes (Scheme 1-6, D).[33] Due to its reliability and mild reaction conditions required, a series of nitro-induced functionalizations and tin-mediated reductive denitration reactions was regarded as a powerful method to construct complex molecules. The use of tin hydride yet suffers from some drawbacks: toxicity of organotin compounds, contamination of tin-containing byproducts, necessity of freshly distilled tin-hydride for high reproducibility, and limited use of generated radicals. Although synthetic chemists have devised several alternatives to solve some of them, practical methods for denitration are still of high demand.[34]

Scheme 1-6. Denitrative transformation of nitroalkanes.



3. Overview of this Thesis

As summarized above, there are many advantages in the preparation and modification of organic nitro compounds. The nitro group induces unique reactivity, while making its removal complicated. To exploit full potential of nitro compounds in organic synthesis, practicable denitrative transformations should be in hand of synthetic chemists.

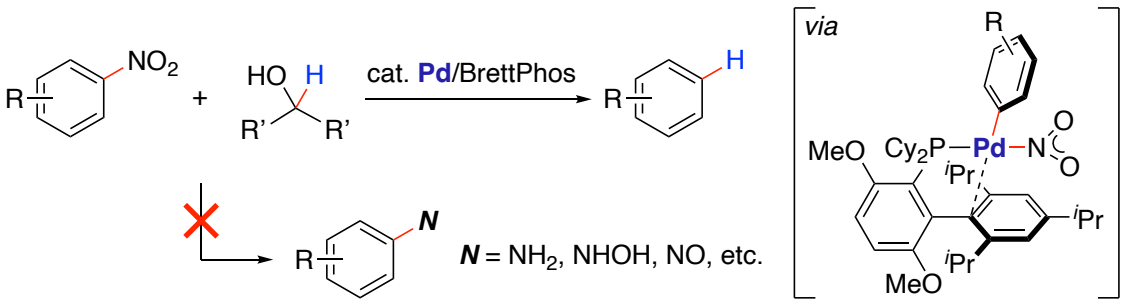
In this context, the author was engaged in the development of new catalytic denitrative transformations of organic nitro compounds. The first approach was the use and refinement of the established Pd-based catalytic system to explore its potential in the functionalization of Ar–NO_2 bonds. A widely accepted catalytic cycle for Pd-catalyzed cross-couplings has now been extended to include nitroarenes as electrophiles, which significantly increases substrate generality and diversity of nucleophiles to form new bonds. Starting with the pioneering reports by the author's group, the Pd-catalyzed denitration protocol is now becoming a fundamental strategy for the functionalization of nitroarenes.[35]

In the course of the research above, the author devised the use of alcohols as a non-toxic and easy-to-handle reductants for nitro compounds instead of tin hydrides. This concept was demonstrated by catalytic reduction of nitroalkanes, in which alkyl radicals were efficiently formed and applied in several transformations.

3-1. Pd-catalyzed reductive denitration of nitroarenes (Chapter 2)

In Chapter 2, the author describes the reductive denitration of nitroarenes (Scheme 1-7). As mentioned above, the reduction of nitroarenes usually provides nitrogen-containing products such as amines, hydroxylamines, and nitroso compounds since their low-lying LUMO usually spreads over the NO_2 group. Substitution of the whole nitro functionality by hydrogen herein was achieved by using the Pd/BrettPhos catalyst in combination with ^{i}PrOH as a mild reductant. The efficiency of the denitration turned out to strongly depend on the nature of the alcohol reductant due to uncatalyzed side reactions. Mechanistic studies revealed that the catalytic cycle involves β-hydride elimination from a Pd alkoxide intermediate.

Scheme 1-7. Reductive denitration of nitroarenes (Chapter 2).

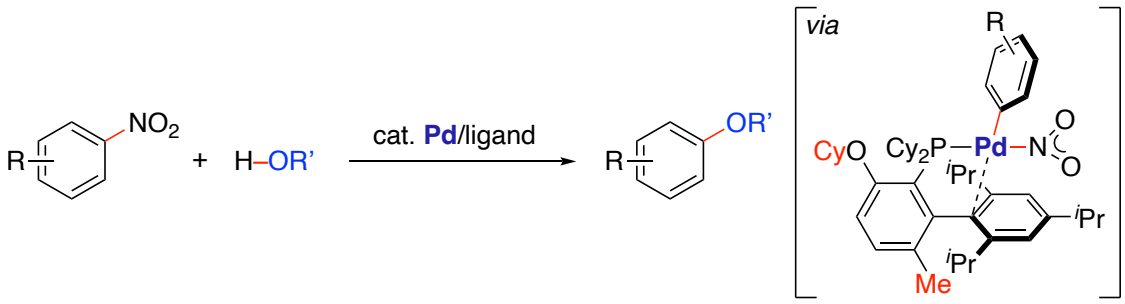


3-2. Pd-catalyzed etherification of nitroarenes (Chapter 3)

Described in Chapter 3 is Pd-catalyzed etherification of nitroarenes (Scheme1-

8). As mentioned above, the use of alcohol nucleophiles resulted in the denitrative hydrogenation *via* rapid *β*-hydride elimination, whereas the formation of C–O bonds *via* reductive elimination could also be potentially feasible. A newly designed ligand bearing both conformationally rigid and flexible moieties was the key to facilitate the reductive elimination while maintaining the activity toward the oxidative addition. Theoretical calculations also indicated the contribution of unique dynamic behavior of the new ligand to the high catalytic performance.

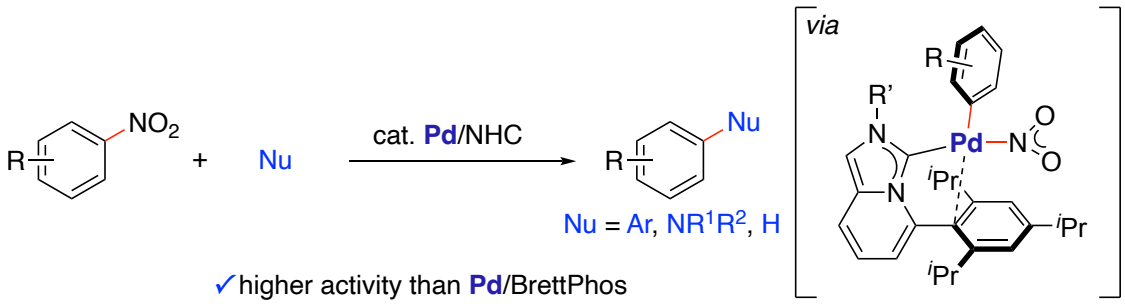
Scheme 1-8. Pd-catalyzed etherification of nitroarenes (Chapter 3).



3-3. Pd/NHC-catalyzed cross-coupling reactions of nitroarenes (Chapter 4)

The Pd/phosphine catalysts applied to the cross-coupling of nitroarenes so far had a general drawback of high catalyst loadings (≥ 5 mol%). Chapter 4 demonstrates a rationally designed Pd/NHC catalytic system, which outperformed the original catalysts in the Suzuki–Miyaura coupling, Buchwald–Hartwig amination, and reductive denitration of nitroarenes (Scheme 1-9). The higher activity of the new catalysts was investigated both experimentally and theoretically.

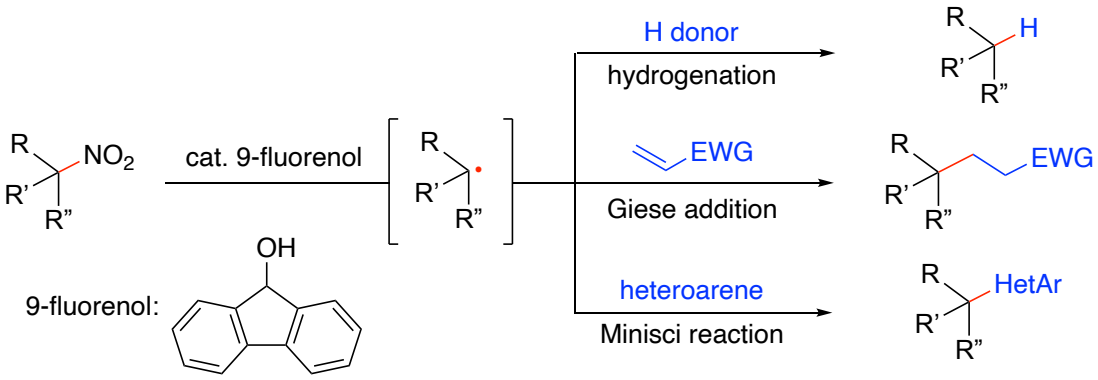
Scheme 1-9. Pd/NHC-catalyzed cross-coupling reactions of nitroarenes (Chapter 5).



3-4. Catalytic radical generation from nitroalkanes (Chapter 5)

In Chapter 5, the author exhibits a new catalytic protocol for denitrative radical generation from nitroalkanes (Scheme 1-10). The use of 9-fluorenol as an electron transfer catalyst induced efficient C–NO_2 bond cleavage. Compared to conventional methods using toxic tin hydride, the present reaction conditions are more practical in terms of safety, cost, and experimental simplicity. The formed alkyl radicals can be involved in hydrogenation, the Giese addition reaction, and the Minisci reactions, expanding the synthetic utility of nitroalkanes.

Scheme 1-10. Catalytic radical generation from nitroalkanes (Chapter 10).



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Chapter 2

Reductive Denitration of Nitroarenes

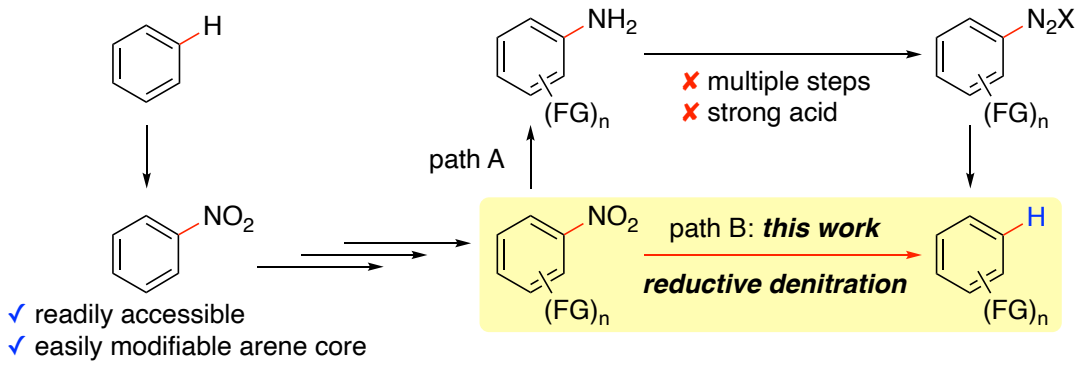
The Pd-catalyzed reductive denitration of nitroarenes has been achieved *via* a direct cleavage of the C–NO_2 bonds. The catalytic conditions reported exhibit a broad substrate scope and good functional-group compatibility. Notably, the use of inexpensive propan-2-ol as a mild reductant suppresses the competitive formation of anilines, which are normally formed by other conventional reductions. Mechanistic studies have revealed that alcohols serve as efficient hydride donors in this reaction, possibly through β-hydride elimination from palladium alkoxides.

Introduction

The reductive denitration of nitroarenes *via* a cleavage of the C–NO_2 bonds is a challenging transformation in organic synthesis. Contrary to the well-established nitration of arenes,[1] examples for the reverse reaction, *i.e.*, the reductive denitration, remain scarce. Previously reported reactions are only applicable to specific substrates, such as highly electron-deficient and amino-substituted nitroarenes, and suffer from low yields of the parent arenes and/or the formation of side products.[2] The difficulties associated with the reductive denitration can be attributed to the inherent reactivity of the nitro group: under reducing conditions nitroarenes are usually converted into anilines and/or other reduced species, such as nitroso compounds and hydroxylamines.[3,4] As a result, the removal of nitro groups on aromatic rings commonly requires the formation of the corresponding anilines and two additional synthetic manipulations, namely diazotization followed by a Sandmeyer-type reaction (Scheme 2-1, path A).[5] Unfortunately, these processes may suffer from a limited substrate scope, as the use of strong acids largely diminishes the functional-group tolerance. Therefore, a more straightforward and general method for the reductive denitration (path B) remains highly attractive. In the chemical industry, the derivatization of fossil aromatic resources often starts with a nitration reaction,[6] and a wide range of nitroarenes is accordingly commercially available from selective nitration reactions followed by S_NAr/S_EAr/VNS and/or *ortho*-selective C–H functionalization reactions,[7,8] which proceed site-selectively thanks to the strong electronic effect of the nitro group. A nitration and decoration sequence for arenes, followed by a single-step denitration reaction under mild conditions, would thus represent an efficient and practical pathway to a diverse range of functionalized arenes starting from simple arenes (Scheme 2-1).

The author has recently reported Pd-catalyzed C–C and C–N bond-forming coupling reactions using nitroarenes as electrophiles.[9,10] Notably, these reactions proceed *via* the unprecedented oxidative addition of the Ar–NO_2 bond to Pd(0), where the reduction of the nitro group does not compete. These results inspired the author to trap the oxidative adduct with an appropriate hydride source to achieve the single-step denitration. Herein, the author reports a denitration of nitroarenes that bypasses for the first time the reduction to anilines followed by diazotization and a Sandmeyer-type reaction, using secondary alcohols as sources of the reducing hydride.

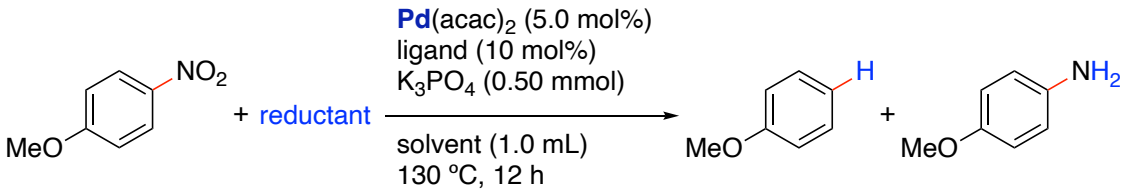
Scheme 2-1. Synthesis of multi-substituted benzenes *via* the reductive denitration of nitroarenes.



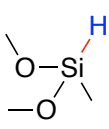
Results and discussion

Initially, the author chose hydrosilanes as hydride sources for the denitration of nitroarenes, given their use in a number of metal-catalyzed defunctionalization reactions.[11] Thus, 4-nitroanisole (**1a**, 0.20 mmol) in DME (1.0 mL) was treated for 12 h at 130 ºC with various hydrosilanes in the presence of $Pd(acac)_2$ (5.0 mol%), BrettPhos (**L1**)[12] (10 mol%), and K_3PO_4 (0.50 mmol). Dimethoxymethylsilane (**2a**) and triethylsilane (**2b**) predominantly afforded undesired *p*-anisidine (**3'a**) through the reduction of the nitro group (Table 2-1, entries 1 and 2), whereas bulkier triisopropylsilane (**2c**) furnished desired anisole (**3a**), albeit only in 3% yield (entry 3). The author then focused on the use of alcohols as hydride sources. To the author's delight, **3a** was obtained in 35% yield with benzhydrol (**2e**), while benzylalcohol (**2d**) generated a trace amount of **3a** (entries 4 and 5). Further optimization studies indicated that a benzhydrol derivative that bears an electron-donating substituent **2g** generates **3a** more effectively than that carrying an electron-withdrawing group **2f** (entries 6 and 7). Sterically demanding dimesitylmethanol (**2h**) significantly improved the yield of **3a** (≤ 60%), while the formation of **3'a** was suppressed (entry 8). Remarkably, the use of propan-2-ol (**2i**)[13] as a hydride source afforded the best yield of **3a** (67%), accompanied by a mere trace amount of **3'a** (entry 9). The formation of the targeted product was slightly improved in 1,4-dioxane (entry 10). Moreover, other Buchwald-type ligands (**L2**–**L5**)[14] were investigated, but the performance of **L1** was clearly superior (entries 10–14). Hence, the author concluded that the conditions shown in entry 10 represent the optimized reaction conditions for this system.

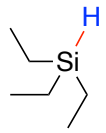
Table 2-1. Optimization studies for the reductive denitration of **1a**.



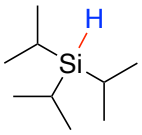
1a 0.20 mmol | **2** 0.30 mmol | **3a** | **3'a**



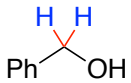
2a



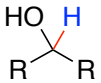
2b



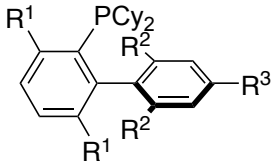
2c



2d



R = Ph (**2e**)
3-$F_3CC_6H_4$ (**2f**)
4-$MeOC_6H_4$ (**2g**)
2,4,6-$Me_3C_6H_2$ (**2h**)
Me (**2i**)



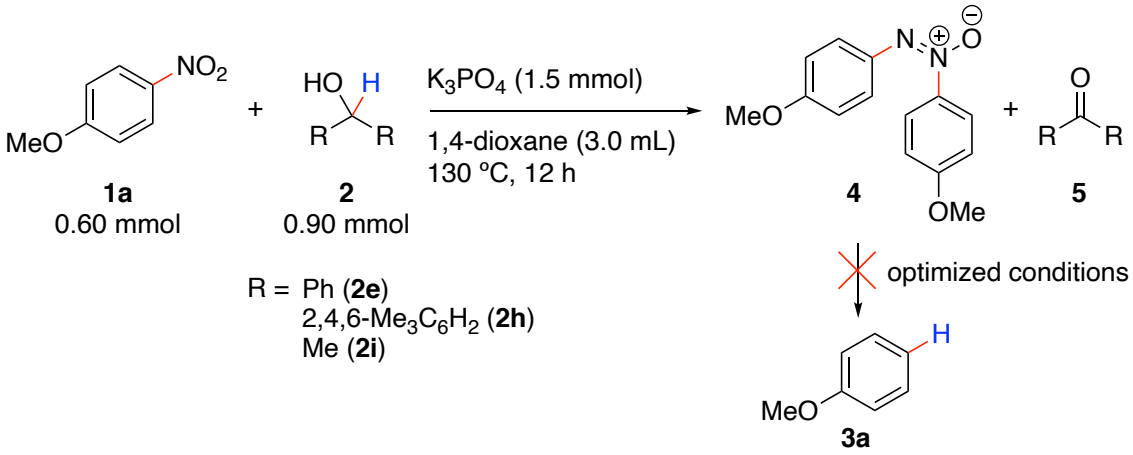
R^1	R^2	R^3	
OMe	^{i}Pr	^{i}Pr	BrettPhos (**L1**)
H	^{i}Pr	^{i}Pr	XPhos (**L2**)
H	O^{i}Pr	H	RuPhos (**L3**)
H	OMe	H	SPhos (**L4**)
H	NMe_2	H	CPhos (**L5**)

entry	reductant	ligand	solvent	yield (%)	
				3a[a]	**3'a**[b]
1	**2a**	**L1**	DME	<1	10
2	**2b**	**L1**	DME	~1	58
3	**2c**	**L1**	DME	3	<1
4	**2d**	**L1**	DME	~1	<1
5	**2e**	**L1**	DME	35	3
6	**2f**	**L1**	DME	<1	6
7	**2g**	**L1**	DME	38	5
8	**2h**	**L1**	DME	60	1
9	**2i**	**L1**	DME	67	~1
10	**2i**	**L1**	1,4-dioxane	68	~1
11	**2i**	**L2**	1,4-dioxane	14	~1
12	**2i**	**L3**	1,4-dioxane	13	~1
13	**2i**	**L4**	1,4-dioxane	6	~1
14	**2i**	**L5**	1,4-dioxane	7	~1

[a] GC yields determined using *n*-$C_{13}H_{28}$ as an internal standard.
[b] GC yields estimated based on the yield of *p*-acetaniside (**3"a**) after treatment of crude reaction mixtures with acetic anhydride.

For comparison, control experiments were undertaken in the absence of the catalyst, using various alcohols, which resulted in the formation of azoxy compound **4** as a major product (Table 2-2).[15] The reaction of **4** with **2i** under the optimized conditions did not give **3a**, showing that it was not a reaction intermediate of the present reductive denitration. The formation of **4** depended significantly on the nature of the alcohol employed: **2e** furnished **4** in high yield (86%), whereas sterically hindered **2h** reacted with **1a** more slowly, while **2i** completely prevented this side reaction.

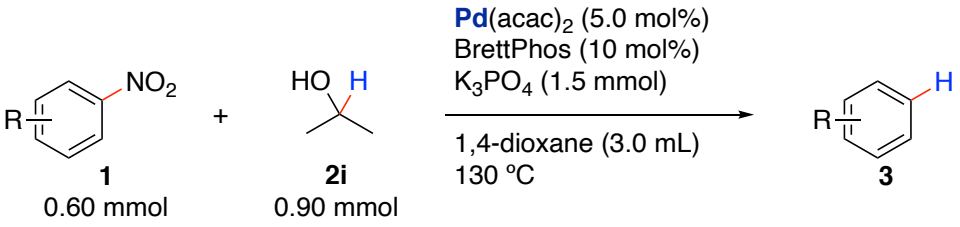
Table 2-2. Control experiments in the absence of Pd catalyst.

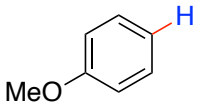


entry	**2**	conversion of **1a** (%)	isolated yield (%)	
			4	**5**
1	**2e**	>95	86	91
2	**2h**	82	77	76
3	**2i**	<1	<1	—

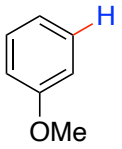
To assess the versatility of this denitration reaction, the author probed a wide range of nitroarenes under the optimized conditions (Scheme 2-2). Electron-rich nitroanisoles were readily converted to the corresponding anisole (**3a**–**3c)** in good to excellent yield. Interestingly, nitro groups in proximity to the methoxy substituent reacted much faster and delivered the product in higher yields. Such rate-enhancement was not observed with 2-nitrotoluene to afford toluene (**3d**) after 8 h in 87% yield estimated by GC analysis. This trend is consistent with the denitration of 2,4-dinitroanisole, which selectively furnished 4-nitroanisole (**3e**) in 69% yield. Alkyl, silyl, and phenyl substituents did not interfere with the reaction and furnished arenes **3f**–**3j** in good yields. 4-Fluorobiphenyl (**3k**) and 4-trifluoromethybiphenyl (**3l**) were obtained from the denitration of the corresponding nitroarenes in 90% and 93% yields, respectively. Nitroarenes bearing protected carbonyl groups or an alkoxycarbonyl functionality were also denitrated in good yields (**3m**–**3o**); in the latter case, bulky dimesitylmethanol (**2h**) was employed as the reductant in order to avoid a potential ester-exchange reaction. An electron-deficient, sulfonyl-substituted nitrobenzene was also successfully denitrated, although longer reaction times were required to generate **3p**. Phenoxy and carbazolyl moieties, which were easily introduced into the nitroarene core *via* S_NAr reactions, were also compatible with the applied reaction conditions (**3q** and **3r**). π-Extended nitroarenes, including nitronaphthalenes and nitroanthracene, furnished the corresponding polyaromatics (**3s**–**3u**) in moderate to good yields.

Scheme 2-2. Substrate scope for the reductive denitration of nitroarenes.

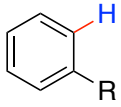




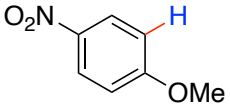
3a, 62%[a] (12 h)



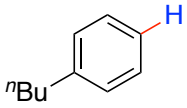
3b, 71%[a] (8 h)



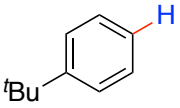
3c, R = OMe, 96%[a] (4 h)
3d, R = Me, 87%[a] (8 h)



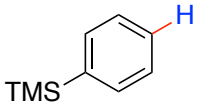
3e, 69%[b,c] (2 h)



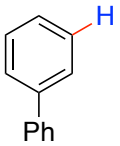
3f, 83%[a] (4 h)



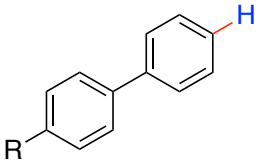
3g, 87%[a] (12 h)



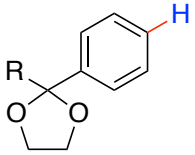
3h, 82%[a] (12 h)



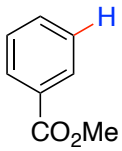
3i, 85%[b] (4 h)



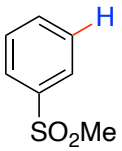
3j, R = H, 73%[b] (4 h)
3k, R = F, 90%[b] (4 h)
3l, R = CF_3, 93%[b] (4 h)



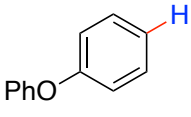
3m, R = H, 92%[a] (4 h)
3n, R = Me, 89%[a] (4 h)



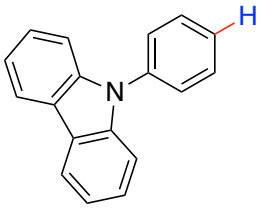
3o, 84%[a,d] (2 h)



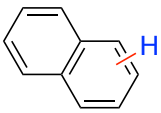
3p, 61%[b] (24 h)



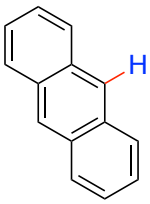
3q, 78%[b] (24 h)



3r, 77%[b] (4 h)



3s, *α*, 87%[a] (4 h)
3t, *β*, 59%[a] (12 h)

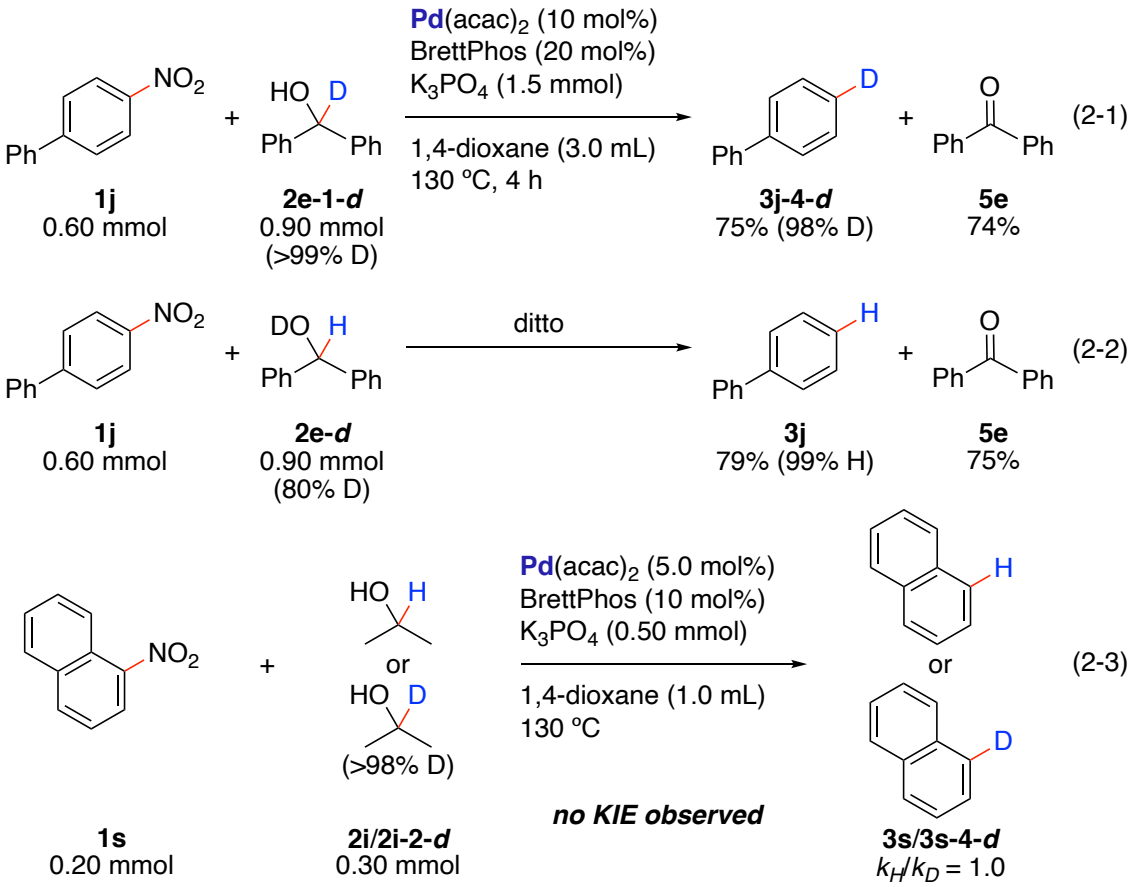


3u, 52%[b] (8 h)

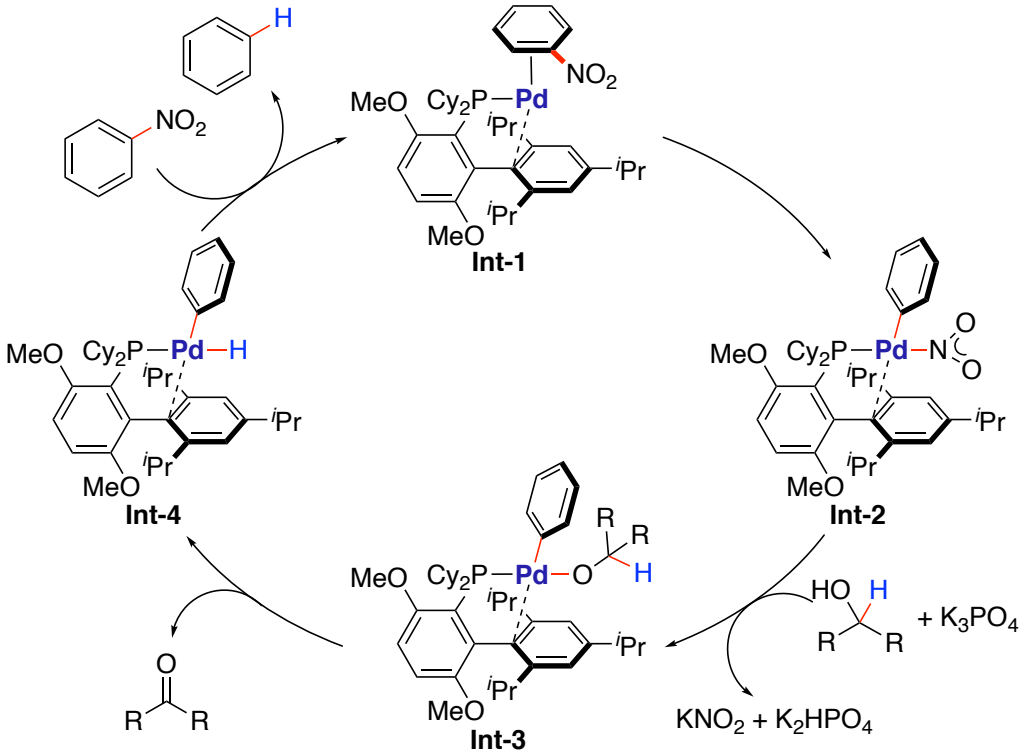
[a] GC yields.
[b] Isolated yields.
[c] The reaction was undertaken in 1.0 mmol scale and 1.0 mmol of **2i** was used. The product was accompanied by 8.3% of 2-nitroanisole (**3e'**).
[d] **2h** was used instead of **2i**.

In order to investigate the reaction mechanism underlying this Pd-catalyzed reductive denitration, the author carried out deuterium-labeling experiments. The use of benzhydrol deuterated at the benzylic position (Ph_2CDOH, **2e-1-*d***) as the reductant resulted in the replacement of the nitro group of **1j** by deuterium (97%) and the generation of benzophenone (**5e**) in 74% yield, indicating the involvement of *β*-hydride elimination (Eq. 2-1). Consistently, the use of Ph_2CHOD (**2e-*d***) as the reductant did not give any deuterated product (Eq. 2-2). These reactions giving both arene **3j** and ketone **5e** in comparable yields also support a mass-balance of the transformation. Furthermore, the author did not observe any KIE when the denitration of **1s** was independently examined using propan-2-ol (**2i**) or deuterated propan-2-ol-2-*d* (**2i-2-*d***) (Eq. 2-3). Based on these results and the author's previous reports,[9] the author postulates a plausible catalytic cycle shown in Scheme 2-3. The initial formation of a *π*-complex (**Int-1**) between the nitroarenes and Pd(0) should be followed by the oxidative addition of the C–NO_2 bond to give **Int-2**. The nitrite group on the Pd center would subsequently be substituted by an alkoxide ligand to generate **Int-3**, and ensuing *β*-hydride elimination would afford arylpalladium hydride **Int-4**. Subsequent reductive elimination would then deliver the corresponding arene and regenerate the Pd(0) catalyst. The author's previous studies[9] suggest that a hemilabile coordination of the methoxy group of BrettPhos may not play any important roles throughout the catalytic cycle. The KIE experiment implied that the *β*-hydride elimination and the reductive elimination are not the rate-determining steps under the stipulated reaction conditions, and that the former is much faster than alternatively possible C–O bond-forming reductive elimination.[16] The author can not discuss about a rate-determining step at this stage with available data. Some reactivity differences observed with electronically different nitroarenes as well as the author's

previous theoretical studies[9a] may support that the oxidative addition is rate-determining. The rate-acceleration observed with 2-nitroanisole may be derived from the methoxy group serving as a directing group to promote the oxidative addition.



Scheme 2-3. Plausible catalytic cycle for the reductive denitration of nitroarenes.



Conclusion

In summary, the author has developed the first example of a palladium-catalyzed reductive denitration of nitroarenes. The combination of the Pd/BrettPhos catalyst and appropriate reductants shows good functional-group tolerance and affords denitrated arenes in good to excellent yields.

Experimental section

General remarks compatible to all the experimental parts in the present Thesis.

All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique under an argon atmosphere or in a glovebox under a nitrogen atmosphere. MPLC was performed using Kanto Chemical silica gel 60 (spherical, 40–50 μm), Biotage® SNAP Ultra, or Biotage® Sfär Silica HC D. Analytical TLC was performed on Merck TLC silica gel 60 F_{254} (0.25 mm) plates. Visualization was accomplished with UV light (254 nm) and/or an alkaline $KMnO_4$ aq. followed by heating. PTLC was performed on Supelco® PLC silica gel 60 F_{254} (0.5 mm) plates.

Proton, deuterium, carbon, fluorine, and phosphorus NMR spectra (^{1}H, ^{2}D, ^{13}C, ^{19}F, and ^{31}P NMR) were recorded on a JEOL ECS-400 (^{1}H NMR, 400 MHz; ^{2}D NMR, 61MHz; ^{13}C NMR, 101 MHz; ^{19}F NMR, 376 MHz; ^{31}P NMR, 162 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR, $CDCl_3$ at 7.26 ppm, 1,4-dioxane-d_8 at 3.50 ppm, C_6D_6 at 7.16 ppm, acetone-d_6 at 2.05 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm, C_6D_6 at 128.0 ppm). In the ^{19}F NMR, C_6F_6 (at –162.0 ppm) was used as the internal standard. NMR data are reported as follows: chemical shift, multiplicity, coupling constants (Hz), and integration. High-resolution mass spectra were obtained with Thermo Fisher Scientific MS: Exactive Plus HPLC: UltiMate 3000 (ESI) and JEOL JMS-SX102A (EI). GC analysis was performed on a Shimadzu GC-2014 equipped with a BP1 column (SGE Analytical Science, 0.25 mm × 30 m, pressure = 149.0 kPa, detector = FID, 290 ºC) with helium gas as a carrier. MPLC was performed with a Yamazen EPLC-W-Prep 2XY or SHOKO SCIENTIFIC Purif-espoir2. Preparative recycling high performance liquid chromatography (HPLC) was performed with a SHIMADZU LC-6AD (CBM-20A controller, SPD-20A diode array detector, FRC-10A fraction collector) equipped with

COSMOSIL 5SL-II (Nacalai Tesque, 20 mm x 250 mm, spherical, 5 μm). Elemental analyses were performed on a J-Science Micro corder JM10, JM11.

Unless otherwise noted, commercially available chemicals were distilled and degassed before use. When commercially available chemicals were solids, they were used without purification. Anhydrous hexane, toluene, THF, Et_2O, and DCM were purchased from Kanto Chemical and purified by passage through activated alumina under positive argon pressure as described by Grubbs *et al*.[17] Superdehydrated 1,4-dioxane, MeOH, EtOH, ^{i}PrOH, DMSO, DMF, and $CHCl_3$ were purchased from FUJIFILM Wako Pure Chemical, stored in a glovebox, and used without further purification, or used after filtration through basic Al_2O_3 to remove stabilizer BHT (1,4-dioxane, chapter 4). K_3PO_4 was obtained by drying K_3PO_4•nH_2O (from Nacalai Tesque) at 160 ºC for more than 8 h under reduced pressure (<1.0 mmHg) and stored in a glovebox. All the other commercially available reagents were purchased from common sources (*e.g.*, Tokyo Chemical Industry, FUJIFILM Wako Pure Chemical, Sigma-Aldrich, Alfa-Aesar, Nacalai Tesque, etc.).

The crystal was mounted on the CryoLoop (Hampton Research Corp.) with a layer of light mineral oil and placed in a nitrogen stream at 143(1) K. The X-ray structural determination was performed as follows: (i) a Rigaku/Saturn724 CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71070 Å) at 143 K, and processed using CystalClear (Rigaku).[18,19] The structures were solved by direct methods using SHELXT[20] and refined by full-matrix least-square refinement on F^2 with SHELXL.[21] or by direct methods using SIR92[22] and refined by full-matrix least-least-square refinement on F^2 with SHELXL.[21] (ii) Rigaku XtaLAB mini using graphite-monochromated MoKα radiation (λ = 0.71075 Å) at 143 K, and processed using CrystalClear (Rigaku). The

structure was solved by a direct method using SHELXL-97 program [23,24] and refinement was carried out by least-squares methods based on F^2 with all measured reflections using SHELXL-97 program. (iii) Rigaku/Saturn70 CCD diffractionmeter using graphite-monochromated MoKα radiation (λ = 0.71075 Å) at 143 K, and processed using CrystalClear (Rigaku). The structure was solved by a direct method using SHELXL-97 program and refinement was carried out by least-squares methods based on F^2 with all measured reflections using SHELXL-97 program. The non-hydrogen atoms were refined anisotropically. For all structures, the non-hydrogen atoms were refined anisotropically except for DCM molecule. All hydrogen atoms were located on the calculated positions. The function minimized was $[\Sigma w(F_o^2 - F_c^2)^2]$ ($w = 1 / [\sigma^2(F_o^2) + (aP)^2 + bP]$), where $P = (\mathrm{Max}(F_o^2,0) + 2F_c^2) / 3$ with $\sigma^2(F_o^2)$ from counting statistics. The function $R1$ and $wR2$ were $(\Sigma||F_o| - |F_c||) / \Sigma|F_o|$ and $[\Sigma w(F_o^2 - F_c^2)^2 / \Sigma(wF_o^4)]^{1/2}$, respectively.

Chemicals

1h,[25] **1j**,[26] **1k**,[27] **1l**,[27] **1p**,[28] **1r**,[29] and **1t**[30] were prepared according to the literature procedures.

General procedure for Table 2-1. A 4-mL vial was charged with 4-nitroanisole (**1a**) (31 mg, 0.20 mmol), $Pd(acac)_2$ (3.0 mg, 0.010 mmol), ligand (0.020 mmol), and a stirring bar. In a glovebox, K_3PO_4 (106 mg, 0.50 mmol), *n*-$C_{13}H_{28}$ (30 mg, 0.16 mmol), reductant (**2**) (0.30 mmol), and solvent (1.0 mL) were added to the vial. The resulting mixture was taken outside and stirred for 12 h at 130 ºC. After the completion of reaction, two drops of Ac_2O was added to the crude mixture and stirred for one minute to convert *p*-anisidine (**3'a**) into *p*-acetaniside (**3"a**). Yields of anisole (**3a**) and *p*-acetaniside (**3"a**) were determined by GC analysis using calibration curves (Figures S2-1 and S2-2).

Table S2-1. Data for the GC calibration curve obtained using an authentic sample of **3a**.

entry	mass (mg)		x = mass of **3a** / mass of $C_{13}H_{28}$	GC area		y = GC area of **3a** / GC area of $C_{13}H_{28}$
	3a	$C_{13}H_{28}$		**3a**	$C_{13}H_{28}$	
1	3.6	15.1	0.238411	37118	253167	0.146615
2	6.5	15.1	0.430464	68104	232655	0.292724
3	8.2	15.1	0.543046	106066	282095	0.375994
4	11.1	15.1	0.735099	120870	223342	0.541187
5	13.1	15.1	0.867550	145996	228103	0.640043
6	16.3	15.1	1.079470	206587	266600	0.774897

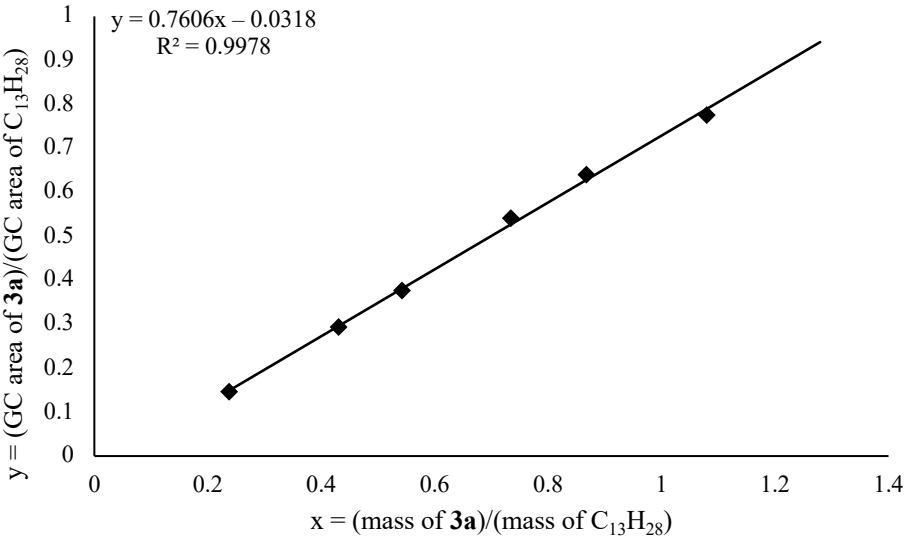


Figure S2-1. GC calibration curve to determine the yield of **3a**.

Table S2-2. Data for the GC calibration curve obtained using an authentic sample of **3"a**.

entry	mass (mg)		x = mass of **3"a** / mass of $C_{13}H_{28}$	GC area		y = GC area of **3"a** / GC area of $C_{13}H_{28}$
	3"a	$C_{13}H_{28}$		**3"a**	$C_{13}H_{28}$	
1	5.9	15.1	0.390728	41788	267924	0.155971
2	9.8	15.2	0.644737	77492	257163	0.301335
3	14.8	15.0	0.986667	91909	192914	0.476426
4	19.8	15.0	1.320000	169056	258554	0.653852
5	24.7	15.1	1.635762	275572	330283	0.834351

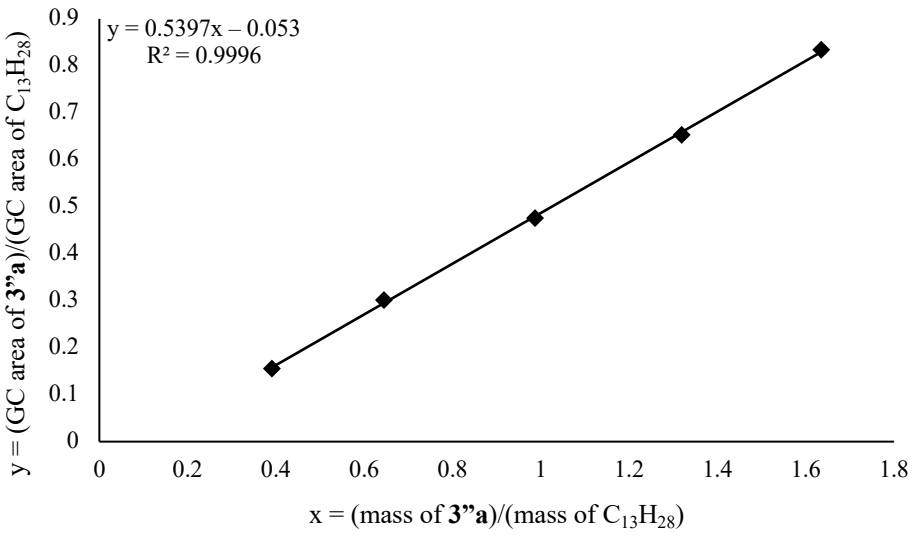
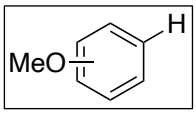
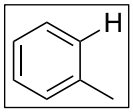


Figure S2-2. GC calibration curve to determine the yield of **3"a**.

General procedure for Scheme 2-2. A 15-mL vial was charged with $Pd(acac)_2$ (9.1 mg, 0.030 mmol), BrettPhos (32 mg, 0.060 mmol), nitroarene (0.60 mmol), and a stirring bar. In a glovebox, K_3PO_4 (0.32 g, 1.5 mmol), propan-2-ol (**2i**) (54 mg, 0.90 mmol), and 1,4-dioxane (3.0 mL) were added to the vial (liquid nitroarenes were added to the vial in a glovebox). The resulting mixture was taken outside and stirred for 1–24 h at 130 ºC. For the reactions of **1a**, **1b**, **1c**, **1f**, **1g**, **1h**, and **1o**, *n*-$C_{13}H_{28}$ (45 mg, 0.25 mmol or 91 mg, 0.49 mmol) was added in a glovebox before the reaction. For the reactions of **1d**, **1m**, **1n**, **1s**, and **1t**, *n*-$C_{10}H_{22}$ (44 mg, 0.31 mmol) was added in a glovebox before the reaction. The reaction of **1e** was undertaken in 1.0 mmol scale. After completion of the reaction, yields of volatile products were calculated by GC analysis of crude mixtures. Otherwise, the mixture was passed through a short pad of silica gel (50 μm) using EtOAc as an eluent, and the filtrate was concentrated in vacuo. The residue was purified by MPLC using Biotage® SNAP Ultra to afford the corresponding arene.



Anisole (3a–3c). The reactions of 4-nitroanisole (**1a**), 3-nitroanisole (**1b**), and 2-nitroanisole (**1c**) (92 mg, 0.60 mmol) was stirred for 12 h, 8 h and 4 h, respectively. The yields of the anisoles 62%, 71% and 96% were determined by GC analysis using the calibration curve (Figure S2-1).



Toluene (3d). The reaction of 2-nitrotoluene (**1d**) (82 mg, 0.60 mmol) was stirred for 8 h. The yield of the title compound (87%) was determined by GC analysis using the calibration curve (Figure S2-3).

Table S2-3. Data for the GC calibration curve obtained using an authentic sample of **3d**.

entry	mass (mg)		$x = \frac{\text{mass of } \mathbf{3d}}{\text{mass of } C_{10}H_{22}}$	GC area		$y = \frac{\text{GC area of } \mathbf{3d}}{\mathbf{3d}}$
	3d	$C_{10}H_{22}$		**3d**	$C_{10}H_{22}$	
1	82.6	43.5	1.898851	424330	235559	1.801374
2	66.3	43.7	1.517162	428791	289403	1.481641
3	55.3	44.3	1.248307	313267	264680	1.183572
4	49.5	43.9	1.127563	380281	352354	1.079257
5	41.1	44.0	0.934091	355787	399078	0.891524
6	27.5	43.7	0.629291	187247	312745	0.598788
7	16.7	44.0	0.379545	104331	287936	0.362340

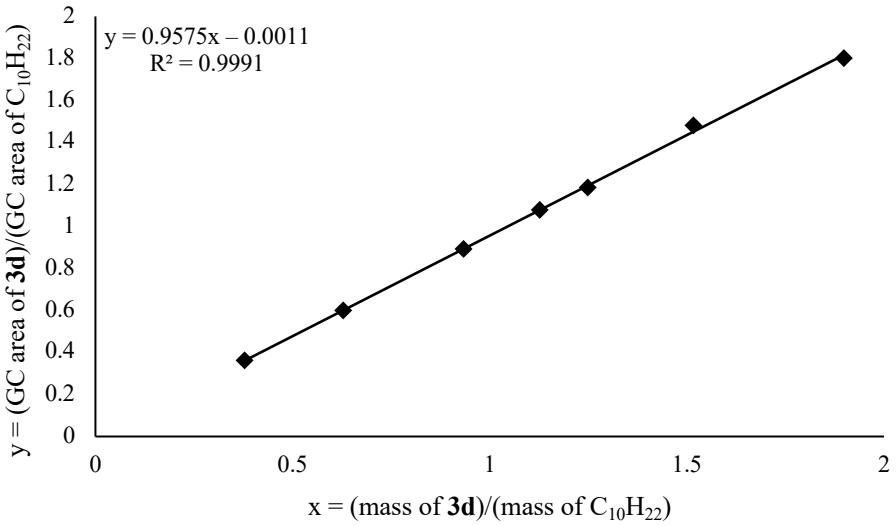
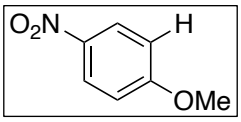
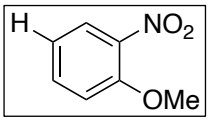


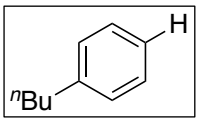
Figure S2-3. GC calibration curve to determine the yield of **3d**.



4-Nitroanisole (3e). The reaction of 2,4-dinitroanisole (**1e**) (153 mg, 1.0 mmol) with **2i** (36 mg, 0.60 mmol) stirred for 1 h, followed by



purification by MPLC (hexane:EtOAc = 95:5 to 90:10) afforded the title compound (106 mg, 0.69 mmol, 69%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.6, 141.5, 125.9, 114.0, 55.9. A small amount of 2-nitroanisole (**3e'**) (13 mg, 0.083 mmol, 8.3%) was also obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H) 7.03 (t, *J* = 7.8 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0, 139.8, 134.2, 125.7, 120.3, 113.5, 56.5. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[31]



***n*-Butylbenzene (3f).** The reaction of 1-*n*-butyl-4-nitrobenzene (**1f**) (108 mg, 0.60 mmol) was stirred for 4 h. The yield of the title compound (83%) was determined by GC analysis using the calibration curve (Figure S2-4).

Table S2-4. Data for the GC calibration curve obtained using an authentic sample of **3f**.

entry	mass (mg)		x =	mass of **3f**	GC area		y =	GC area of **3f**
	3f	$C_{13}H_{28}$		mass of $C_{13}H_{28}$	**3f**	$C_{13}H_{28}$	**3f**	$C_{13}H_{28}$
1	20.2	15.1		1.337748	379046	277052		1.368140
2	16.2	15.1		1.072848	286713	255428		1.122481
3	13.5	15.1		0.894040	303441	326359		0.929777
4	12.1	15.0		0.806667	234499	276772		0.847261
5	10.3	15.0		0.686667	164852	233929		0.704709
6	8.0	15.0		0.533333	116773	192792		0.605697
7	4.3	15.0		0.286667	78971	283382		0.278673

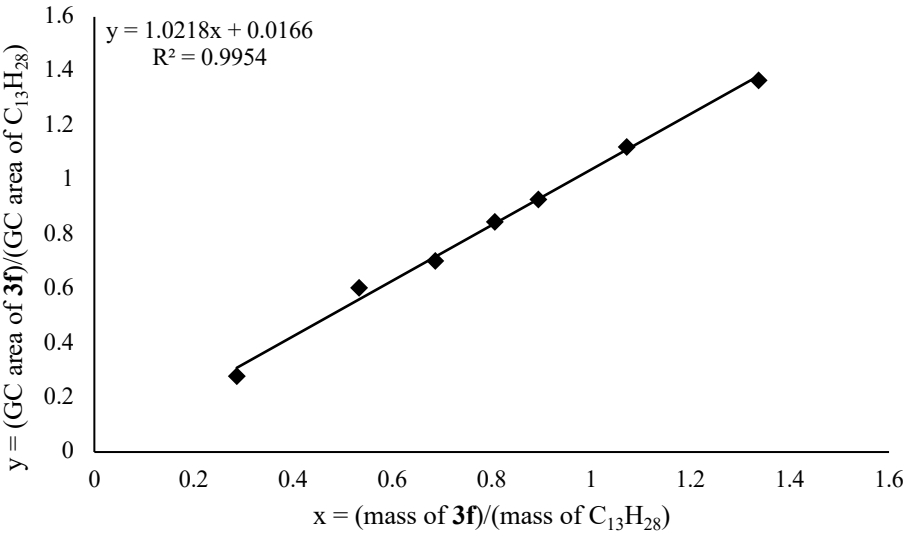
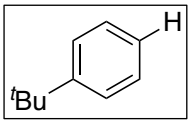


Figure S2-4. GC calibration curve to determine the yield of **3f**.



***tert*-Butylbenzene (3g).** The reaction of 1-*tert*-butyl-4-nitrobenzene (**1g**) (108 mg, 0.60 mmol) was stirred for 12 h. The yield of the title compound (87%) was determined by GC analysis using the calibration curve (Figure S2-5).

Table S2-5. Data for the GC calibration curve obtained using an authentic sample of **3g**.

entry	mass (mg)		x = mass of **3g** / mass of $C_{13}H_{28}$	GC area		y = GC area of **3g** / $C_{13}H_{28}$
	3g	$C_{13}H_{28}$		**3g**	$C_{13}H_{28}$	
1	21.0	15.1	1.390728	530214	365298	1.451456
2	16.2	15.1	1.072848	436709	387480	1.127049
3	13.6	15.2	0.894737	325224	350783	0.927137
4	12.2	15.1	0.807947	338947	403055	0.840944
5	9.5	15.1	0.629139	268452	427527	0.627917
6	8.6	15.2	0.565789	208417	373390	0.558174
7	4.2	15.1	0.278146	86056	304836	0.282305

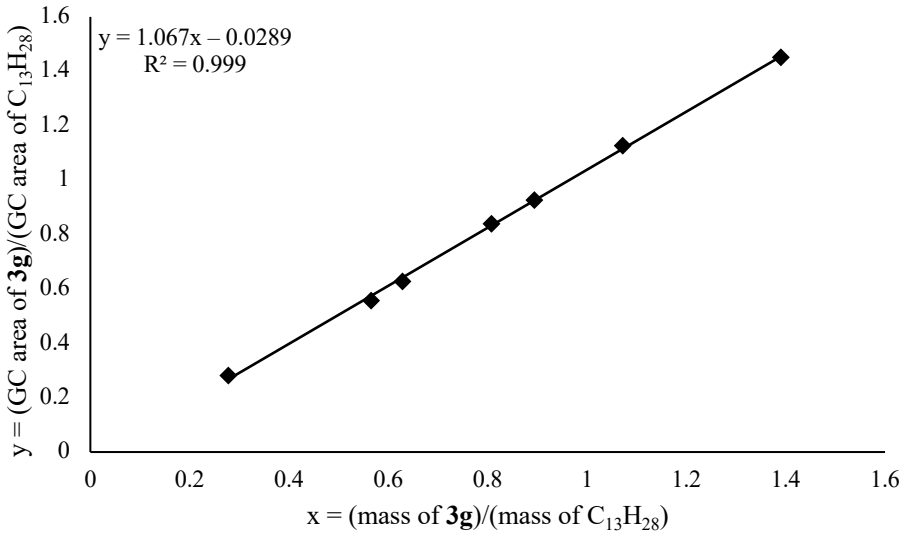
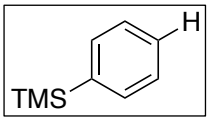


Figure S2-5. GC calibration curve to determine the yield of **3g**.



Trimethyl(phenyl)silane (3h). The reaction of trimethyl(4-nitrophenyl)silane (**1h**) (117 mg, 0.60 mmol) was stirred for 12 h. The yield of the title compound (82%) was determined by GC analysis using the calibration curve (Figure S2-6).

Table S2-6. Data for the GC calibration curve obtained using an authentic sample of **3h**.

entry	mass (mg)		x = mass of **3h** / mass of $C_{13}H_{28}$	GC area		y = GC area of **3h** / $C_{13}H_{28}$
	3h	$C_{13}H_{28}$		**3h**	$C_{13}H_{28}$	
1	22.2	7.6	2.921053	552588	222885	2.479245
2	17.9	7.6	2.355263	350421	179171	1.955795
3	15.0	7.6	1.973684	336662	200630	1.678027
4	13.4	7.6	1.763158	290933	197551	1.472696
5	11.3	7.5	1.506667	295441	236500	1.249221
6	9.2	7.6	1.210526	184059	181274	1.015366
7	4.7	7.5	0.626667	106765	220461	0.484280

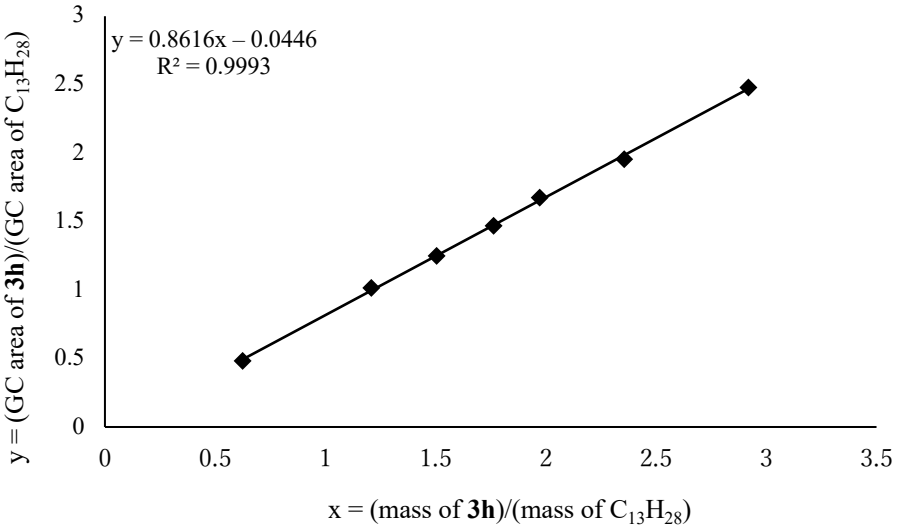
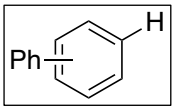
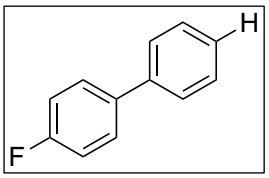


Figure S2-6. GC calibration curve to determine the yield of **3h**.

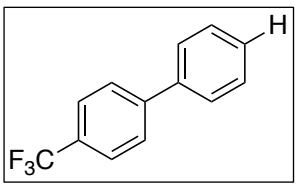


Biphenyl (3i and 3j). The reaction of 3-nitrobiphenyl (**1i**) or 4-nitrobiphenyl (**1j**) (119 mg, 0.60 mmol) stirred for 4 h, followed by purification by MPLC (hexane) afforded the title compounds (79 mg, 0.51 mmol, 85%; 68 mg, 0.44 mmol, 73%, respectively.) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.8 Hz, 4H), 7.45 (t, *J* = 7.6 Hz, 4H), 7.35 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2, 128.7, 127.2, 127.1. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[32]

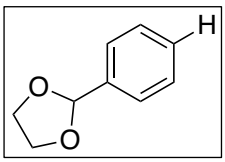


4-Fluorobiphenyl (3k). The reaction of 4-fluoro-4'-nitrobiphenyl (**1k**) (130 mg, 0.60 mmol) stirred for 4 h, followed by purification by MPLC (hexane) afforded the title compound (93 mg, 0.54 mmol, 90%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.51 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4 (d, *J* = 246.3 Hz), 140.2, 137.3 (d, *J* = 3.8 Hz), 128.8, 128.7 (d, *J* = 7.8

Hz), 127.2, 127.0, 115.6 (d, J = 21.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ –116.2. All resonances of ^{1}H, ^{13}C, and ^{19}F NMR spectra were consistent with the reported values.[33]



4-(Trifluoromethyl)biphenyl (3l). The reaction of 4-nitro-4'-(trifluoromethyl)biphenyl (**1l**) (160 mg, 0.60 mmol) stirred for 4 h, followed by purification by MPLC (hexane) afforded the title compound (124 mg, 0.56 mmol, 93%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 4H), 7.60 (d, J = 7.8 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.7, 139.7, 129.3 (q, J = 32.6 Hz), 129.0, 128.2, 127.4, 127.3, 125.7 (q, J = 3.8 Hz), 124.3 (q, J = 280.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.7. All resonances of ^{1}H, ^{13}C, and ^{19}F NMR spectra were consistent with the reported values.[34,35]



2-Phenyl-1,3-dioxolane (3m). The reaction of 2-(4-nitrophenyl)-1,3-dioxolane (**1m**) (117 mg, 0.60 mmol) was stirred for 4 h. The yield of the title compound (92%) was determined by GC analysis using the calibration curve (Figure S2-7).

Table S2-7. Data for the GC calibration curve obtained using an authentic sample of **3m**.

entry	mass (mg)		$x = \frac{\text{mass of } \mathbf{3m}}{\text{mass of } C_{10}H_{22}}$	GC area		$y = \frac{\text{GC area of } \mathbf{3m}}{C_{10}H_{22}}$
	3m	$C_{10}H_{22}$		**3m**	$C_{10}H_{22}$	
1	22.4	7.4	3.027027	287249	130842	2.195383
2	18.0	7.3	2.465753	229586	133989	1.713471
3	14.8	7.2	2.055556	189929	131347	1.446010
4	13.2	7.2	1.833333	154520	115383	1.339191
5	11.3	7.5	1.506667	295441	236500	1.249221
6	9.2	7.6	1.210526	184059	181274	1.015366
7	4.7	7.5	0.626667	106765	220461	0.484280

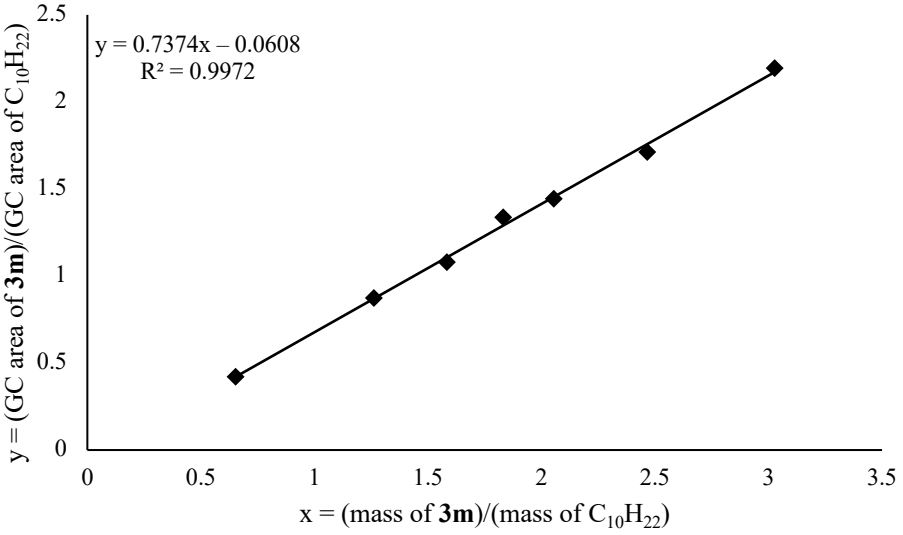
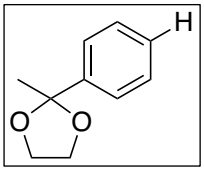


Figure S2-7. GC calibration curve to determine the yield of **3m**.



2-Methyl-2-phenyl-1,3-dioxolane (3n). The reaction of 2-methyl-2-(4-nitrophenyl)-1,3-dioxolane (**1n**) (126 mg, 0.60 mmol) under the optimized conditions was stirred for 4 h. The yield of the title compound (89%) was determined by GC analysis using the calibration curve (Figure S2-8).

Table S2-8. Data for the GC calibration curve obtained using an authentic sample of **3n**.

entry	mass (mg)		x = mass of **3n** / mass of $C_{10}H_{22}$	GC area		y = GC area of **3n** / $C_{10}H_{22}$
	3n	$C_{10}H_{22}$		**3n**	$C_{10}H_{22}$	
1	24.6	7.3	3.369863	372981	157733	2.36464
2	19.7	7.4	2.662162	210907	107603	1.960041
3	16.4	7.2	2.277778	275937	162115	1.702100
4	14.7	7.3	2.013699	169800	119423	1.421844
5	12.8	7.2	1.777778	227276	176590	1.287024
6	9.9	7.4	1.337838	131178	138201	0.949184
7	4.9	7.3	0.671233	70987	162866	0.435860

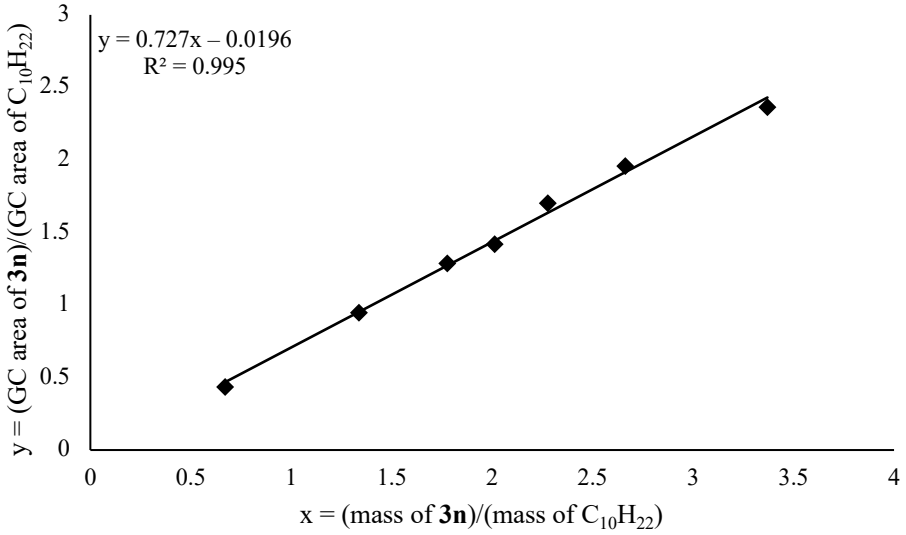
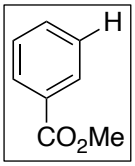


Figure S2-8. GC calibration curve to determine the yield of **3n**.



Methyl benzoate (3o). The reaction of methyl 3-nitrobenzoate (**1o**) (109 mg, 0.60 mmol) with dimesitylmethanol (**2h**) (0.24 g, 0.90 mmol) was stirred for 2 h. The yield of the title compound (84%) was determined by GC analysis using the calibration curve (Figure S2-9).

Table S2-9. Data for the GC calibration curve obtained using an authentic sample of **3o**.

entry	mass (mg)		x = mass of **3o** / mass of $C_{13}H_{28}$	GC area		y = GC area of **3o** / $C_{13}H_{28}$
	3o	$C_{13}H_{28}$		**3o**	$C_{13}H_{28}$	
1	16.1	15.0	1.073333	252260	392262	0.643091
2	14.1	15.2	0.927632	218459	410311	0.532423
3	11.3	15.0	0.753333	157379	365994	0.430005
4	8.7	15.1	0.576159	121175	422174	0.287025
5	4.7	15.2	0.309211	68163	406399	0.167723

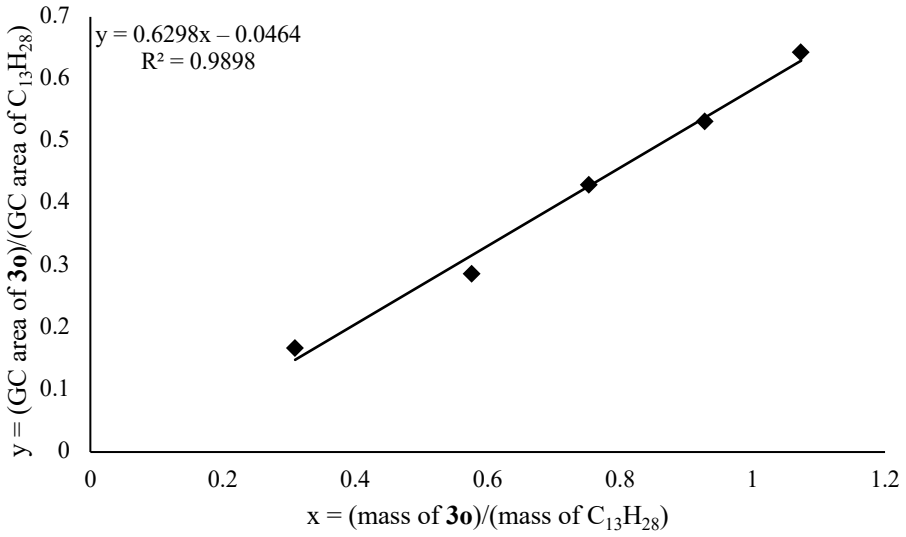
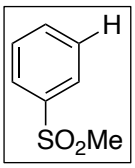
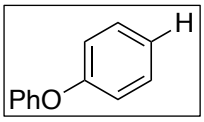


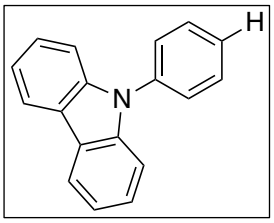
Figure S2-9. GC calibration curve to determine the yield of **3o**.



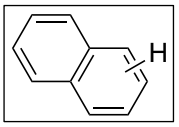
(Methylsulfonyl)benzene (3p). The reaction of 1-(methylsulfonyl)-3-nitrobenzene (**1p**) (121 mg, 0.60 mmol) stirred for 24 h, followed by puification by MPLC (hexane:EtOAc = 88:12 to 62:38) afforded the title compound (58 mg, 0.37 mmol, 61%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 2H), 3.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.5, 133.7, 129.3, 127.3, 44.5. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[36]



Phenoxybenzene (3q). The reaction of 1-nitro-4-phenoxybenzene (**1q**) (129 mg, 0.60 mmol) stirred for 24 h, followed by purification by MPLC (hexane) afforded the title compound (80 mg, 0.47 mmol, 78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.8 Hz, 4H), 7.10 (t, *J* = 7.3 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.2, 129.7, 123.2, 118.8. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[37]



9-Phenyl-9*H*-carbazole (3r). The reaction of 9-(4-nitrophenyl)-9*H*-carbazole (**1r**) stirred for 4 h, followed by purification by MPLC (hexane) afforded the title compound (112 mg, 0.46 mmol, 77%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.8 Hz, 2H), 7.64–7.55 (m, 4H), 7.47 (t, *J* = 7.1 Hz, 1H), 7.41 (t, *J* = 3.7 Hz, 4H), 7.31–7.26 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.8, 137.6, 129.8, 127.4, 127.1, 125.9, 123.3, 120.3, 119.8, 109.7. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[38]



Naphthalene (3s and 3t). The reaction of 1-nitronaphthalene (**1s**) or 2-nitronaphthalene (**1t**) (104 mg, 0.60 mmol) was stirred for 4 h or 12 h, respectively. The yields of the naphthalenes 87% and 59% were determined by GC analysis using the calibration curve (Figure S2-10).

Table S2-10. Data for the GC calibration curve obtained using an authentic sample of **3s**.

entry	mass (mg)		$x = \frac{\text{mass of } \mathbf{3s}}{\text{mass of } C_{10}H_{22}}$	GC area		$y = \frac{\text{GC area of } \mathbf{3s}}{C_{10}H_{22}}$
	3s	$C_{10}H_{22}$		**3s**	$C_{10}H_{22}$	
1	15.4	7.3	2.109589	231190	103996	2.223076
2	12.9	7.3	1.767123	193523	97621.9	1.982374
3	11.5	7.3	1.575342	147782	85024.8	1.738108
4	9.6	7.3	1.315068	158599	109480	1.448662
5	7.9	7.3	1.082192	117020	106479	1.098990
6	3.9	7.3	0.534247	62737.0	112909	0.555643

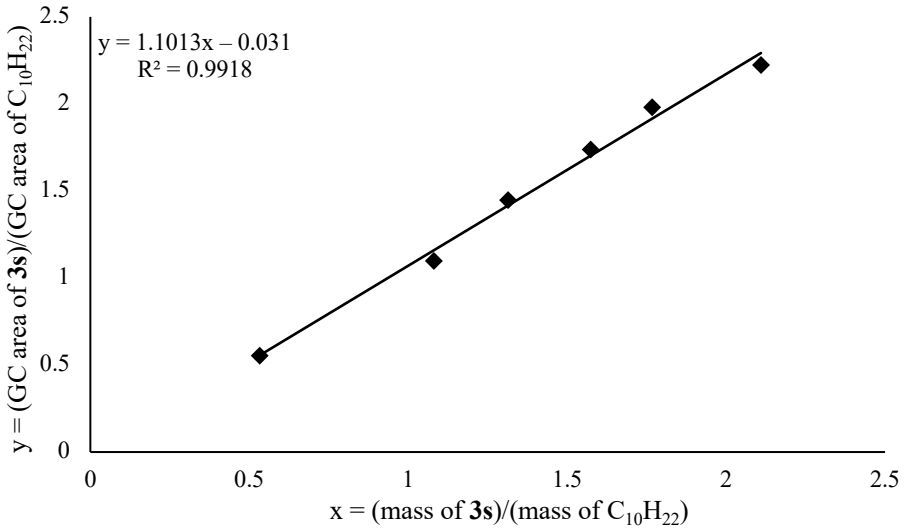
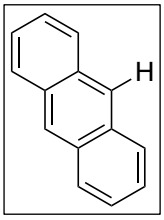


Figure S2-10. GC calibration curve to determine the yield of **3s** and **3t**.



Anthracene (3u). The reaction of 9-nitroanthracene (**1u**) under the optimized conditions stirred for 8 h, followed by purification by MPLC (24 g silica gel, hexane) afforded the title compound (56 mg, 0.31 mmol, 52%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 2H), 8.05–7.99 (m, 4H), 7.50–7.45 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 131.6, 128.1, 126.2, 125.3. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[39]

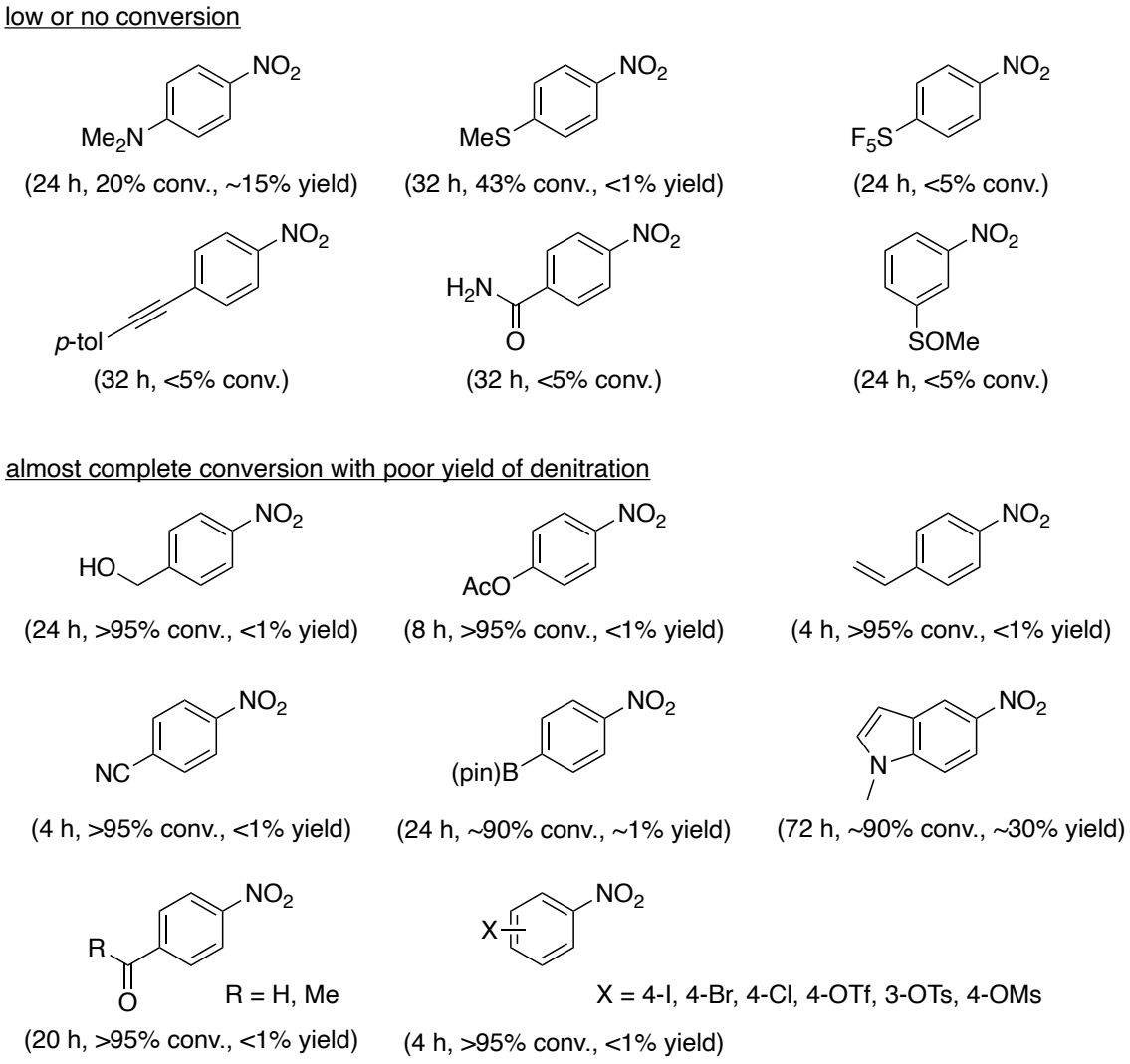
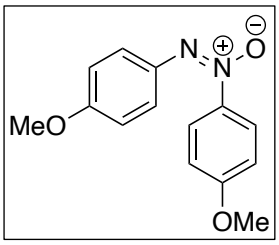


Figure S2-11. Unsuccessful substrates.

General procedure for Scheme 2-2. A 15-mL vial was charged with 4-nitroanisole (**1a**) (92 mg, 0.60 mmol) and a stirring bar. In a glovebox, K_3PO_4 (0.32 g, 1.5 mmol), *n*-$C_{13}H_{28}$ (91 mg, 0.49 mmol), benzhydrol (**2e**) (166 mg, 0.90 mmol) or dimesitylmethanol (**2h**) (0.24 g, 0.90 mmol) or propan-2-ol (**2i**) (54 mg, 0.90 mmol), and 1,4-dioxane (3.0 mL) were added to the vial. The resulting mixture was taken outside and stirred for 12 h at 130 ºC. After the indicated reaction time, the conversion of **1a** was calculated by GC analysis. The crude reaction mixture was passed through a short pad of silica gel (50 μm) using

EtOAc as an eluent, and the filtrate was concentrated in vacuo. The residue was purified by MPLC (Biotage® SNAP Ultra, hexane:EtOAc = 95:5 to 85:15) to isolate remaining **1a**, 4,4'-dimethoxyazoxybenzene (**4**), and ketones.

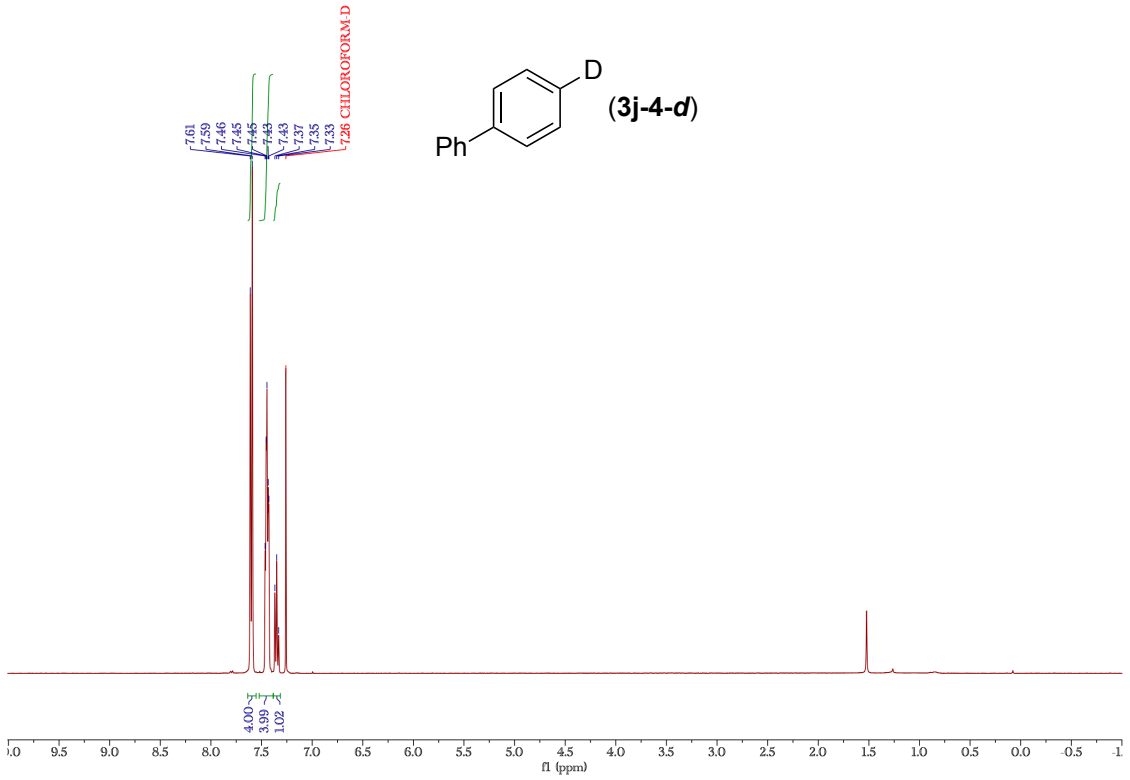


4,4-Dimethoxyazoxybenzene (4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30–8.22 (m, 4H), 7.00–6.93 (m, 4H), 3.88$_4$ (s, 3H), 3.87$_7$ (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8, 160.2, 141.7, 138.0, 127.8, 123.7, 113.7, 113.6, 55.6, 55.5. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[16]

General Procedure for Eq. 1-1 and 1-2. A 15-mL vial was charged with 4-nitrobiphenyl (**1j**) (119 mg, 0.60 mmol), $Pd(acac)_2$ (18.3 mg, 0.060 mmol), BrettPhos (64 mg, 0.12 mmol), and a stirring bar. In a glovebox, K_3PO_4 (0.32 g, 1.5 mmol), benzhydrol-1-d (**2e-1-*d***) (>99% D) or benzhydrol-*d* (**2e-*d***) (80% D) (167 mg, 0.90 mmol), and 1,4-dioxane (3.0 mL) were added to the vial. The resulting reaction mixture was taken outside and stirred for 4 h at 130 ºC. After the completion of the reaction, the crude mixture was passed through a short pad of silica gel (50 μm) eluted with EtOAc, and the filtrate was concentrated in vacuo. The residue was purified by MPLC (Biotage® SNAP Ultra, hexane:EtOAc = 0:100 to 95:5) to isolate biphenyl (**3j**) and benzophenone (**5e**).

The reaction with **2e-1-*d*** as the reductant afforded deuterated biphenyl **3j-4-*d*** (70 mg, 0.45 mmol, 75%, 98% D) and **5e** (121 mg, 0.67 mmol, 74%), whereas **2e-*d*** furnished biphenyl **3j** (73 mg, 0.47 mmol, 79%, 99% H) and **5e** (123 mg, 0.68 mmol, 75%). The incorporation of deuterium was determined by NMR analysis (Figure S2-12).

(a)



(b)

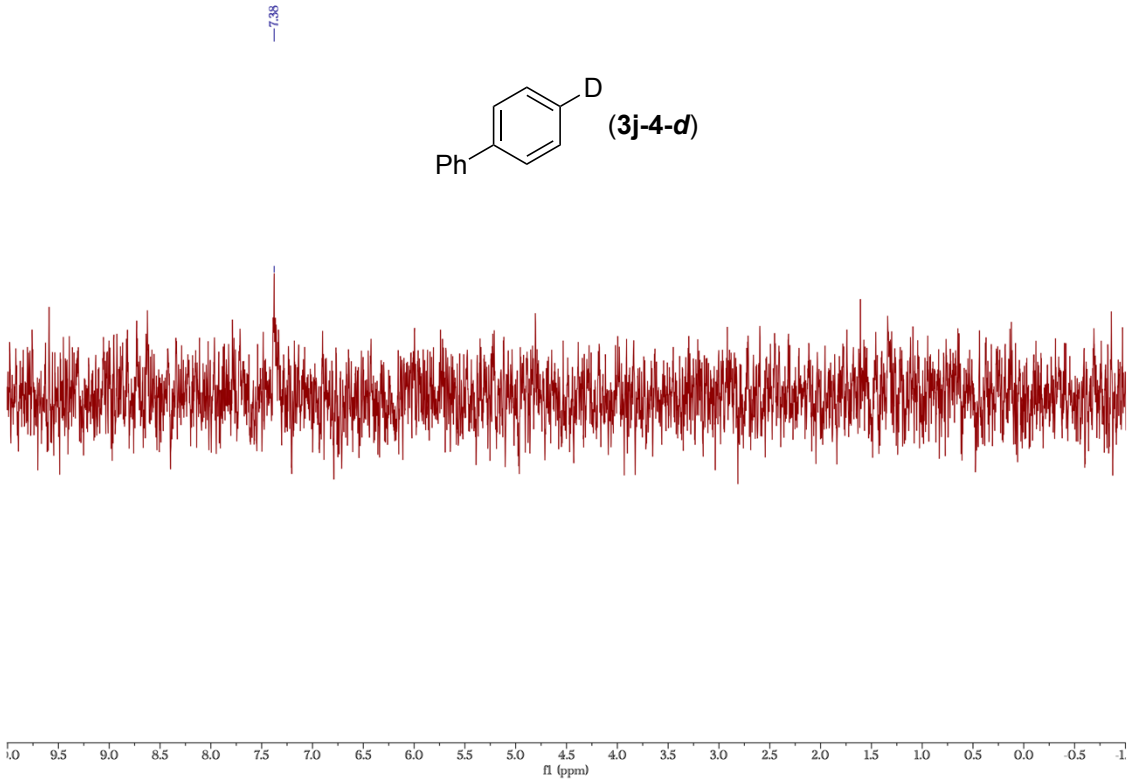
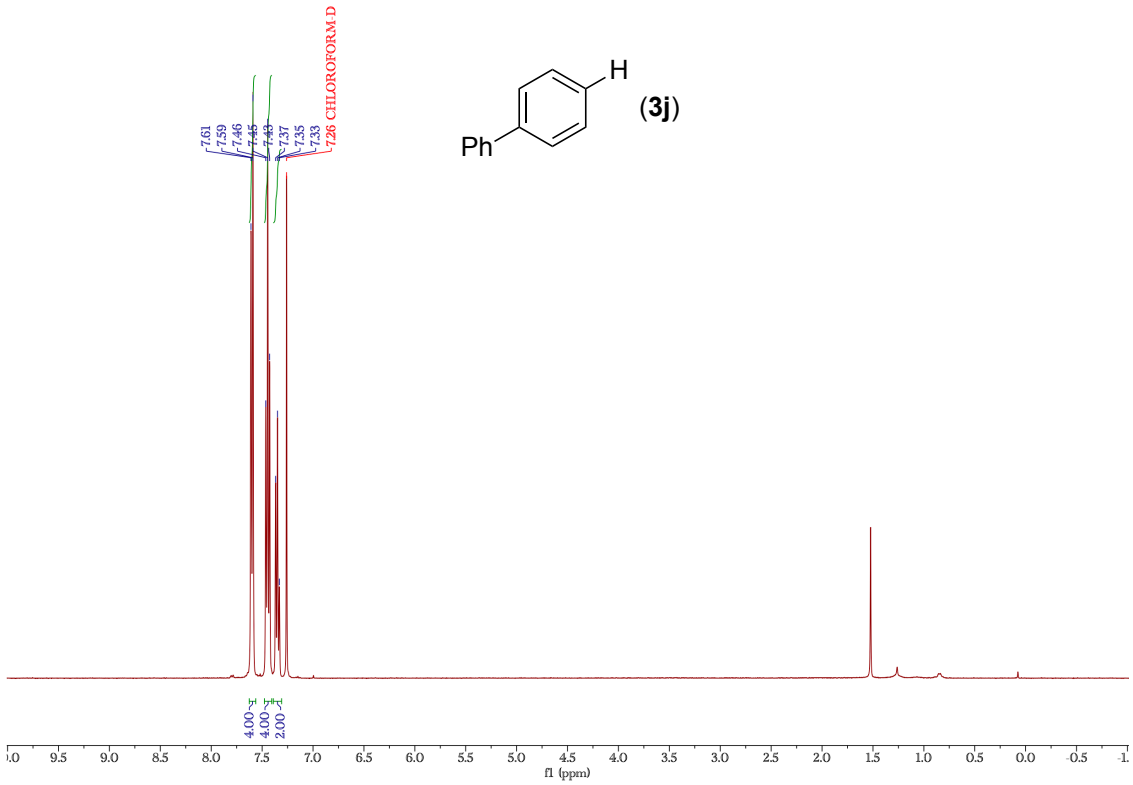


Figure S2-12. (a) ^{1}H NMR spectrum of **3j-4-*d***. (b) ^{2}D NMR spectrum of **3j-4-*d***.

(c)



(d)

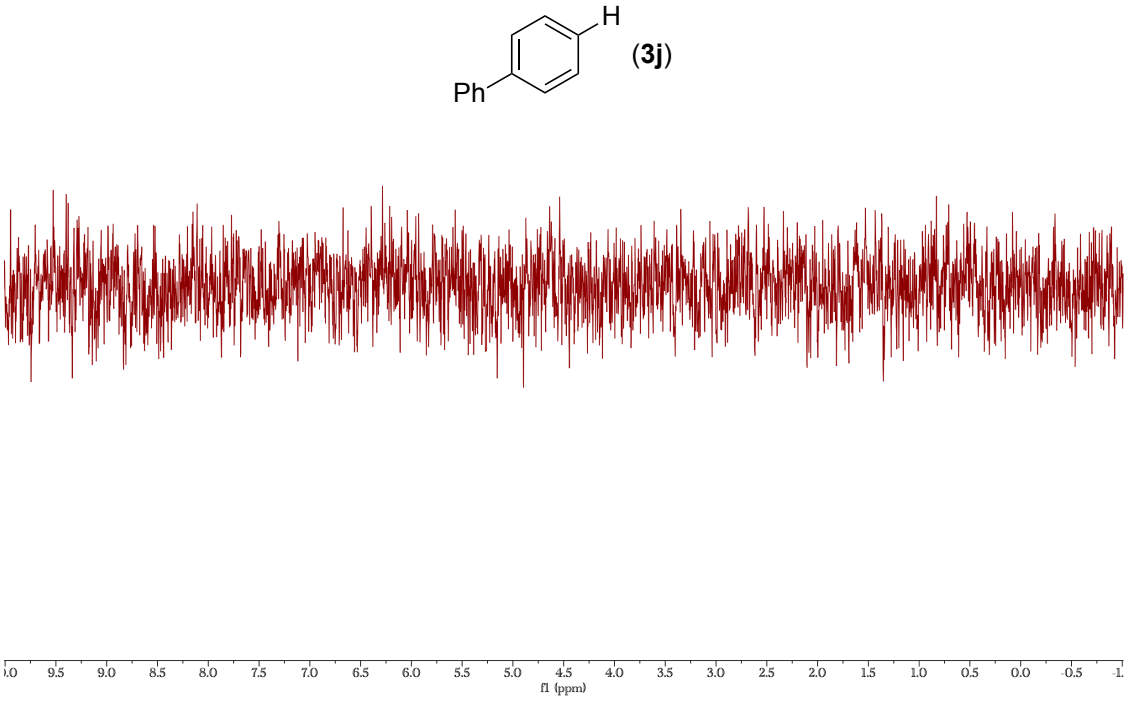


Figure S2-12. (c) ^{1}H NMR spectrum of **3j**. (d) ^{2}D NMR spectrum of **3j**.

General Procedure for Eq. 1-3. A 4-mL vial was charged with 1-nitronaphthtalene (**1s**) (35 mg, 0.20 mmol), $Pd(acac)_2$ (3.0 mg, 0.010 mmol), BrettPhos (0.020 mmol), and a stirring bar. In a glovebox, K_3PO_4 (106 mg, 0.50 mmol), *n*-$C_{10}H_{22}$ (14.6 mg, 0.084 mmol), propan-2-ol (**2i**) or propan-2-ol-2-*d* (**2i-2-*d***) (18.0 mg, 0.30 mmol), and 1,4-dioxane (1.0 mL) were added to the vial. The resulting mixture was taken outside and stirred at 130 ºC. At 4, 8, 12, 16, and 21 min, the vial was soaked into an ice-cooled acetone bath to stop the reaction immediately. The cooled vial was brought into a glovebox and an aliquot of the reaction mixture was taken for GC analysis. The vial was returned to a hot stirrer and stirred at 130 ºC till the time for the next sampling. The yield of naphthalene (**3s** or **3s-1-*d***) at each time interval was determined by GC analysis using calibration curve (Figure S2-10). The reactions were repeated for four times, and the results are listed in Table S2-11 and Figures S2-13. k_H/k_D value was calculated by the equation indicated below. Rates were calculated as the average of the slope of the four graphs drawn independently based on data from the same experiments for four times. Based on these data, k_H/k_D = 0.97.

$$k_H/k_D = \frac{\text{initial rate of the formation of } \mathbf{3s} \text{ using } \mathbf{2i}}{\text{initial rate of the formation of } \mathbf{3s\text{-}1\text{-}}\boldsymbol{d} \text{ using } \mathbf{2i\text{-}2\text{-}}\boldsymbol{d}} \quad \text{(S2-1)}$$

Table S2-11. Yield of **3s**/**3s-1-*d*** (%) at each timepoint in KIE measurement. (*GC error.)

entry (**2i**/**2i-2-*d***)	time (min)				
	4	8	12	16	21
1 (**2i**)	0.20	2.4	4.0	7.5	11.4
2 (**2i**)	0.20	2.1	3.7	5.9	9.3
3 (**2i**)	0.20	2.5	4.7	8.2	13.6
4 (**2i**)	0.20	1.2	4.5	7.5	—*
5 (**2i-2-*d***)	0.40	2.7	4.6	7.3	11.5
6 (**2i-2-*d***)	0.30	2.0	5.1	5.9	11.1
7 (**2i-2-*d***)	0.20	2.7	3.7	7.8	12.3
8 (**2i-2-*d***)	0.10	2.3	4.6	6.8	12.6

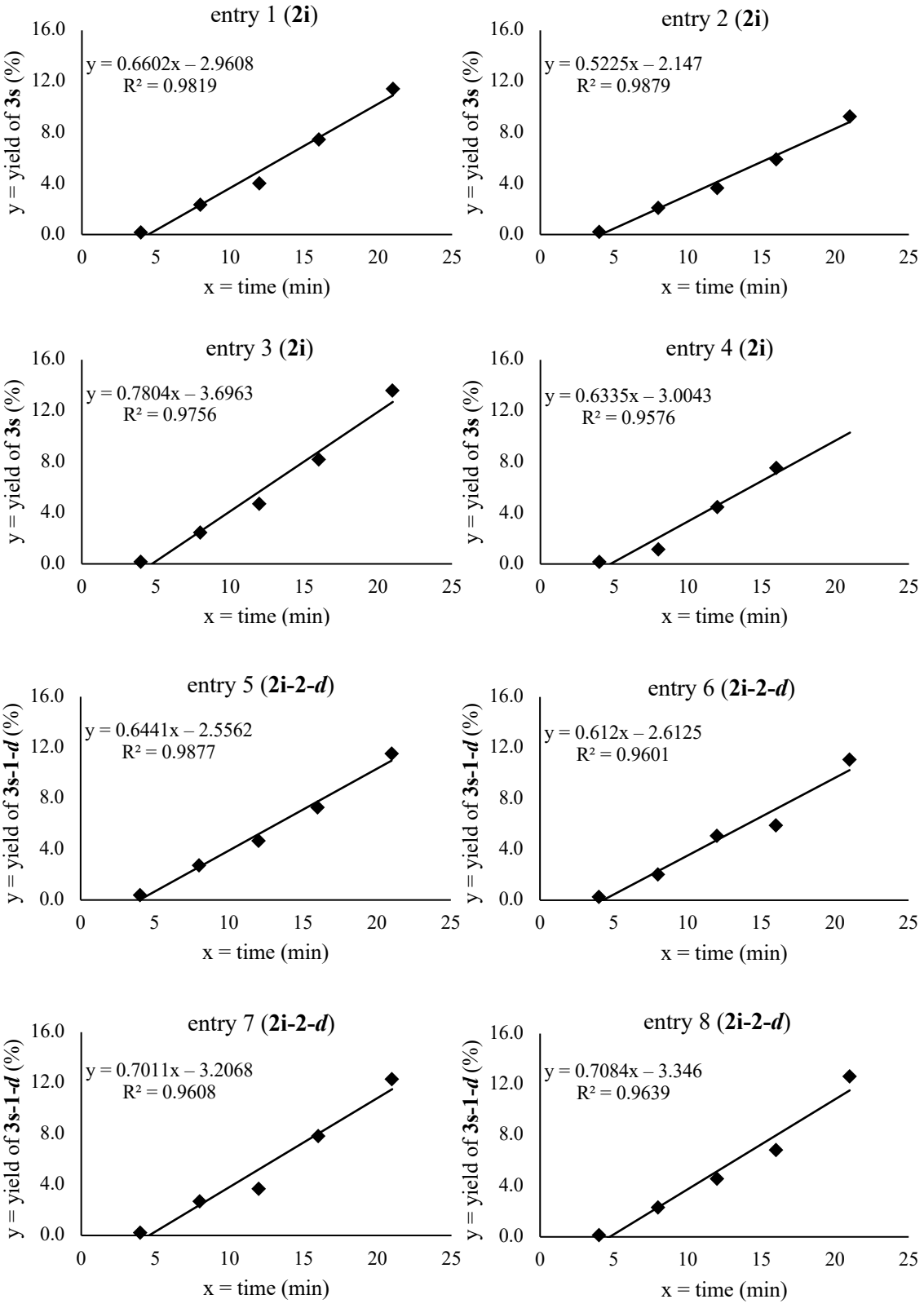


Figure S2-13. Results of KIE measurement based on the formation of **3s** and **3s-1-*d***.

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Chapter 3

Pd-Catalyzed Etherification of Nitroarenes

The Pd-catalyzed etherification of nitroarenes with arenols has been achieved using a new rationally designed ligand. Mechanistic insights were used to design the ligand so that both the oxidative addition and reductive elimination steps of a plausible catalytic cycle were facilitated. The catalytic system established here provides direct access to a range of unsymmetrical diaryl ethers from nitroarenes.

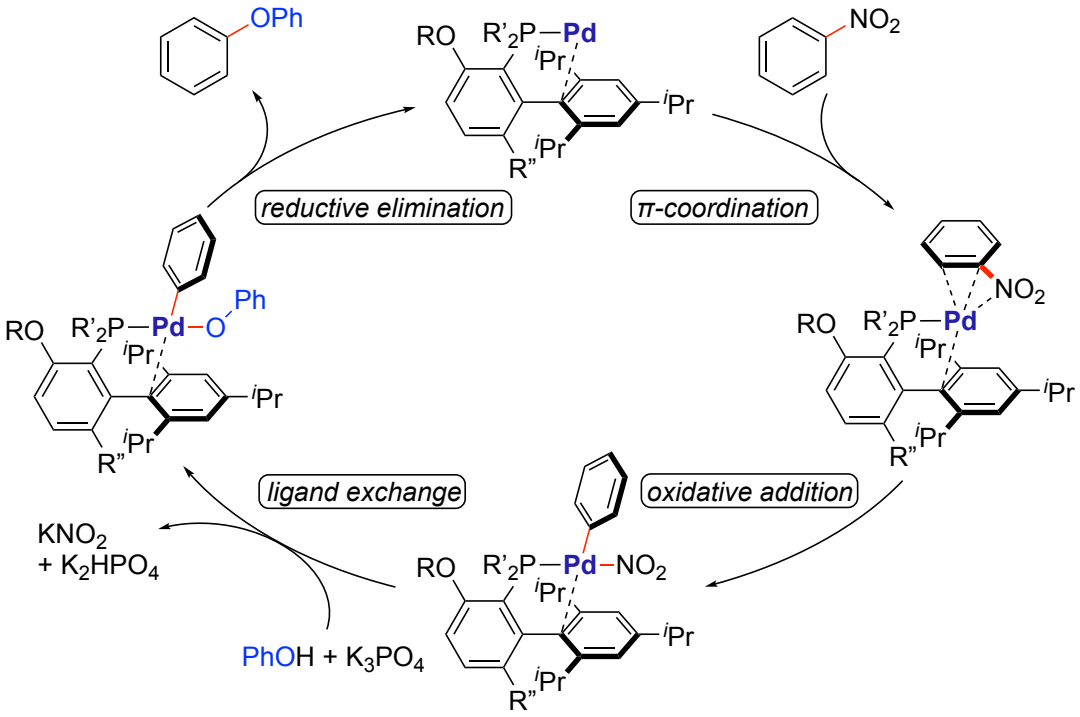
Introduction

The diaryl ether moiety is an important structural motif often found in natural products and bioactive substances.[1] Classically, diaryl ethers have been synthesized *via* the Ullmann condensation of aryl halides and arenols, mediated by a stoichiometric amount of copper, which typically requires relatively high reaction temperatures.[2] S_NAr reactions offer a transition-metal-free alternative, albeit only highly electron-deficient aryl (pseudo)halides are applicable in this approach.[3] Recent advances in this field have led to improved Ullmann-type coupling reactions that only require a catalytic amount of Cu[3b,4] or Fe.[5] In addition, Pd-catalyzed coupling reactions that form carbon–oxygen bonds, known as Buchwald–Hartwig etherifications, have been developed.[6] All of these methods rely on the use of haloarenes, aryl electrophile substrates that can be difficult to prepare or that result in the emission of environmentally harmful byproducts. In a complementary approach, Yamaguchi and Itami have reported a halogen-free synthesis of diaryl ethers *via* the decarbonylation of aryl benzoates.[7] However, this method, which requires two formal synthetic steps starting from a benzoic acid derivative and a phenol, is limited to the reaction of aryl azinecarboxylate substrates.

Nitroarenes, on the other hand, are materials that are industrially easy to access, obtained by the nitration of benzenes, and are readily modifiable through various aromatic substitution reactions or metal-catalyzed functionalizations.[8] Thus, the substitution of the nitro group of a nitroarene with an aryloxy group provides an attractive synthetic route to produce diaryl ethers. In 2011, Wu and co-workers developed the first aryloxylation of nitroarenes *via* the use of arylboronic acids as pronucleophiles.[9a] Following this work, several groups reported transition-metal-catalyzed denitrative C–O coupling reactions of nitroarenes and phenol derivatives.[9b–9d] Collectively, however, these reactions are only

applicable to nitroarenes that contain at least one additional electron-withdrawing group or to nitropyridines. This is presumably because these reactions have characteristics akin to those of S_NAr reactions.

Recently, the author has reported C–C and C–N bond forming cross-coupling reactions and the reductive denitration of nitroarenes catalyzed by Pd complexes bearing Buchwald-type ligands.[10a–10c,11] These catalytic systems enable the oxidative addition of C(aryl)–NO_2 bonds to the Pd center, enabling even nitroarenes with electron-donating group to undergo aromatic substitutions and improving the substrate tolerance of the reaction. The author therefore assumed that the use of arenol nucleophiles in the same catalytic system would deliver diaryl ethers *via* an established catalytic cycle without compromising the substrate generality. Scheme 3-1 shows a plausible catalytic cycle whereby a nitroarene undergoes oxidative addition, ligand exchange (transmetalation), and reductive elimination to give a diaryl ether.



Scheme 3-1. Plausible mechanism for the Pd-catalyzed etherification of nitroarenes.

Results and discussion

The denitrative etherification reaction was first attempted using relatively electron-rich 4-nitroanisole (**1a**) and phenol (**2a**) in the presence of various Pd catalysts that had been effective in the author's previous studies (Table 3-1). To the author's disappointment, the use of BrettPhos (**L1**), *i.e.*, one of the most promising ligands, failed to yield any of the desired product (**3a**) (entry 1).[6g] Furthermore, the imidazo[1,5-*a*]pyridinylidene **L2**/Pd system, which has recently been established as a more active catalyst for C–NO_2 activations,[10d–10f] also resulted in no reaction (entry 2). In the proposed catalytic cycle (Scheme 3-1), the oxidative addition of C–NO_2 bond should proceed with Pd/**L1** or Pd/**L2**, and the phenoxide should be nucleophilic enough to replace the nitrite ligand following the oxidative addition step. The author thus hypothesized that acceleration of the reductive elimination would be crucial to achieve the denitrative C–O bond formation. Buchwald and coworkers have previously reported a guideline for the modification of their ligands (Scheme 3-2);[12] the installation of a methyl group at the C6 position of the upper ring should increase the conformational rigidity, whilst bulky substituents at the C3 position and the phosphine atom should stabilize the P–C bidentate ligation, thus promoting the reductive elimination. RockPhos (**L3**), which has a methoxy substituent at the C3 position and ^{t}Bu groups at the phosphorus center, successfully delivered the target diaryl ether in a low, yet promising, 7% yield (entry 3). However, a bulkier isopropoxy group at the C3 position (**L4**) did not enhance the yield (entry 4). Theoretical calculations indicated that the steric hindrance around the Pd center destabilizes the Ar–Pd–NO_2 species, rendering the oxidative addition thermodynamically unfavorable.[10g] Thus, the author hypothesized that it was necessary to ensure that the ligand had sufficient flexibility to enable cleavage of the C–NO_2 bond while still

promoting the reductive elimination. To verify this hypothesis, the author prepared ligands that bear cyclohexyl groups on the P atom (**L5**–**L9**) and assessed their activity in the denitrative etherification. Pleasingly, a higher yield of **3a** was obtained upon increasing the steric bulk of the substituent at the C3 position (entries 5–9). During further optimization studies, it was determined that, due to overconsumption of **1a**, the stoichiometry of the substrates is critical for efficient product formation (see below). By adding an excess of **1a** relative to **2a** (entries 10 and 11) and when using **L7** and **L9**, the yield of **3a** was improved to 68% and 86% (based on **2a**), respectively.

Scheme 3-2. Ligand design to promote the reductive elimination.

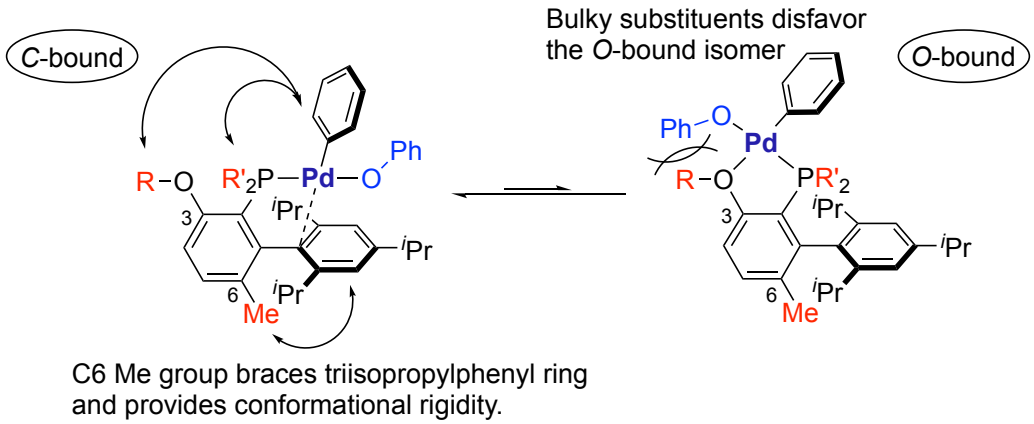
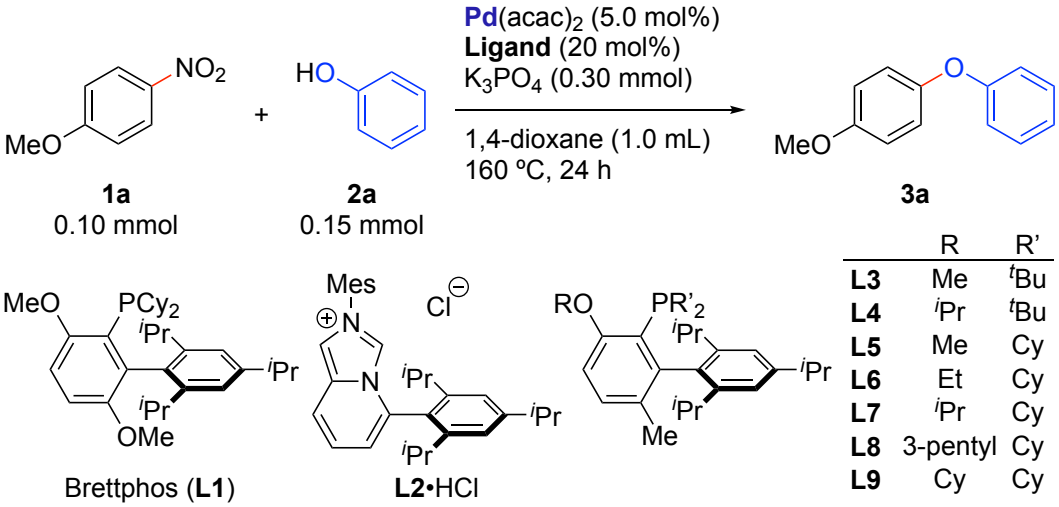


Table 3-1. Optimization studies for the phenoxylation of **1a**.



	R	R'
L3	Me	^{t}Bu
L4	^{i}Pr	^{t}Bu
L5	Me	Cy
L6	Et	Cy
L7	^{i}Pr	Cy
L8	3-pentyl	Cy
L9	Cy	Cy

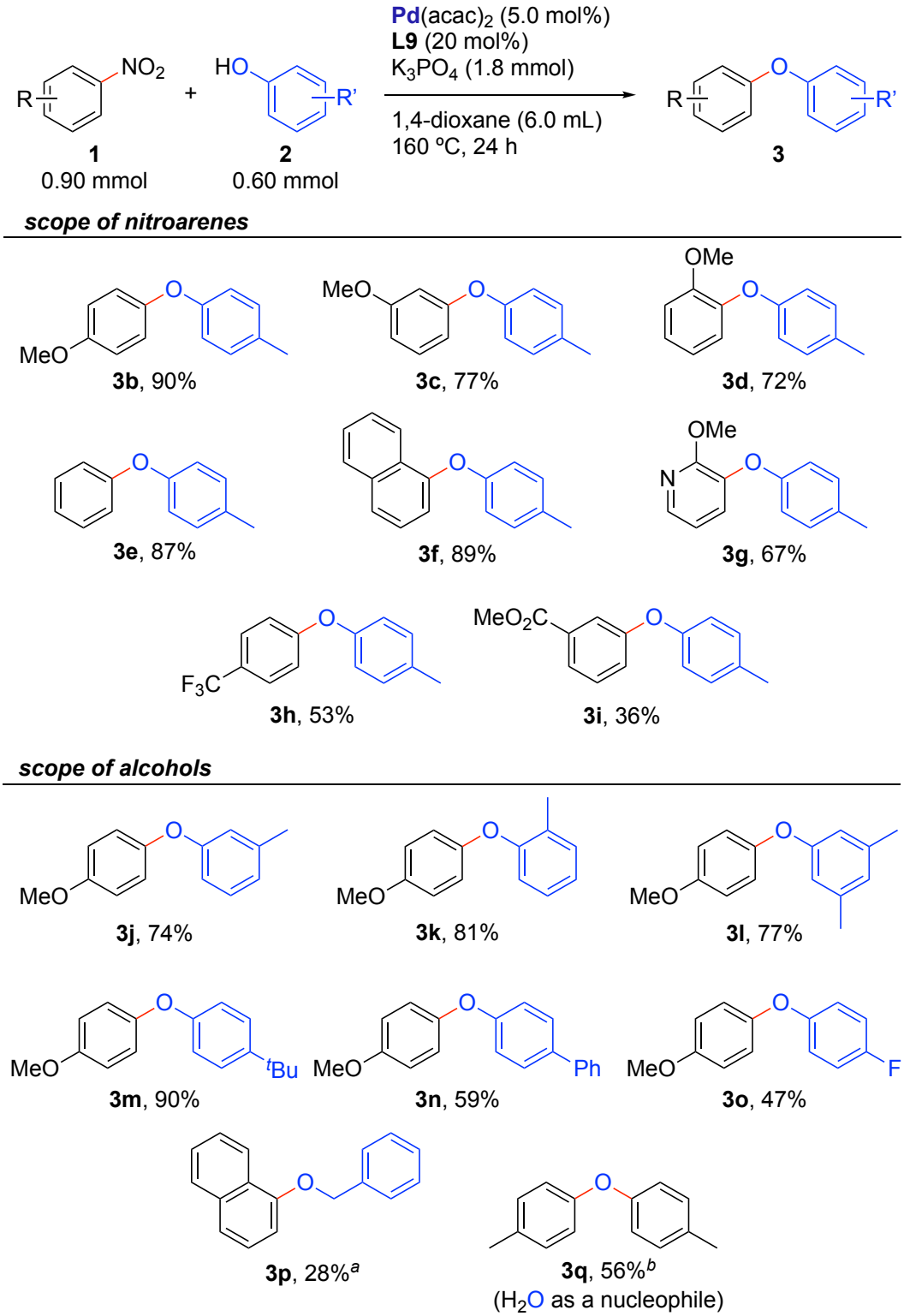
entry	ligand	yield of **3a** (%)[a]
1	**L1**	<1
2	**L2**•HCl	<1
3	**L3**	7
4	**L4**	3
5	**L5**	5
6	**L6**	23
7	**L7**	32
8	**L8**	38
9	**L9**	45
10[b]	**L7**	68
11[b]	**L9**	86

[a] ^{1}H NMR yields determined using mesitylene as an internal standard.
[b] 0.15 mmol of **1a** and 0.10 mmol of **2a** were used.

With the optimized conditions in hand, the substrate scope of the etherification was investigated (Scheme 3-3). In contrast to other reported methods,[9] it was possible to couple relatively electron-rich nitroanisoles (**1a**–**1c**) with *p*-cresol (**2b**) to generate the corresponding diaryl ethers (**3b**–**3d**) in good yield. While an *o*-methoxy substituent on the nitroarene did not affect the reaction, *o*-nitrotoluene was found to be particularly unreactive. The electronically neutral nitrobenzene (**1d**) and nitronaphthalene (**1e**) were also reactive under these conditions. 3-Aryloxypyridine (**3g**) was obtained from 3-

nitropyridine (**1f**) in 67% yield. These examples also represent challenging nitroarene substrates for S_NAr-type transformations. Electron-withdrawing groups on the nitroarene electrophile impeded the reaction; 4-trifluoromethylnitrobenzene (**1g**) and methyl 3-nitrobenzoate (**1h**) delivered the corresponding products (**3h** and **3i**) in moderate yield.[13] Next, the author examined the scope of the arenols. In addition to *p*-cresol (**2b**) and *m*-cresol (**2c**), the sterically hindered *o*-cresol (**2d**) also underwent coupling with 4-nitroanisole (**1a**) in 81% yield. Other alkylphenols such as 3,5-dimethylphenol (**2e**) and 4-*tert*-butylphenol (**2f**) were excellent nucleophiles for this reaction. In line with reported etherification reaction,[14] the introduction of a fluorine substituent (**2h**) diminished the nucleophilicity of the phenol, leading to poor reaction efficiency. It is notable that nitronaphthalene (**1e**) could be coupled with benzyl alcohol (**2i**), albeit in a lower yield, representing, to the best of the author's knowledge, the first example of the alkoxylation of an electronically unbiased nitroarene.[15] The author found that ^{t}BuOH could be coupled with **1i** to afford the corresponding aryl *tert*-butyl ether in a very low yield. Other 1º- and 2º-alcohols gave denitrated arenes as major products possibly through *β*-hydride elimination from arylpalladium alkoxide intermediates (*vide infra*). The author also found that the symmetrical ether **3q** could be obtained by adding H_2O as the nucleophile, probably *via* the *in situ* formation of phenoxide.[4d,6g,16]

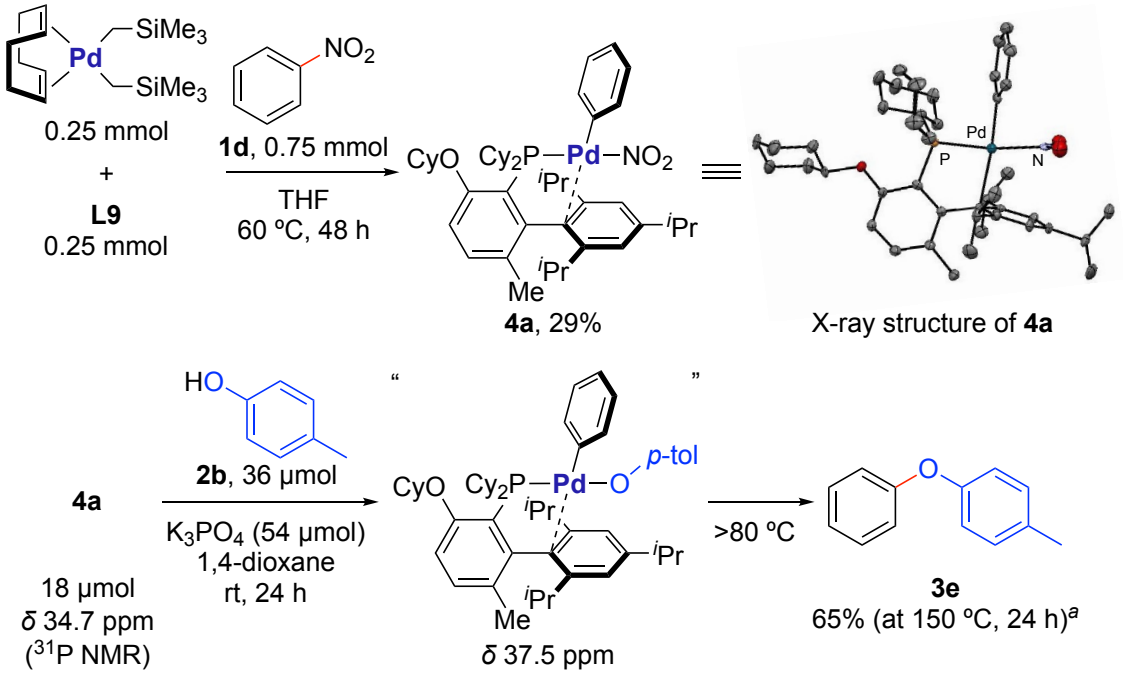
Scheme 3-3. Substrate scope for the etherification of nitroarenes.



[a] The reaction was performed using 0.60 mmol of **1a** and 0.90 mmol of **2i** for 12 h.
[b] The reaction was performed with 0.60 mmol of *p*-nitrotoluene (**1i**) and 0.90 mmol of H_2O in 3.0 mL of 1,4-dioxane for 12 h.

To gain insight into the reaction mechanism, the author performed stoichiometric studies. First, (cod)Pd(CH_2SiMe_3)$_2$ was used as a Pd(0) precursor and treated with nitrobenzene (**1d**) in the presence of **L9** at 60 ºC for 48 h to afford the oxidative adduct (**L9**)Pd(II)(Ph)(NO_2) (**4a**) in 29% yield (Scheme 3-4). A single-crystal X-ray diffraction analysis revealed that, in the solid state, **4a** adopts a structure similar to that of the previously reported (**L1**)Pd(II)(Ph)(NO_2) (**4b**).[10a] The Pd–N bond lengths in **4a** and **4b** are identical, indicating that **L9** has an electron-donating ability comparable to that of **L1**. These results could support the oxidative addition of nitroarenes to (**L9**)Pd(0) may be a facile process. Next, the nitrite-phenoxide exchange step was investigated by adding premixed *p*-cresol (**2b**) and K_3PO_4 to a solution of **4a** in 1,4-dioxane-d_8. After stirring the mixture at ambient temperature for 24 h, a signal in the ^{31}P NMR spectrum was observed 3 ppm downfield from that of **4a** (Figure 3-1). Although the author failed to fully characterize the product, the author assumes that this signal could be attributed to the presence of (**L9**)Pd(II)(Ph)(O–*p*-tol) (**5**) because diaryl ether **3e** was observed upon heating this complex to 80 ºC. An identical ^{31}P NMR peak was observed during the catalytic reaction of **1d** and **2b**, indicating the involvement of this complex in the catalytic cycle as a resting state (Figure 3-2). Furthermore, the thermally inert nature of this complex below 80 ºC indicates, as expected, that the reductive elimination is the rate-determining step.

Scheme 3-4. Stoichiometric reactions.



[a] GC yield of the reaction of **4a** (18 μmol), **2b** (36 μmol), and K_3PO_4 (54 μmol) in 1,4-dioxane (1.0 mL) at 150 °C for 24 h using *n*-$C_{13}H_{28}$ as an internal standard.

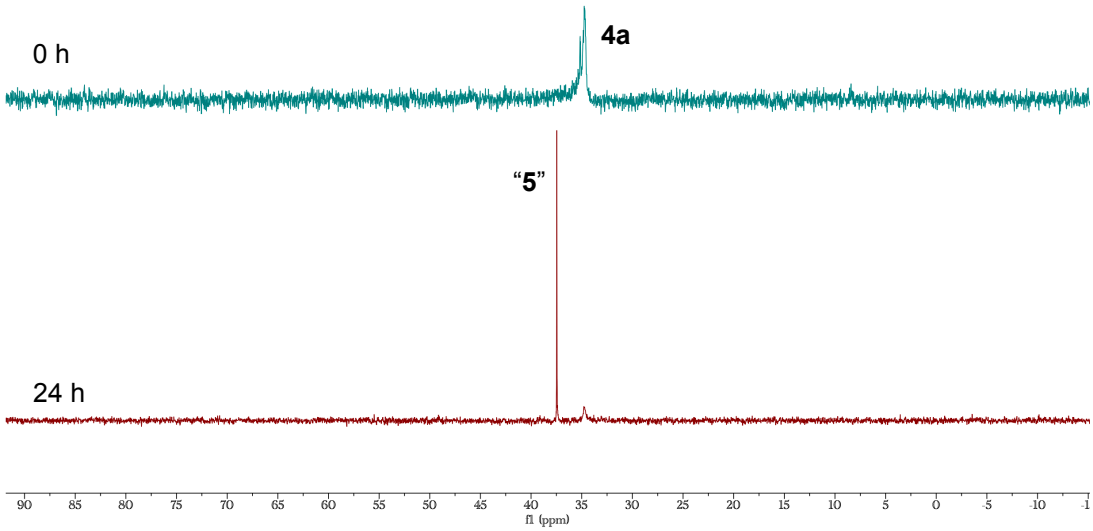


Figure 3-1. ^{31}P NMR spectra before and after the reaction of **4a** and **2b** at rt.

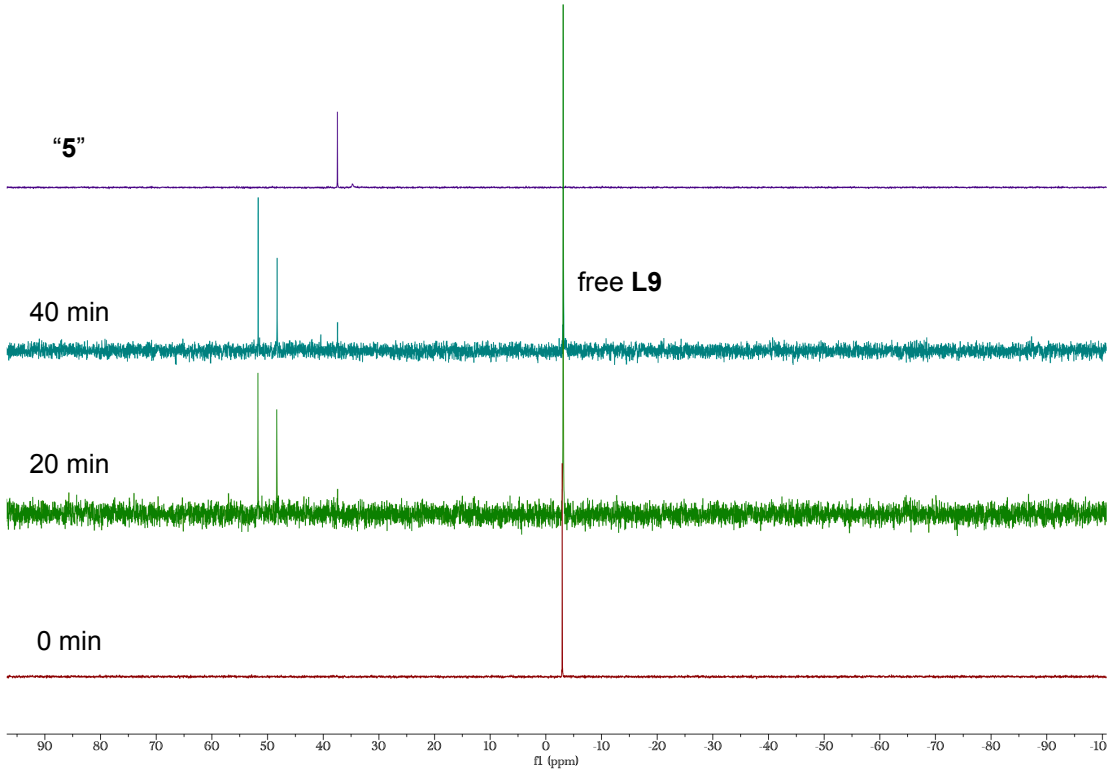


Figure 3-2. ^{31}P NMR spectra during the catalytic reaction of **1d** and **2b**.

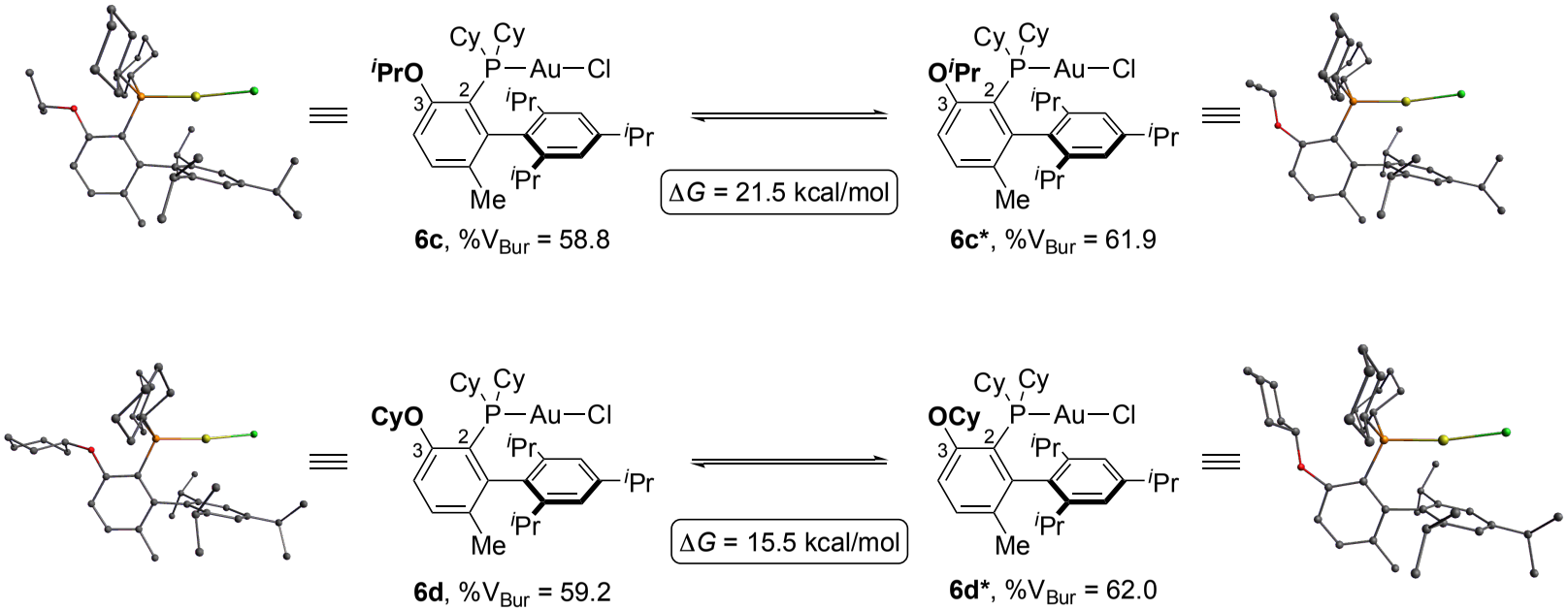
These experiments revealed that the reductive elimination is a key step and prompted us to further investigate the steric properties of the ligand. The author synthesized a series of AuCl complexes (**6b**–**6d**) with **L5**, **L7**, and **L9** as the ligands concerning their facile preparation and the prevalence of crystal structures of AuCl complexes bearing various types of ligands.[17] **L5**, **L7**, and **L9** contain a Me, ^{i}Pr, and Cy substituent at the C3-O atom, respectively. Single-crystal X-ray diffraction analyses revealed no substantial differences in the Au–Cl bond lengths between (**L1**)AuCl (**6a**)[10d] and **6b**–**6d**, implying that the strong electron-donating effects of these ligands facilitate the oxidative addition (Table 3-2). To compare the steric properties, the author then calculated $\%V_{Bur}$ of each complex.[18a] As expected, all the Au complexes synthesized had slightly higher $\%V_{Bur}$ values than **6a**. However, the author uncovered an unexpected

pattern where the $\%V_{Bur}$ value has an inverse relationship with the size of the O-substituent [**6b** (Me) > **6c** (^{i}Pr) > **6d** (Cy)]. The steric bulk around the metal in the solid-state seemed to have no correlation with the catalytic activity. The author therefore performed DFT calculations to study the dynamic behavior of the ligands, in particular, the rotation of the C–O bond. The calculated structures of **6c** and **6d** showed $\%V_{Bur}$ values almost identical to those obtained experimentally. The author then optimized the structures with the C2–C3–O–R dihedral angle fixed at 0º (**6c*** and **6d***) (Scheme 3-5), thus allowing to study the metal centers in their most sterically hindered states. As summarized in Table 3-2, the ligands in these confined structures occupy a significantly larger space around the Au center than in the corresponding unstrained structures. It should also be noted that the sterically hindered (**L7**)AuCl (**6c***) was calculated to be 21.5 kcal/mol higher in energy than the ground state (**6c**), while a smaller energy gap of 15.5 kcal/mol was found for (**L9**)AuCl (**6d** and **6d***). This difference can be correlated with the observation that the reactivity of Pd/**L9** is higher than that of Pd/**L7** and with the fact that the rate-limiting reductive elimination has a lower barrier for **L9** compared to **L7**.

Table 3-2. Comparison of AuCl complexes of ligands **L1**, **L5**, **L7**, and **L9**.

entry	complex	Au–Cl length (Å)	$\%V_{Bur}$[a]
1	(**L1**)AuCl (**6a**)	2.291	57.5
2	(**L5**)AuCl (**6b**)	2.295	58.8
3	(**L7**)AuCl (**6c**)	2.2851(14)	58.4 (58.8)
4	(**L9**)AuCl (**6d**)	2.2967(8)	57.9 (59.2)
5	(**L7**)AuCl (**6c***)[b]	--	(61.9)
6	(**L9**)AuCl (**6d***)[b]	--	(62.0)

[a] Calculated using SambVca 2.1[18b] with the following parameters: radius of sphere = 3.5 Å; distance from sphere = 2.0 Å; mesh step = 0.05 Å; H atoms omitted; Bondi radii scaled by 1.17. Values in parentheses were determined using the calculated structures.
[b] C2–C3–O–R dihedral angle was fixed to 0º.



Scheme 3-5. $\%V_{Bur}$ values and Energy gaps of the calculated structures of (**L7**)AuCl (**6c**, **6c***) and (**L9**)AuCl (**6d**, **6d***).

Conclusion

In conclusion, the author has developed a novel catalytic system for the etherification of nitroarenes. Using the newly synthesized **L9** as a supporting ligand, the author has succeeded in promoting the C–O bond formation *via* reductive elimination whilst maintaining the activity of the catalyst towards the oxidative addition of the C–NO_2 bond. Experimental and theoretical analyses indicated that the flexibility and mobility of the ligand substituents are crucial for these elementary steps to proceed efficiently. The protocol established here covers both the aryloxylation and alkoxylation of nitroarenes with electron-donating group, and the formation of symmetrical ethers complementing the existing S_NAr-like denitrative C–O couplings.

Experimental section

Chemicals

L3–**L7** were prepared according to literature procedures.[12]

Preparation of L8. A 250-mL Schlenk flask was charged with a magnetic stir bar and 2-bromo-2',4',6'-triisopropyl-3-methoxy-6-methyl-1,1'-biphenyl[12a] (3.9 g, 9.6 mmol). The flask was evacuated and backfilled with argon three times and anhydrous DCM (40 mL) was added *via* a syringe. After the flask was cooled to –78 ºC (acetone/dry ice), BBr_3 (1.0 M in DCM, 11.6 mL, 11.6 mmol) was added slowly, warmed to rt, and stirred for 12 h. Saturated $NaHCO_3$ aq. was added and the reaction mixture was extracted with EtOAc (50 mL, three times). The combined organic layer was washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 95:5) to afford 2-bromo-3-hydroxy-2',4',6'-triisopropyl-6-methy-1,1'-biphenyl as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.3 Hz, 1H), 7.06 (s, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 5.51 (br s, 1 H), 2.95 (sept, *J* = 6.9 Hz, 1H), 2.36 (sept, *J* = 6.9 Hz, 2H), 1.93 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H), 1.07 (d, *J* = 6.9 Hz, 6H).

A 20-mL Schlenk flask was charged with a magnetic stir bar, 2-bromo-3-hydroxy-2',4',6'-triisopropyl-6-methy-1,1'-biphenyl (0.58 g, 1.5 mmol), and K_2CO_3 (0.66 g, 4.5 mmol). The flask was evacuated and backfilled with argon three times. DMF (3.0 ml) and 3-bomopentane (1.1 mL, 9.0 mmol) were added *via* a syringe and the reaction mixture was stirred overnight at 100 ºC. After cooling to rt, H_2O (20 mL) was added and the reaction mixture was extracted with Et_2O (20 mL, three times). The combined organic

layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 97:3) to afford 2-bromo-2',4',6'-triisopropyl-6-methyl-3-(3-pentyloxy)-1,1'-biphenyl as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.3 Hz, 1H), 7.09 (s, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.20 (quint, *J* = 4.6 Hz, 1H), 2.98 (sept, *J* = 6.9 Hz, 1H), 2.41 (sept, *J* = 6.9 Hz, 2H), 1.94 (s, 3H), 1.77 (quint, *J* = 7.3 Hz, 4H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.17 (d, *J* = 7.0 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H), 1.02 (t, *J* = 7.5 Hz, 6H).

A 20-mL Schlenk flask was charged with a magnetic stir bar and 2-bromo-2',4',6'-triisopropyl-6-methyl-3-(3-pentyloxy)-1,1'-biphenyl (0.23 g, 0.50 mmol). The flask was evacuated and backfilled with argon three times, and anhydrous THF (2.0 mL) was added *via* a syringe. After the flask was cooled to –78 ºC (acetone/dry ice), *t*-BuLi (1.5 M in pentane, 0.70 ml, 1.1 mmol) was added slowly and the reaction mixture was stirred for 30 min at –78 ºC. The solution was added with $ClPCy_2$ (0.12 mL, 0.55 mmol) slowly, warmed to rt, and then stirred for 4 h. The crude mixture was filtered through a short pad of Celite® and the filtrate was evaporated under reduced pressure. The obtained solid was recrystallized using hot acetone to afford the title compound (0.26 g, 4.5 mmol, 90%) as a colorless solid. mp. 166.9–167.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.4 Hz, 1H), 6.98 (s, 2H), 6.68 (d, *J* = 8.6 Hz, 1H), 4.20 (quint, *J* = 6.0 Hz, 1H), 2.92 (sept, *J* = 7.5 Hz, 1H), 2.45 (sept, *J* = 6.7 Hz, 2H), 2.35–2.28 (m, 2H), 1.83 (q, *J* = 7.1 Hz, 4H), 1.75–1.69 (m, 7H), 1.65–1.58 (m, 4H), 1.46 (d, *J* = 13.2 Hz, 2H), 1.29 (d, *J* = 6.4 Hz, 6H), 1.26–1.10 (m, 13H), 1.10–1.01 (m, 7H), 1.00–0.93 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7 (d, *J* = 2.0 Hz), 150.4 (d, *J* = 36.7 Hz), 147.0, 145.1, 136.4 (d, *J* = 8.5

Hz), 131.7, 129.4 (d, J = 7.8 Hz), 123.7 (d, J = 26.8 Hz), 120.8, 108.9, 78.8, 37.6, 37.5, 33.9, 33.6, 33.3, 30.1, 30.1, 27.8, 27.7, 27.7, 27.5, 26.4, 25.4, 25.1, 24.9, 24.0, 21.0, 10.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ –2.0. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{39}H_{61}OPNa$, 599.4352; found, 599.4371.

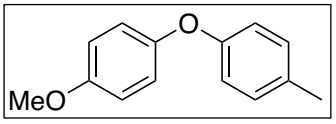
Preparation of L9. An 80-mL Schlenk flask was charged with a magnetic stir bar, 2-bromo-3-hydroxy-2',4',6'-triisopropyl-6-methy-1,1'-biphenyl (3.5 g, 9.1 mmol), and K_2CO_3 (3.7 g, 27 mmol). The flask was evacuated and backfilled with argon three times. DMF (25 ml) and bromocyclohexane (6.7 mL, 55 mmol) were added *via* a syringe and the reaction mixture was stirred overnight at 100 ºC. After cooling to rt, H_2O (100 mL) was added and the reaction mixture was extracted with Et_2O (50 mL, three times). The combined organic layer was washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 99:1 to 97:3) to afford 2-bromo-3-cyclohexyloxy-2',4',6'-triisopropyl-6-methyl-1,1'-biphenyl as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.2 Hz, 1H), 7.08 (s, 2H), 6.88 (d, J = 8.2 Hz, 1H), 4.32 (quint, J = 4.4 Hz, 1H), 2.97 (sept, J = 7.1 Hz, 1H), 2.39 (sept, J = 7.0 Hz, 2H), 2.07–1.79 (m, 7H), 1.75–1.67 (m, 2H), 1.45–1.25 (m, 10H), 1.16 (d, J = 6.9 Hz, 6H), 1.08 (d, J = 6.9 Hz, 6H).

An 80-mL Schlenk flask was charged with a magnetic stir bar and 2-bromo-3-cyclohexyloxy-2',4',6'-triisopropyl-6-methyl-1,1'-biphenyl (0.83 g, 1.8 mmol). The flask was evacuated and backfilled with argon three times, and anhydrous THF (15 mL) was added *via* a syringe. After the flask was cooled to –78 ºC (acetone/dry ice), ^{t}BuLi (1.61 M in pentane, 2.2 ml, 3.5 mmol) was added slowly and the reaction mixture was

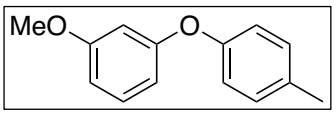
stirred for 50 min at –78 ºC. The solution was added with $ClPCy_2$ (0.47 mL, 2.1 mmol) slowly, warmed to rt, and then stirred for 2 days at 80 ºC. The crude mixture was filtered through a short pad of Celite® and the filtrate was evaporated under reduced pressure. The obtained solid was recrystallized using hot acetone to afford **L9** (0.67 g, 1.1 mmol, 65%) as a colorless solid. mp. 183.9–184.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 2H), 6.72 (d, *J* = 8.7 Hz, 1H), 4.30 (quint, *J* = 5.0 Hz, 1H), 2.93 (sept, *J* = 7.1 Hz, 1H), 2.45 (sept, *J* = 7.1 Hz, 2H), 2.38–2.24 (m, 2H), 2.20–2.12 (m, 2H), 2.00–1.76 (m, 4H), 1.79–1.52 (m, 11H), 1.52–1.08 (m, 26H), 0.98 (d, *J* = 6.9 Hz, 8H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2 (d, *J* = 2.9 Hz), 150.2 (d, *J* = 35.9 Hz), 147.0, 145.1, 136.4 (d, *J* = 8.1 Hz), 131.7, 129.3 (d, *J* = 7.2 Hz), 123.5 (d, *J* = 26.4 Hz), 120.8, 108.5, 74.4, 38.2, 38.1, 33.9, 33.6, 33.4, 32.1, 30.2, 30.1, 30.0, 28.1, 28.0, 27.7, 27.6, 26.4, 25.7, 25.0, 24.9, 24.3, 24.0, 21.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ –2.7. HRMS–ESI (+) (*m/z*): $[M+H]^+$ calcd for $C_{40}H_{62}OP$, 589.4533; found, 589.4554.

General procedure for Scheme 3-3. A 15-mL vial was charged with nitroarene (0.90 mmol), arenol (0.60 mmol), $Pd(acac)_2$ (9.1 mg, 0.030 mmol), **L9** (71 mg, 0.120 mmol), and a magnetic stir bar. In a glovebox, K_3PO_4 (382 mg, 1.8 mmol) and 1,4-dioxane (6.0 mL) were added to the vial (liquid nitroarenes and arenols were added in a glovebox). The resulting mixture was taken outside and stirred for 24 h at 160 ºC. After completion of the reaction, the mixture was filtered through a short pad of Celite®. The filtrate was added with H_2O_2 (30 wt% aq., 5 mL) and H_2O (20 mL), and stirred for 5 min at rt. The organic layer was separated. The remaining aqueous layer was washed with EtOAc (10 mL) three times and the combined organic layer was dried over anhydrous $MgSO_4$, and filtered. All volatiles were removed in vacuo and the residue was purified by MPLC using

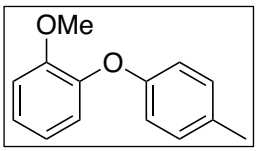
Biotage® SNAP Ultra to afford the corresponding product.



1-Methoxy-4-(*p*-tolyloxy)benzene (3b). The reaction of 4-nitroanisole (**1a**) (0.14 g, 0.90 mmol) and *p*-cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 95:5) afforded the title compound (0.12 g, 0.54 mmol, 90%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.7 Hz, 2H), 6.95 (d, *J* = 9.3 Hz, 2H), 6.90–6.81 (m, 4H), 3.80 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1, 155.6, 150.7, 132.0, 130.1, 120.3, 117.8, 114.8, 55.6, 20.6. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[14]

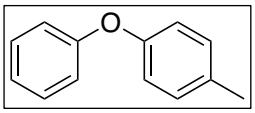


1-Methoxy-3-(*p*-tolyloxy)benzene (3c). The reaction of 3-nitroanisole (**1b**) (0.14 g, 0.90 mmol) and *p*-cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3 to 90:10) afforded the title compound (99 mg, 0.46 mmol, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (t, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 7.3 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.60–6.54 (m, 2H), 3.78 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9, 159.1, 154.4, 133.0, 130.2, 130.0, 119.3, 110.4, 108.4, 104.3, 55.3, 20.7. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[19]

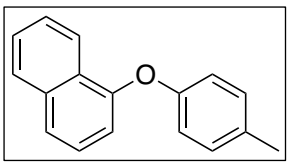


1-Methoxy-2-(*p*-tolyloxy)benzene (3d). The reaction of 2-nitroanisole (**1c**) (0.14 g, 0.90 mmol) and *p*-cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3 to 90:10) afforded the

title compound (92 mg, 0.43 mmol, 72%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.0 Hz, 3H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.97–6.84 (m, 4H), 3.86 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.4, 151.2, 145.7, 132.0, 130.0, 124.3, 121.0, 120.3, 117.5, 112.7, 56.0, 20.6. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[20]

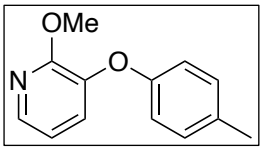


1-Methyl-4-phenoxybenzene (3e). The reaction of nitrobenzene (**1d**) (92 μL, 0.90 mmol) and *p*-cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3) afforded the title compound (96 mg, 0.52 mmol, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.8, 154.7, 132.9, 130.2, 129.6, 122.8, 119.1, 118.3, 20.7. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[21]

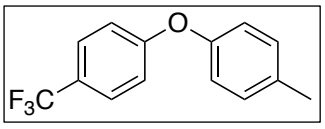


1-(*p*-Tolyloxy)naphthalene (3f). The reaction of 1-nitronaphthalene (**1e**) (0.16 g, 0.90 mmol) and *p*-cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3) afforded the title compound (0.13 g, 0.53 mmol, 89%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.64–7.54 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.3, 153.6, 134.9, 132.8, 130.3, 127.7, 126.7, 126.5, 125.8, 125.7, 122.8, 122.1, 118.8, 112.5, 20.7. All resonances of ^{1}H and ^{13}C NMR spectra were

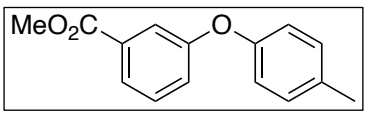
consistent with the reported values.[22]



2-Methoxy-3-(*p*-tolyloxy)pyridine (3g). The reaction of 2-methoxy-3-nitropyridine (**1f**) (0.14 g, 0.90 mmol) and *p*-cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3) afforded the title compound (86 mg, 0.40 mmol, 67%) as a colorless solid. R_f 0.40 (hexane:EtOAc = 97:3). mp. 50.1–50.7 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 4.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.82 (t, *J* = 6.2 Hz, 1H), 4.01 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 154.1, 141.5, 140.4, 133.2, 130.3, 125.7, 118.3, 116.9, 53.7, 20.7. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{13}NO_2Na$, 238.0838; found, 238.0847.

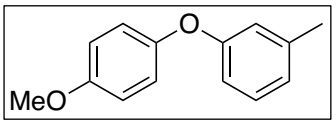


1-Methyl-4-(4-trifluoromethylphenoxy)benzene (3h). The reaction of 4-nitrobenzotrifluoride (**1g**) (0.17 g, 0.90 mmol) and *p*-cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 95:5) afforded the title compound (80 mg, 0.32 mmol, 53%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.0, 153.2, 134.4, 130.5, 127.0 (q, *J* = 4.6 Hz), 124.4 (q, *J* = 32.5 Hz) 124.2 (q, *J* = 273.0 Hz), 120.0, 117.3, 20.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.0. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[4d]

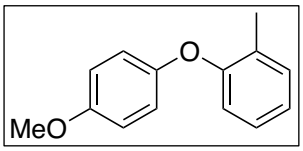


Methyl 3-(*p*-tolyloxy)benzoate (3i). The reaction of methyl 3-nitrobenzoate (**1h**) (0.16 g, 0.90 mmol) and *p*-

cresol (**2b**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3) afforded the title compound (52 mg, 0.21 mmol, 36%) as a colorless oil. R_f 0.30 (hexane:EtOAc = 97:3).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.22–7.13 (m, 3H), 6.92 (d, *J* = 6.7 Hz, 2H), 3.89 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 158.0, 154.1, 133.4, 131.8, 130.4, 129.6, 123.9, 122.8, 119.2, 118.9, 52.2, 20.7. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{14}O_3Na$, 265.0835; found, 265.0834.

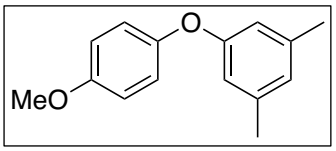


1-(4-Methoxyphenoxy)-3-methylbenzene (3j). The reaction of 4-nitroanisole (**1a**) (0.14 g, 0.90 mmol) and *m*-cresol (**2c**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3) afforded the title compound (96 mg, 0.45 mmol, 74%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.92–6.83 (m, 3H), 6.75 (d, 2H), 3.81 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5, 155.8, 150.2, 139.8, 129.3, 123.2, 120.8, 118.2, 114.8, 114.6, 55.6, 21.4. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[23]

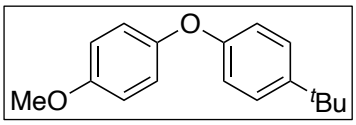


1-(4-Methoxyphenoxy)-2-methylbenzene (3k). The reaction of 4-nitroanisole (**1a**) (0.14 g, 0.90 mmol) and *o*-cresol (**2d**) (65 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3 to 95:5) afforded the title compound (0.10 g, 0.49 mmol, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.94–6.84 (m, 4H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.29 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8, 155.3, 151.1, 131.3, 129.0, 126.9, 123.0, 119.3, 118.0, 114.8,

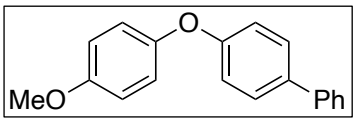
55.6, 16.2. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[21]



1-(4-Methoxyphenoxy)-3,5-dimethylbenzene (3l). The reaction of 4-nitroanisole (**1a**) (0.14 g, 0.90 mmol) and 3,5-dimethylphenol (**2e**) (73 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3) afforded the title compound (0.10 g, 0.46 mmol, 77%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01–6.93 (m, 2H), 6.91–6.85 (m, 2H), 6.69 (s, 1H), 6.56 (s, 2H), 3.81 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (101 MHz,$CDCl_3$): δ 158.5, 155.7, 150.3, 139.4, 124.2, 120.8, 115.3, 114.8, 55.6, 21.3. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[21]

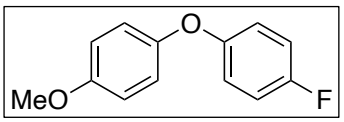


1-(4-*tert*-Butylphenoxy)-4-methoxybenzene (3m). The reaction of 4-nitroanisole (**1a**) (0.14 g, 0.90 mmol) and 4-*tert*-butylphenol (**2f**) (90 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 90:10) afforded the title compound (0.12 g, 0.54 mmol, 90%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 9.2 Hz, 2H), 6.88 (d, J = 8.0 Hz, 4H), 3.80 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 155.7, 150.5, 145.2, 126.4, 120.6, 117.1, 114.8, 55.6, 34.2, 31.5. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[14]

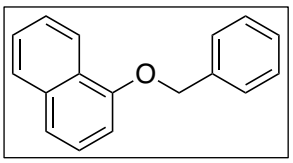


4-(4-Methoxyphenoxy)-1,1'-biphenyl (3n). The reaction of 4-nitroanisole (**1a**) (0.14 g, 0.90 mmol) and 4-phenylphenol (**2g**) (0.10 mg, 0.60 mmol) followed by purification by MPLC

(hexane:EtOAc = 97:3 to 90:10) afforded the title compound (98 mg, 0.35 mmol, 59%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.49 (m, 4H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36–7.28 (m, 1H), 7.06–6.98 (m, 4H), 6.91 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1, 156.0, 150.0, 140.6, 135.5, 128.7, 128.3, 126.9, 126.8, 120.9, 117.7, 114.9, 77.3, 77.0, 76.7, 55.7. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[14]

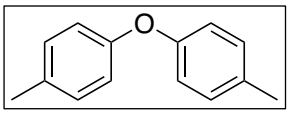


1-Fluoro-4-(4-methoxyphenoxy)benzene (3o). The reaction of 4-nitroanisole (**1a**) (0.14 g, 0.90 mmol) and 4-fluorophenol (**2h**) (67 mg, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3) afforded the title compound (61 mg, 0.28 mmol, 47%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02–6.82 (m, 8H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.3 (d, *J* = 240.4 Hz), 155.8, 154.2 (d, *J* = 2.0 Hz), 150.6, 120.2, 119.1 (d, *J* = 8.1 Hz), 116.1 (d, *J* = 23.2 Hz), 114.9, 55.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ –121.6. All resonances of ^{1}H, ^{13}C, and ^{19}F NMR spectra were consistent with the reported values.[21]



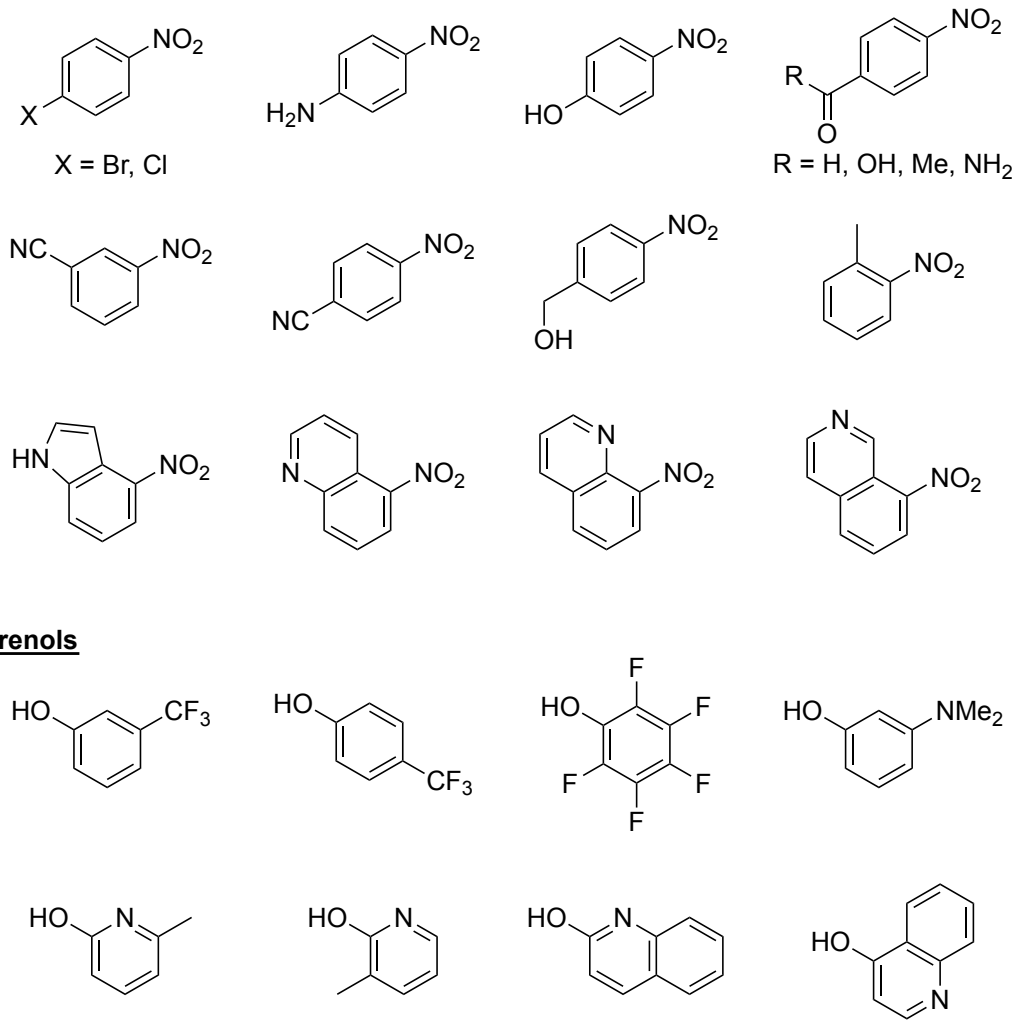
1-(Benzyloxy)naphthalene (3p). The reaction of 1-nitronaphthalene (**1e**) (0.10 g, 0.60 mmol) and benzyl alcohol (**2i**) (93 μL, 0.90 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 95:5) afforded the title compound (39 mg, 0.17 mmol, 28%) as a pale red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.58–7.34 (m, 9H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.27 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.5, 137.1, 134.5, 128.6, 127.9, 127.4, 127.4, 126.4, 125.8, 125.7, 125.2,

122.2, 120.5, 105.2, 70.1. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[24]



4,4'-Dimethyldiphenyl ether (3q). The reaction of 4-nitrotoluene (**1i**) (82 mg, 0.60 mmol) and H_2O (16 μL, 0.90 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 95:5) afforded the title compound (32 mg, 0.16 mmol, 54%) as a pale red solid.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.2 Hz, 4H), 6.89 (d, J = 6.4 Hz, 4H), 2.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.3, 132.4, 130.1, 118.6, 20.6. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[19]

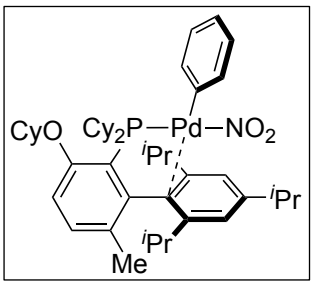
Nitroarenes



Arenols

Figure S3-1. Unsuccessful substrates.

Procedures for Scheme 3-4.



Reaction of (cod)Pd(CH_2SiMe_3)$_2$ with nitrobenzene (1d) in the presence of L9: Synthesis of (L9)Pd(Ph)(NO_2) (4a). A 15-mL vial was charged with **L9** (97 mg, 0.25 mmol) and a magnetic stir bar. In a glovebox, nitrobenzene (**1d**) (0.15 μL, 1.5 mmol), (cod)Pd(CH_2SiMe_3)$_2$ (0.14 g, 0.25 mmol) and THF (8.0 mL) were added to the vial and allowed to stir for 10 min at ambient temperature. The resulting mixture was stirred for 48 h at 60 ºC. After completion of the reaction, removal of the solvent under reduced pressure gave a black solid, which was washed with hexane (2 mL, 5 times) to remove unreacted **L9** and **1d**. The residue was extracted with 10 mL of $CHCl_3$. The obtained solution was evaporated under reduced pressure to afford the title compound as a yellow solid (60 mg, 73 μmol, 29%). Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a saturated $CHCl_3$ solution at rt. mp. 183.0 ºC (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.07 (m, 5H), 6.78 (d, *J* = 7.0 Hz, 4H), 4.44–4.28 (m, 1H), 2.96–2.71 (m, 3H), 2.60 (sept, *J* = 7.1 Hz, 2H), 2.19 (d, *J* = 11.7 Hz, 2H), 1.95 (d, *J* = 6.6 Hz, 5H), 1.88 (d, *J* = 12.8 Hz, 2H), 1.78 (d, *J* = 9.5 Hz, 2H), 1.74–1.63 (m, 11H), 1.58–1.35 (m, 5H), 1.33–1.04 (m, 18H), 0.96 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.5, 153.9, 149.6, 148.3, 148.1, 140.8, 136.9, 134.9, 131.0, 130.9, 126.1, 125.0, 123.6, 122.3, 120.8, 111.0, 76.1, 35.8, 35.5, 34.0, 32.0, 31.7, 29.6, 29.2, 27.7, 27.6, 26.6, 26.0, 25.5, 24.6, 24.4, 24.3, 23.0, 19.3. Observed complexity is due to C–P coupling. ^{31}P NMR (162 MHz, $CDCl_3$): δ 35.5 (34.7 in 1,4-dioxane-*d*$_8$). HRMS–ESI (+) (*m/z*): $[M–NO_2]^+$ calcd for $C_{46}H_{66}OPPd$, 771.3881; found, 771.3894. Anal. Calcd for $C_{46}H_{66}O_3NPPd\cdot 0.8CHCl_3$: C, 61.51; H, 7.37; N, 1.53. Found: C, 61.42; H, 7.34; N, 1.46. Elemental analysis was carried out using crystals of **4a**, which were prepared as well as

those for X-ray crystallographic analysis. The X-ray analysis showed that the obtained crystals include the equimolar amount of $CHCl_3$ molecule (Fig. S6). It was difficult to remove $CHCl_3$ completely in spite of long-time evacuation. Elemental analysis suggested only 20% of $CHCl_3$ was removed.

Reaction of (L9)Pd(Ph)(NO_2) (4a) with *p*-cresol (2b) in the presence of K_3PO_4: Synthesis of (L9)Pd(Ph)(O–*p*-tol) (5) and reductive elimination to afford 3e.

A 4-mL vial (A) was charged with (**L9**)Pd(Ph)(NO_2) (**4a**) (25 mg, 18 μmol), 1,4-dioxane-d_8 (0.50 mL) and a stirring bar. A separate 4-mL vial (B) was charged with *p*-cresol (**2b**) (3.9 mg, 36 μmol), K_3PO_4 (12 mg, 54 μmol), 1,4-dioxane-d_8 (0.50 mL) and a stirring bar. After the reaction mixture in vial (A) was stirred for 30 min at ambient temperature, the contents of vial (B) were transferred to vial (A) using a pipet. The resulting mixture was stirred for 24 h at rt, then filtered with glass fiber filter and eluted with 1,4-dioxane into a J. Young NMR tube. ^{31}P NMR (162 MHz, 1,4-dioxane-d_8): δ 37.5 (Figure 3-1). Although the author failed to fully characterize the obtained complex probably because of residual **2b**, this was assumed to be a transmetalation product (**L9**)Pd(Ph)(O–*p*-tol) (**5**) based on ^{1}H NMR spectrum compared with an analogous complex found in the literature.[12a]

The reaction mixture in the NMR tube was then heated at 60 ºC for 1 h, at 80 ºC for 1 h, at 100 ºC for 1 h. The reaction was monitored by ^{1}H NMR to observe the formation of **3e** upon heating at higher temperature than 80 ºC (Figure S3-2). To determine the yield of **3e**, another 4-mL vial was charged with **(L9)**Pd(Ph)(NO_2) (**4a**) (25 mg, 18 μmol), *p*-cresol (**2b**) (3.9 mg, 36 μmol), K_3PO_4 (12 mg, 54 μmol), and 1,4-dioxane (1.0 mL) and a stirring bar, and the resulting mixture was stirred for 24 h at 150 ºC. The yield of **3e** based

on **4a** was calculated to be 65% by GC analysis of reaction mixture using a calibration curve (Figure S3-3).

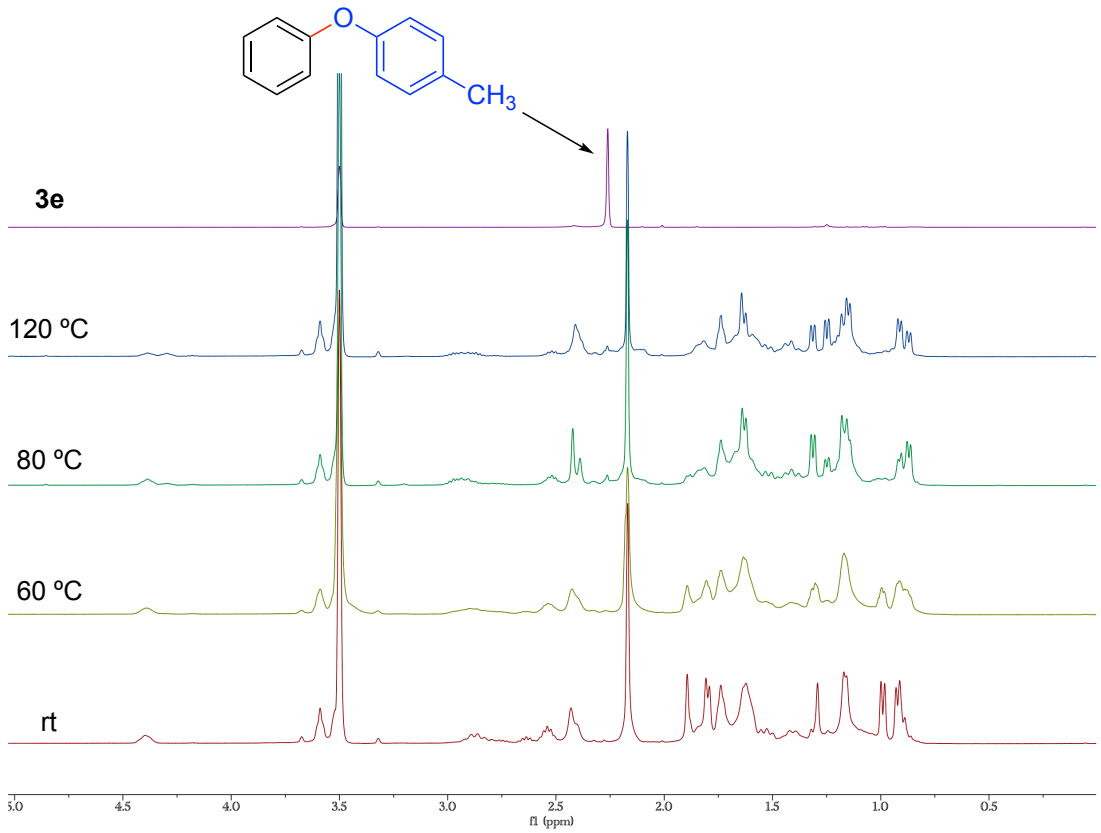


Figure S3-3. ^{1}H NMR monitoring upon heating of "**5**".

Table S3-1. Data for the GC calibration curve obtained using an authentic sample of **3e**.

entry	mass (mg)		$x = \frac{\text{mass of } \mathbf{3e}}{\text{mass of } C_{13}H_{28}}$	GC area		$y = \frac{\text{GC area of } \mathbf{3e}}{\text{GC area of } C_{13}H_{28}}$
	3e	$C_{13}H_{28}$		**3e**	$C_{13}H_{28}$	
1	5.8	7.5	0.773333	6199458	8844709	0.700923
2	9.9	7.4	1.337838	10873101	9583978	1.134508
3	12.7	7.5	1.693333	13265164	9307997	1.425136
4	15.2	7.6	2.000000	16192853	9491905	1.705964
5	18.8	7.5	2.506667	18910052	9709914	1.947499
6	23.8	7.4	3.216216	23941517	9243468	2.590101

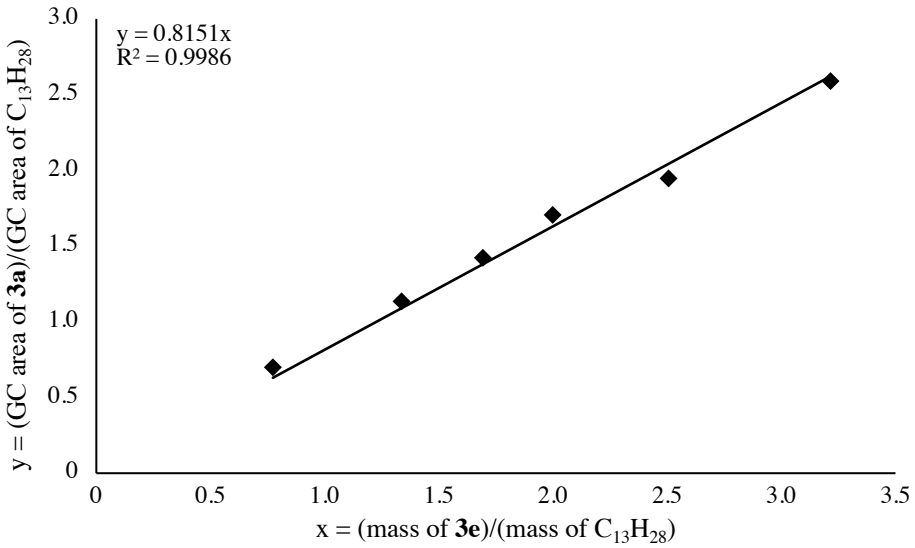


Figure S3-3. GC calibration curve to determine the yield of **3e**.

X-ray analysis of 4a. Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a saturated $CHCl_3$ solution at rt.

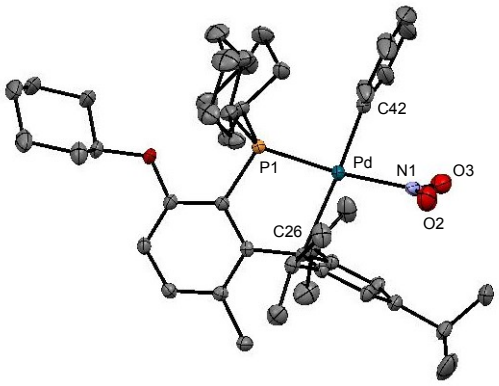


Figure S3-6. Crystal structure of **4a** (hydrogen atoms and $CHCl_3$ solvate molecules omitted for clarity; only selected atoms are labeled). Selected bond length (Å): Pd1–N1 2.1114(18), Pd1–C42 2.017(2), Pd1–C26 2.4416(18), Pd1–P1 2.2875(6). Selected bond angles (º): C42–Pd1–N1 79.79(7), C42–Pd1–P1 94.09(6), P1–Pd1–C26 83.38(4), N1–Pd1–C26 102.79(6).

General procedure for the synthesis of Au complexes. A 4-mL vial was charged with **L5**, **L7** or **L9** (50 μmol) and a stirring bar. In a glovebox, AuCl·SMe_2 (26 mg, 50 μmol) and toluene (1.0 mL) were added to the vial. (In the case of **L5**, DCM was used as a solvent.) The resulting mixture was stirred for 5 h at rt. The solvent was removed under reduced pressure and the residue was triturated with hexane to give the desired gold complex as a colorless solid.

Analytical data of 6b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.5 Hz, 1H), 7.06 (s, 2H), 6.89 (d, *J* = 8.5 Hz, 1H), 3.92 (s, 3H), 2.97 (sept, *J* = 8.5, 7.9 Hz, 1H), 2.58–2.43 (m, 2H), 2.28 (sept, *J* = 6.9 Hz, 2H), 2.03–1.92 (m, 2H), 1.85–1.68 (m, 7H), 1.67–1.52 (m, 4H), 1.52–1.41 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.34–1.26 (m, 8H), 1.24–1.06 (m, 6H), 0.95 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 150.2, 148.8 (d, *J* = 13.7 Hz), 144.8, 134.8, 134.6, 134.5, 132.8, 132.7, 122.3, 116.2, 115.8, 109.4 (d, *J* = 4.8 Hz), 55.4, 39.4, 39.1, 34.5, 34.5, 34.2, 30.4, 29.6, 27.5, 27.4, 26.9, 26.7, 25.8, 25.5, 24.8, 24.5, 21.5. ^{31}P NMR (162 MHz, $CDCl_3$): δ 41.6. mp. 269.0 ºC (decomp.). HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{35}H_{53}AuClOPNa$, 775.3080; found, 775.3082. Anal. Calcd for $C_{35}H_{53}AuClOP$: C, 55.81; H, 7.09. Found: C, 55.55; H, 7.10. Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a saturated DCM solution at rt.

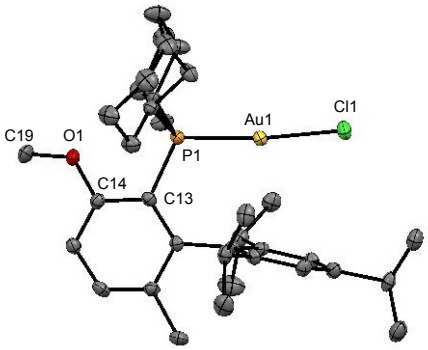


Figure S3-7. Crystal structure of **6b** (hydrogen atoms omitted for clarity; only selected atoms are labeled). Selected bond length (Å): Au1–P1 2.2375(8), Au1–Cl1 2.2950(8), P1–C13 1.841(3). Selected bond angles (º): P1–Au1–Cl1 172.55(3), C13–P1–Au1 113.57(10). Selected dihedral angle (º): C19–O1–C14–C13 157.3(3).

Analytical data of 6c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.2 Hz, 1H), 7.06 (s, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 4.75 (sept, *J* = 5.4 Hz, 1H), 3.04–2.90 (m, 1H), 2.68–2.53 (m, 2H), 2.33–2.23 (m, 2H), 2.04–1.91 (m, 2H), 1.87–1.41 (m, 20H), 1.36 (d, *J* = 6.9 Hz, 6H), 1.33 (d, *J* = 7.0 Hz, 6H), 1.29–1.25 (m, 1H), 1.24–1.10 (m, 6H), 0.96 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.3, 150.1, 149.2 (d, *J* = 14.1 Hz), 144.8, 134.7, 134.6, 131.9 (d, *J* = 8.1 Hz), 122.2, 115.8, 115.3, 109.5 (d, *J* = 5.1 Hz), 69.5, 39.6, 39.2, 34.9, 34.8, 34.2, 30.3, 29.1, 27.5, 27.4, 27.0, 26.8, 25.8, 25.6, 24.8, 24.5, 21.9, 21.4. ^{31}P NMR (162 MHz, $CDCl_3$): δ 40.9. mp. 274.0 ºC (decomp.). HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{57}AuClOPNa$, 803.3393; found, 803.3386. Anal. Calcd for $C_{35}H_{53}AuClOP$: C, 56.88; H, 7.35. Found: C, 56.93; H, 7.22. Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a saturated benzene solution at rt.

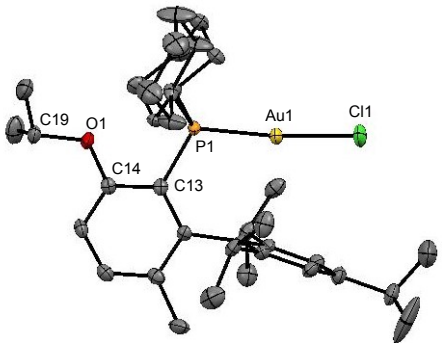


Figure S3-8. Crystal structure of **6c** (hydrogen atoms omitted for clarity; only selected atoms are labeled). Selected bond length (Å): Au1–P1 2.2342(13), Au1–Cl1 2.2851(14), P1–C13 1.839(6). Selected bond angles (º): P1–Au1–Cl1 173.70(6), C13–P1–Au1 114.39(19). Selected dihedral angle (º): C19–O1–C14–C13 179.3(5).

Analytical data of 6d. ^{1}H NMR (400 MHz, CDCl3): δ 7.30 (d, *J* = 8.2 Hz, 1H), 7.06 (s, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 4.45–4.33 (m, 1H), 3.05–2.88 (m, 1H), 2.72–2.55 (m, 2H), 2.30 (sept, *J* = 6.9 Hz, 2H), 2.23–2.14 (m, 2H), 2.03–1.84 (m, 4H), 1.84–1.66 (m, 8H), 1.66–1.41 (m, 10H), 1.40–1.25 (m, 15H), 1.25–1.07 (m, 6H), 0.95 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.1, 149.2 (d, *J* = 14.0 Hz), 144.8, 134.8, 134.6, 131.8 (d, *J* = 8.5 Hz), 122.2, 115.6, 115.1, 109.5 (d, *J* = 4.7 Hz), 75.7, 39.3, 38.9, 34.8, 34.7, 34.2, 32.0, 30.3, 29.1, 27.5, 27.4, 27.0, 26.8, 25.7, 25.6, 25.5, 24.8, 24.5, 24.2, 21.5. ^{31}P NMR (162 MHz, $CDCl_3$): δ 41.2. mp. 276.0 ºC (decomp.). HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{40}H_{61}AuClOPNa$, 843.3706; found, 843.3704. Anal. Calcd. for $C_{40}H_{61}AuClOP$: C, 58.50; H, 7.49. Found: C, 58.28; H, 7.39. Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a saturated toluene solution at rt.

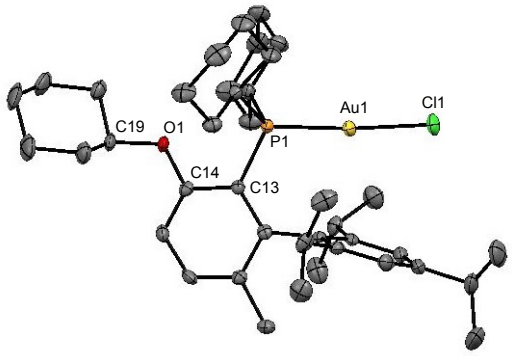


Figure S3-9. Crystal structure of **6d** (hydrogen atoms and C_7H_7 omitted for clarity; only selected atoms are labeled). Selected bond length (Å): Au1–P1 2.2387(7), Au1–Cl1 2.2967(8), P1–C13 1.833(3). Selected bond angles (º): P1–Au1–Cl1 175.57(3), C13–P1–Au1 114.36(9). Selected dihedral angle (º): C19–O1–C14–C13 –175.7(2).

X-ray crystallographic analysis. Crystallographic data of **4a**, **6b**, **6c**, and **6d** were summarized in Tables S3-2 and S3-3. CCDC 2067444 (**4a**), 2067443 (**6b**), 2060380 (**6c**), and 2057920 (**6d**) (Depositions Number) contain the supplementary crystallographic data. These data can be obtained from The Cambridge Crystallographic Data Centre.

Table S3-2. Crystallographic data of **4a**.

compound	**4a**
empirical formula	$C_{46}H_{66}NO_3PPd$, $CHCl_3$
formula weight	937.73
crystal system	monoclinic
space group	*P* $2_1/c$ (#14)
a, Å	17.041(2)
b, Å	10.8543(12)
c, Å	25.171(3)
α, deg.	90
β, deg.	98.532(2)
γ, deg.	9
V, Å^3	4604.3(9)
Z	4
$D_{calcd.}$, g/cm^3	1.353
μ [Mo-*K*α], mm^{-1}	0.652
T, K	143
crystal size, mm	0.12 x 0.09 x 0.06
θ range, deg.	3.10 to 27.50
reflections measured	14327
unique data	10543
restraints	0
parameters	523
*R*1 ($I > 2.0\sigma(I)$)	0.0356
*wR*2 ($I > 2.0\sigma(I)$)	0.0843
*R*1 (all data)	0.0405
*wR*2 (all data)	0.0874
GOF on F^2	1.0

Table S3-3. Crystallographic data of **6b**, **6c**, and **6d**.

compound	**6b**	**6c**	**6d**
empirical formula	$C_{35}H_{53}AuClOP$	$C_{37}H_{57}AuClOP$	$2(C_{40}H_{61}AuClOP), C_7H_7$
formula weight	753.20	781.25	1733.67
crystal system	monoclinic	orthorhombic	triclinic
space group	$P\ 2_1/c$ (#14)	$P\ 2_1\ 2_1\ 2_1$ (#19)	$P\ \bar{1}$
a, Å	9.9629(9)	9.9243(14)	11.5108(16)
b, Å	14.1957(12)	15.578(2)	12.398(2)
c, Å	23.797(3)	23.092(3)	16.701(3)
α, deg.	90	90	70.526(8)
β, deg.	98.246(5)	90	70.491(6)
γ, deg.	90	90	71.5290(10)
V, Å^3	3330.8(6)	3570.0(8)	2060.7(6)
Z	4	4	1
$D_{calcd.}$, g/cm^3	1.502	1.453	1.397
μ [Mo-$K\alpha$], mm^{-1}	4.585	4.281	3.704
T, K	143	293	143
crystal size, mm	0.18 x 0.16 x 0.09	0.12 x 0.11 x 0.07	0.21 x 0.13 x 0.11
θ range, deg.	3.22 to 27.53	3.00 to 27.51	3.23 to 27.49
reflections measured	10029	29183	16587
unique data	7612	8116	8991
restraints	0	0	9
parameters	352	370	436
$R1$ ($I > 2.0\sigma(I)$)	0.0286	0.0327	0.0279
$wR2$ ($I > 2.0\sigma(I)$)	0.0587	0.0484	0.0545
$R1$ (all data)	0.0345	0.0361	0.0327
$wR2$ (all data)	0.0609	0.0496	0.0560
GOF on F^2	1.046	0.977	0.990

Computational details. All geometry optimizations were performed by the DFT with B3PW91[25]-D3 functional[26] in the gas phase because this functional reproduced the geometry of (**L9**)AuCl (**6d**). The LANL2DZ basis sets were used for Au atom with Los Alamos ECP.[27] The 6-31G(d) basis sets were used for all other atoms.[28] All DFT calculations were performed using Gaussian 16.[29] The Gibbs energy change was evaluated at 298.15 K and 1 atm.

Cartesian coordinates for calculated structures.

6c

Au	0.76088	–1.26639	0.86304
Cl	2.67863	–2.43867	1.53503
P	–1.22621	–0.36995	0.18657
O	–3.45379	0.93841	–1.12495
C	–2.36196	0.13249	1.58729
H	–3.35909	–0.19985	1.26429
C	–1.98271	–0.60135	2.88547
H	–1.89926	–1.68104	2.72202
H	–0.98422	–0.26999	3.20089
C	–2.99350	–0.30010	3.99487
H	–2.70000	–0.82259	4.91365
H	–3.97908	–0.69693	3.70717
C	–3.10435	1.20484	4.24573
H	–3.85766	1.41276	5.01602
H	–2.14387	1.57516	4.63328
C	–3.44087	1.95113	2.95327
H	–3.47651	3.03360	3.13089
H	–4.44630	1.65420	2.61605
C	–2.42955	1.64260	1.84521
H	–2.69585	2.18459	0.93452
H	–1.44150	2.00161	2.15170
C	–2.18721	–1.69647	–0.70422
H	–3.16817	–1.26502	–0.92429
C	–1.50531	–2.07098	–2.02382
H	–0.48634	–2.42203	–1.81309
H	–1.41601	–1.18546	–2.66442
C	–2.27794	–3.17014	–2.75688
H	–3.26534	–2.78412	–3.05340
H	–1.75229	–3.43471	–3.68305
C	–2.46165	–4.40247	–1.87049
H	–1.47631	–4.83700	–1.64765
H	–3.03646	–5.17368	–2.39861
C	–3.15240	–4.02625	–0.55936
H	–3.25817	–4.90612	0.08742
H	–4.17083	–3.66864	–0.77548
C	–2.38158	–2.93222	0.18720
H	–2.92400	–2.66557	1.10182
H	–1.40062	–3.31930	0.49865
C	–1.11058	1.05288	–0.97029
C	–2.31111	1.55578	–1.52792
C	–2.28377	2.61882	–2.42625
H	–3.19628	3.00363	–2.86671
C	–1.06515	3.20414	–2.74996
H	–1.05570	4.04153	–3.44409
C	0.13648	2.76206	–2.20263
C	0.11782	1.66242	–1.31084
C	–4.74806	1.43044	–1.49582
H	–4.75074	1.65597	–2.57141
C	–5.70008	0.27593	–1.23175
H	–6.72642	0.56213	–1.48303
H	–5.42402	–0.59809	–1.82987
H	–5.66706	–0.00368	–0.17288
C	–5.09961	2.67318	–0.68821
H	–6.07390	3.06579	–0.99845
H	–5.14863	2.42352	0.37675
H	–4.35297	3.46212	–0.81921
C	1.41774	3.48349	–2.53821
H	2.22783	2.79518	–2.79309
H	1.26872	4.17048	–3.37760
H	1.77495	4.06857	–1.68404
C	1.46094	1.24632	–0.78913
C	2.25367	0.35062	–1.53935

C	3.58938	0.16155	–1.17856
H	4.18771	–0.53493	–1.75559
C	4.16581	0.82178	–0.09582
C	3.35045	1.67109	0.65238
H	3.77895	2.16868	1.52059
C	2.01232	1.89741	0.33539
C	1.67807	–0.43062	–2.70973
H	0.58874	–0.39126	–2.61766
C	2.04364	0.19498	–4.06243
H	1.60950	1.19315	–4.17439
H	3.13206	0.27985	–4.16884
H	1.67103	–0.42636	–4.88620
C	2.08804	–1.90876	–2.67450
H	1.94794	–2.34138	–1.67799
H	1.49235	–2.48084	–3.39617
H	3.14159	–2.04340	–2.94584
C	5.61018	0.62040	0.32677
H	6.00512	1.61565	0.58374
C	6.50382	0.03985	–0.77037
H	6.43876	0.61968	–1.69869
H	7.54927	0.03789	–0.44208
H	6.23291	–0.99876	–0.99524
C	5.67669	–0.25124	1.59077
H	5.08473	0.17965	2.40501
H	5.26464	–1.24484	1.39004
H	6.71384	–0.35527	1.93357
C	1.18047	2.78447	1.24706
H	0.15852	2.80980	0.85112
C	1.68886	4.23036	1.30121
H	1.06098	4.83296	1.96879
H	2.71666	4.27563	1.67966
H	1.67596	4.70084	0.31303
C	1.12767	2.18455	2.66006
H	0.44887	2.75703	3.30491
H	0.79385	1.14184	2.63246
H	2.11758	2.19325	3.12980

6d

C	–1.55547	–1.56474	–0.14121
C	–2.08831	–1.60893	1.16726
C	–3.46311	–1.44584	1.33945
C	–4.32633	–1.22611	0.26826
C	–3.77497	–1.16744	–1.01002
C	–2.40871	–1.33000	–1.23978
C	–0.12401	–1.94955	–0.36791
C	0.10887	–3.33075	–0.56086
C	1.41570	–3.77362	–0.76053
C	2.49011	–2.89595	–0.80051
C	2.27053	–1.53298	–0.61761
C	0.96365	–1.04353	–0.38994
H	–3.87644	–1.45719	2.34433
H	–4.42845	–0.97171	–1.85644
H	1.59890	–4.83514	–0.91176
H	3.48693	–3.26849	–0.99993
O	3.25192	–0.59473	–0.73702
C	4.59736	–0.77736	–0.25998
P	0.75263	0.76943	–0.16476
C	1.43950	1.62024	–1.68495
C	1.44506	0.75601	–2.95278
C	0.69342	2.94018	–1.94795
C	2.07333	1.52082	–4.12226
H	1.99263	–0.17446	–2.78598
C	1.33043	3.70498	–3.11063
H	–0.35319	2.71383	–2.19166
C	1.36114	2.84995	–4.37839
H	3.13314	1.71301	–3.89535
H	2.35711	3.99397	–2.83868
H	1.84702	3.39375	–5.19840
C	1.92469	1.27649	1.19402
C	1.86231	2.79230	1.43781
C	1.63392	0.50077	2.48248
C	2.80118	3.20242	2.57712
H	2.13381	3.33896	0.52730
C	2.56747	0.92625	3.61824
H	0.59395	0.68577	2.78156
C	2.49070	2.43367	3.86169
H	3.84233	3.00502	2.27864
H	3.60384	0.65499	3.36391
H	3.18081	2.72919	4.66192
C	–5.81540	–1.05406	0.48903
H	–5.97957	–1.00676	1.57436
C	–6.33770	0.25514	–0.11470
H	–7.39126	0.40447	0.15126
H	–5.75351	1.10716	0.24531
H	–6.27475	0.24014	–1.20991
C	–6.58766	–2.26538	–0.05242
H	–6.45239	–2.35797	–1.13734
H	–6.24079	–3.19776	0.40791
H	–7.66186	–2.16228	0.14374
H	2.93083	1.02545	0.84454
H	0.83147	3.08102	1.68848
H	2.72171	4.28354	2.74554
H	1.47800	2.69342	4.20246
H	2.31265	0.37230	4.53048
H	1.72554	–0.57709	2.30145

H	0.41615	0.48449	–3.21133
H	2.05445	0.89431	–5.02327
H	0.32839	2.64861	–4.69932
H	0.77726	4.63587	–3.28649
H	0.66003	3.56349	–1.04780
H	2.48485	1.84192	–1.42623
Au	–1.34368	1.45670	0.42990
Cl	–3.38249	2.32599	1.20537
C	–1.19560	–1.79151	2.38409
C	–1.18338	–3.24345	2.88102
C	–1.57012	–0.83760	3.52578
H	–0.17531	–1.54645	2.07425
H	–0.58117	–3.33205	3.79380
H	–2.20068	–3.58164	3.11313
H	–1.71571	0.18559	3.16265
H	–2.49781	–1.14487	4.02236
H	–0.78102	–0.83516	4.28754
C	–1.88344	–1.17764	–2.65769
C	–2.19127	0.23038	–3.18832
C	–2.44283	–2.23919	–3.61308
H	–0.79405	–1.29902	–2.63022
H	–1.83057	0.99837	–2.49622
H	–1.72617	0.39089	–4.16913
H	–3.27028	0.38231	–3.30326
H	–2.19738	–3.25249	–3.28026
H	–3.53431	–2.16869	–3.68755
H	–2.03038	–2.10507	–4.62045
C	–1.02330	–4.32632	–0.60869
H	–0.65145	–5.34608	–0.46447
H	–1.53066	–4.29153	–1.57930
H	–1.78828	–4.12519	0.14494
H	–0.75980	–3.92118	2.13374
C	4.70099	–1.50178	1.07865
C	5.52388	–1.37075	–1.31907
H	4.91923	0.26110	–0.09544
C	6.15227	–1.46256	1.57112
H	4.37928	–2.54439	0.97788
H	4.02673	–1.03035	1.80201
C	6.97213	–1.33527	–0.81790
H	5.24123	–2.40842	–1.53431
H	5.40904	–0.80711	–2.25219
C	7.10828	–2.05161	0.52925
H	7.29182	–0.28860	–0.70564
H	7.63694	–1.78605	–1.56428
H	8.14317	–1.99297	0.88783
H	6.88115	–3.11965	0.39507
H	6.23480	–2.00509	2.52036
H	6.43868	–0.42109	1.77977

6c*

Au	–0.65144	–1.01915	–1.03366
Cl	–2.44821	–2.15569	–2.02242
P	1.30228	–0.18415	–0.16570
O	3.57697	1.39812	1.96820
C	2.34517	0.60326	–1.52078
H	3.35698	0.18571	–1.41352
C	1.85027	0.19817	–2.92035
H	1.76706	–0.89068	–3.00594
H	0.83834	0.59169	–3.07268
C	2.77945	0.75649	–4.00157
H	2.40413	0.46786	–4.99090
H	3.77690	0.30229	–3.89825
C	2.89946	2.27776	–3.89530
H	3.58834	2.66378	–4.65692
H	1.91732	2.72967	–4.09733
C	3.36350	2.69298	–2.49793
H	3.40685	3.78628	–2.41406
H	4.38674	2.32335	–2.33182
C	2.44210	2.12951	–1.41238
H	2.78748	2.43457	–0.41960
H	1.44118	2.55714	–1.53358
C	2.26671	–1.68301	0.38830
H	3.24619	–1.35943	0.74052
C	1.56416	–2.38851	1.55313
H	0.55694	–2.68572	1.23533
H	1.44717	–1.69560	2.39521
C	2.34063	–3.63098	1.99705
H	3.31533	–3.32772	2.40890
H	1.79829	–4.12939	2.81012
C	2.56235	–4.59172	0.82846
H	1.58909	–4.96414	0.47755
H	3.13841	–5.46648	1.15501
C	3.27434	–3.88516	–0.32569
H	3.40776	–4.56883	–1.17312
H	4.28205	–3.58322	–0.00120
C	2.49761	–2.64740	–0.78642
H	3.04730	–2.14922	–1.59436
H	1.52812	–2.95471	–1.20342
C	1.14718	0.97729	1.26838
C	2.22119	1.51118	2.04326
C	1.93484	2.35841	3.12753
H	2.78462	2.72611	3.69333
C	0.65161	2.72882	3.44871
H	0.48334	3.39904	4.28842
C	–0.43279	2.26543	2.70255

C	–0.18631	1.38451	1.63094
C	4.48969	0.71879	1.11041
H	3.97401	0.28501	0.25942
C	5.48496	1.75618	0.60998
H	6.23999	1.28138	–0.02631
H	4.98253	2.53562	0.03155
H	5.99123	2.22933	1.45789
C	5.16920	–0.36650	1.93718
H	5.85563	–0.95449	1.31777
H	5.73857	0.09260	2.75214
H	4.43362	–1.04302	2.38296
C	–1.82006	2.74462	3.06016
H	–2.52086	1.92122	3.22078
H	–1.78990	3.35157	3.97098
H	–2.25464	3.35400	2.26195
C	–1.46299	0.97036	0.94978
C	–2.23502	–0.07942	1.49922
C	–3.55864	–0.23789	1.08463
H	–4.13935	–1.05173	1.50526
C	–4.14664	0.60221	0.14122
C	–3.35424	1.60646	–0.41522
H	–3.79193	2.25117	–1.17543
C	–2.02905	1.81093	–0.03510
C	–1.64451	–1.05328	2.50684
H	–0.55693	–0.95458	2.44315
C	–2.04485	–0.72833	3.95236
H	–1.62986	0.22926	4.28005
H	–3.13636	–0.68491	4.05269
H	–1.67444	–1.50347	4.63453
C	–1.99926	–2.50877	2.17271
H	–1.84470	–2.72930	1.11089
H	–1.38435	–3.19234	2.77074
H	–3.04746	–2.73116	2.40430
C	–5.57718	0.43514	–0.33688
H	–5.98350	1.44849	–0.47840
C	–6.48382	–0.28880	0.66045
H	–6.43872	0.16741	1.65637
H	–7.52365	–0.25679	0.31612
H	–6.20779	–1.34583	0.75581
C	–5.59943	–0.27350	–1.70020
H	–4.99117	0.26150	–2.43674
H	–5.17811	–1.27978	–1.61346
H	–6.62594	–0.34641	–2.08116
C	–1.22046	2.89912	–0.72079
H	–0.19230	2.82646	–0.34986
C	–1.71855	4.31321	–0.39827
H	–1.14081	5.05993	–0.95670
H	–2.77353	4.43195	–0.67215
H	–1.61649	4.54200	0.66689
C	–1.19595	2.67283	–2.23879
H	–0.48530	3.35320	–2.72488
H	–0.91671	1.64154	–2.47620
H	–2.18099	2.85268	–2.68393

6d*

C	1.83329	0.92039	–0.91085
C	2.40227	1.74709	0.08183
C	3.71639	1.51103	0.48725
C	4.49217	0.49295	–0.05950
C	3.90359	–0.32995	–1.02227
C	2.59132	–0.14750	–1.45132
C	0.57373	1.35616	–1.60955
C	0.85418	2.22333	–2.68363
C	–0.21027	2.70464	–3.44796
C	–1.50401	2.35802	–3.14736
C	–1.82333	1.51761	–2.06660
C	–0.77277	0.97375	–1.26474
H	4.15314	2.13966	1.26133
H	4.47959	–1.15295	–1.43373
H	–0.01584	3.36799	–4.28739
H	–2.33807	2.73569	–3.72982
O	–3.18064	1.40159	–2.03002
C	–4.08659	0.76376	–1.14258
P	–0.96673	–0.16545	0.18491
C	–1.94226	–1.66306	–0.35160
C	–1.23606	–2.39784	–1.49476
C	–2.20050	–2.60033	0.83888
C	–2.02182	–3.63986	–1.92241
H	–1.10349	–1.72145	–2.34922
C	–2.97647	–3.84485	0.39502
H	–1.24015	–2.90332	1.28063
C	–2.25773	–4.57730	–0.73862
H	–2.99104	–3.33399	–2.34517
H	–3.98056	–3.54702	0.05477
H	–2.83582	–5.45515	–1.05310
C	–2.01348	0.65793	1.51760
C	–1.54993	0.26342	2.93021
C	–2.07931	2.18421	1.39030
C	–2.49593	0.84730	3.98376
H	–1.48270	–0.82502	3.03121
C	–3.01567	2.77606	2.44808
H	–1.07382	2.59440	1.53111
C	–2.59105	2.36890	3.85950
H	–3.49730	0.40596	3.86229
H	–4.04104	2.42372	2.26306

H	–3.29108	2.77233	4.60173
C	5.93067	0.28905	0.37006
H	6.12688	0.98959	1.19430
C	6.18109	–1.12922	0.89612
H	7.20261	–1.21816	1.28490
H	5.47009	–1.38477	1.68667
H	6.06461	–1.87345	0.09905
C	6.89251	0.63551	–0.77545
H	6.73965	–0.03812	–1.62775
H	6.73847	1.66165	–1.12870
H	7.93563	0.53425	–0.45203
H	–3.03073	0.25822	1.39926
H	–0.53673	0.64627	3.09894
H	–2.14840	0.56264	4.98540
H	–1.60729	2.80784	4.08008
H	–3.03702	3.86886	2.35127
H	–2.39631	2.48580	0.38717
H	–0.23512	–2.69963	–1.16122
H	–1.47969	–4.15764	–2.72380
H	–1.28992	–4.94779	–0.37166
H	–3.12118	–4.50979	1.25490
H	–2.76141	–2.07976	1.62444
H	–2.91346	–1.33526	–0.72213
Au	0.96525	–0.99681	1.10527
Cl	2.74211	–2.08153	2.18533
C	1.60786	2.85687	0.74914
C	2.12838	4.25696	0.40196
C	1.57273	2.66087	2.27123
H	0.58001	2.79275	0.37495
H	1.56481	5.02292	0.94988
H	3.18606	4.36174	0.67138
H	1.28219	1.63763	2.52904
H	2.55615	2.84152	2.71902
H	0.86505	3.35788	2.73766
C	1.98760	–1.11851	–2.45552
C	2.30713	–2.57630	–2.09679
C	2.40910	–0.82104	–3.90091
H	0.90195	–0.99430	–2.40365
H	2.13710	–2.77663	–1.03321
H	1.68408	–3.25612	–2.69065
H	3.35284	–2.82386	–2.31328
H	2.01890	0.14076	–4.24399
H	3.50229	–0.80307	–3.99042
H	2.02856	–1.59729	–4.57618
C	2.25675	2.66738	–3.02836
H	2.24724	3.29591	–3.92463
H	2.93016	1.82467	–3.20843
H	2.71122	3.24165	–2.21541
H	2.02705	4.46991	–0.66678
C	–5.08078	1.79796	–0.62227
C	–4.81388	–0.33689	–1.90881
H	–3.56291	0.33897	–0.29139
C	–6.10766	1.12219	0.29236
H	–5.58185	2.26209	–1.48229
H	–4.54779	2.59477	–0.09266
C	–5.83758	–1.03004	–1.00603
H	–5.31566	0.12708	–2.77004
H	–4.08990	–1.05188	–2.31810
C	–6.83267	–0.01997	–0.42710
H	–5.30975	–1.53293	–0.18100
H	–6.36159	–1.81544	–1.56395
H	–7.52873	–0.52044	0.25660
H	–7.43666	0.39741	–1.24581
H	–6.82717	1.86411	0.65902
H	–5.59347	0.72291	1.17951

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Chapter 4

Pd/NHC-Catalyzed Cross-Coupling Reactions of Nitroarenes

NHC ligands effective for the cross-coupling of nitroarenes were identified. A rational design of the NHC ligand structures enabled significant reduction of catalyst loadings compared with the previous system employing BrettPhos as a phosphine ligand. Experimental and theoretical studies to compare these ligands gave some insights into high activity of the newly developed NHC ligands.

Introduction

Denitrative transformations of nitroarenes are advantageous in synthetic chemistry because they serve as an important class of chemical feedstocks readily available from simple nitration of aromatic compounds.[1] In addition, well-established functionalizations of nitroarenes including S_NAr/S_EAr/VNS and/or C–H functionalization[2,3] to afford multi-substituted nitroarenes in a site-selective manner make the transformations highly attractive to access a variety of substituted arenes. Conventionally, the replacement of the NO_2 group with various functional groups could be achieved in 3 steps including reduction, diazotization, and Sandmeyer/cross-coupling reactions. Direct transformations of nitro groups have been therefore of high demand to upgrade the synthetic utility of nitroarenes. Some examples of such single-step transformations of Ar–NO_2 bonds have been reported but lacked generality in terms of scope of nitroarenes.[4] The difficulty in the use of nitroarenes for cross-coupling reactions is partly derived from reduction of the NO_2 group by low-valent metal catalysts.[5] Nevertheless, the author previously reported that the combination of palladium as a metal center and BrettPhos[6a] as a supporting ligand enabled the unprecedented oxidative addition of Ar–NO_2 bonds to palladium(0) to enable the Suzuki–Miyaura coupling,[7a] Buchwald–Hartwig amination,[7b] and reductive denitration of nitroarenes.[7c] Although these coupling reactions opened a novel aspect in chemistry of nitroarenes, there still remained serious issues from a practical point of view such as high loadings of precious Pd (>5 mol%) and expensive Buchwald-type ligands[6] (10–20 mol%). Phosphine ligands could also be deactivated through oxidation by the NO_2 group.

To deviate from phosphine ligands, the author turned attention to the use of NHC ligands.[8] In 2005, the groups of Lassaletta and Glorius independently reported the use of

imidazo[1,5-*a*]pyridinylidenes,[9a,b] which appeared to be a hybrid form of the Buchwald-type ligands and NHC ligands (Figure 4-1). Subsequently, some derivatives were investigated and published.[9c–9k] Despite being structural mimics of the Buchwald-type ligands, they have rarely been applied to metal-catalyzed reactions. The author conceived the use of imidazo[1,5-*a*]pyridinylidene bearing an Ar group at the C5 position as a supporting ligand in the cross-coupling reactions of nitroarenes. NHC ligands generally possess higher electron-donicity and tolerance toward oxidation than phosphine ligands. The author expected that the NHC ligands could facilitate the rate-determining oxidative addition of Ar–NO_2 bond and elongate a catalyst lifetime by preventing the ligand oxidation.

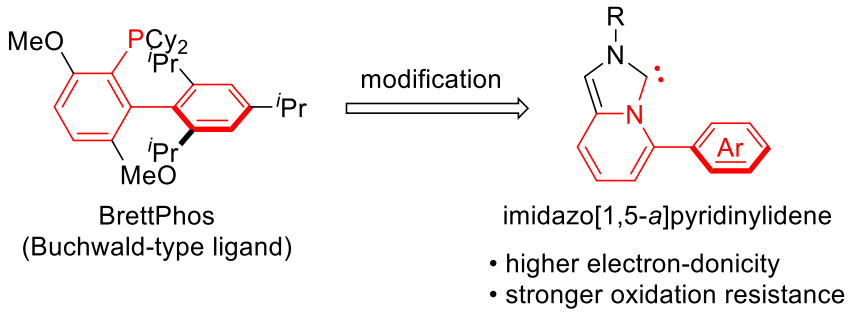
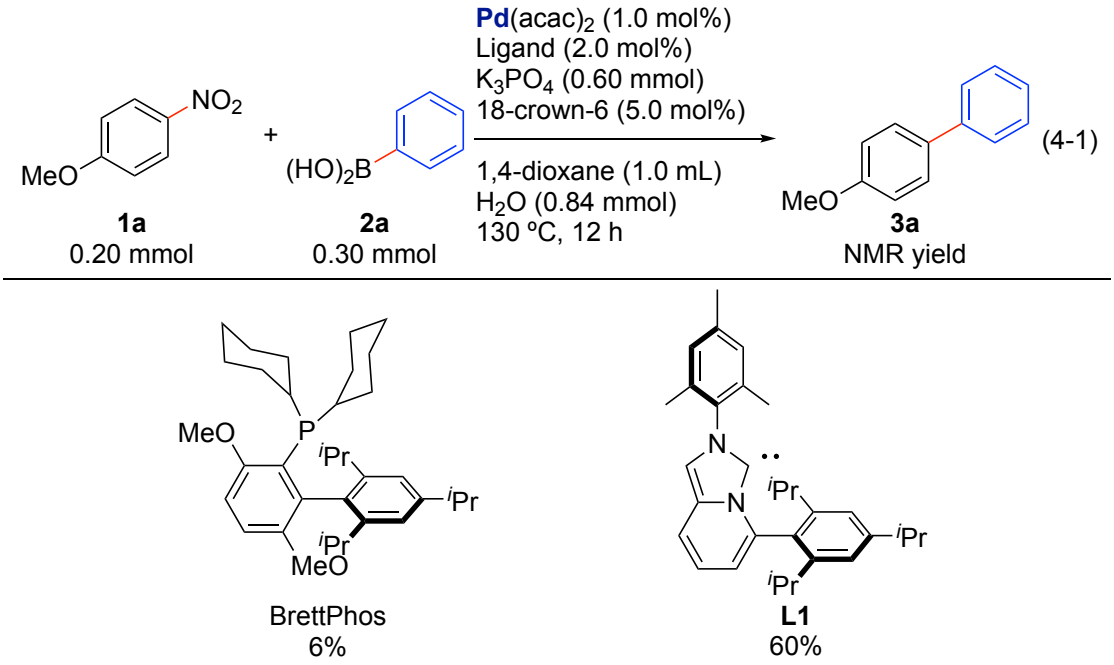


Figure 4-1. Design of imidazo[1,5-*a*]pyridinylidene ligands for the cross-coupling of nitroarenes.

Results and discussion

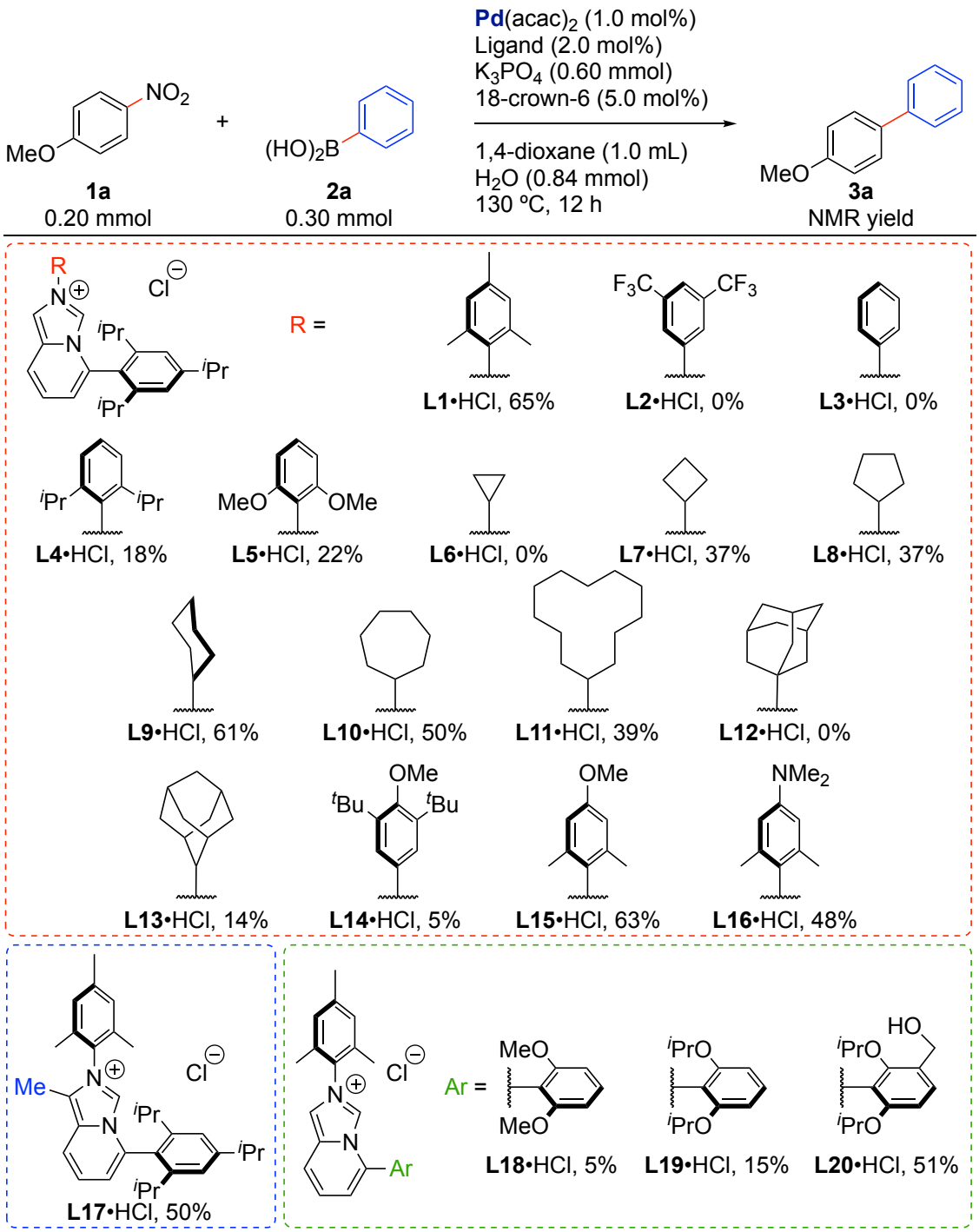
The author examined the Suzuki–Miyaura coupling of 4-nitroanisole (**1a**) and phenylboronic acid (**2a**) in the presence of 1.0 mol% $Pd(acac)_2$ and 2.0 mol% **L1**[9i] (Eq. 4-1). In contrast to the use of BrettPhos, which resulted in only 6% of the desired product **3a**, the use of **L1** drastically improved the yield of **3a** to 60%.



Motivated by the preliminary result, the author screened various imidazo[1,5-*a*]pyridinylidenes as ligands in the reaction of **1a** with **2a** using 1 mol% Pd (Scheme 4-1). The HCl adduct of **L1** could be used directly without any loss of the yield (entry 1).[10] Regarding the substituent on nitrogen, electron-withdrawing 3,5-bistrifluoromethyphenyl in **L2** and even the phenyl group in **L3** were not suitable at all, while sterically hindered 2,6-diisopropylphenyl in **L4** and 2,6-dimethoxyphenyl in **L5** deteriorated catalytic activity as well, though they were electron-donating. Cycloalkyl substituents seemed good for this system, except for the cyclopropyl group in **L6**, which could react with Pd(0).[11] **L9** showed the best performance among these, producing **3a** in 61% yield. The bulky adamantyl groups in **L12** and **L13**, and 3,5-di-*tert*-butyl-4-methoxyphenyl in **L14** retarded the reaction. **L15** and **L16**, which were expected to be more electron-donating than **L1**, unfortunately failed to improve catalytic activity. Similarly, introducing an electron-donating methyl substituent on the backbone in **L17** did not bring any positive effects. By analogy with the Buchwald-type phosphines, the properties of the C5-aryl group were found to be important. **L18** and **L19** were less active than **L1** in line with the

competition of the Buchwald phosphines (SPhos and RuPhos respectively vs. XPhos or BrettPhos) in the author's previous report.[7a] To the author's surprise, NHC bearing a hydroxymethyl group **L20** marked higher yield of **3a** than **L19**.[12]

Scheme 4-1. Optimization of ligand structures.



To make this system more efficient, the author made an attempt to use (**L1**)Pd complexes as catalyst precursors (Table 4-1). (**L1**)Pd(acac)Cl was prepared and examined first, but the yield was similar to the case where $Pd(acac)_2$ and **L1**•HCl were independently used. Another complex (**L1**)Pd(allyl)Cl proved to be effective to afford **3a** in 76%.

Table 4-1. Optimization of catalyst precursors.

Pd/**L1**	yield of **3a** (%)
$Pd(acac)_2$ (1.0 mo%) + **L1**•HCl (2.0 mol%)	65
(**L1**)Pd(acac)Cl (1.0 mol%)	61
(**L1**)Pd(allyl)Cl (1.0 mol%)	76

The author then carried out some analyses to verify the properties of **L1**. Figure 4-2 shows the time-course of the Suzuki–Miyaura coupling of **1a** with **2a** catalyzed by 5.0 mol%Pd/BrettPhos and 1.0 mol%Pd/**L1**. The former system turned out to be deactivated within 3 h,[13] whereas the coupling proceeded with the latter system much faster and the yield of **3a** kept increasing even after 4 h. These reaction profiles obviously revealed two significant effects associated with **L1**: rate-acceleration and longer catalyst lifetime. The higher reaction rate was also supported by DFT calculations. The activation barrier for the rate-limiting oxidative addition of **1a** to (**L1**)Pd^0 was calculated to be 27.2 kcal/mol, which was smaller than that to (BrettPhos)Pd^0 (30.1 kcal/mol) (Figure 4-3).[14] This difference was likely to derive from their HOMO energies. The higher HOMO level of (**L1**)Pd^0 could enable the faster oxidative addition of the Ar–NO_2 bond (Figure 4-4). Experimentally, a large difference of $\%V_{Bur}$[15] between (BrettPhos)AuCl and (**L1**)AuCl was noted (57.5% vs. 51.9%,[9i] respectively), illustrating that **L1** occupied less space around the Pd center, possibly allowing easier access of the substrate to Pd than with

BrettPhos. Furthermore, the rigid skeleton of **L1** could inhibit its flip in the coordination sphere, unlike BrettPhos which could show two different coordination modes. This rigidity could partly contribute to the robustness of (**L1**)Pd system in collaboration with reluctance to oxidation by nitroarenes.

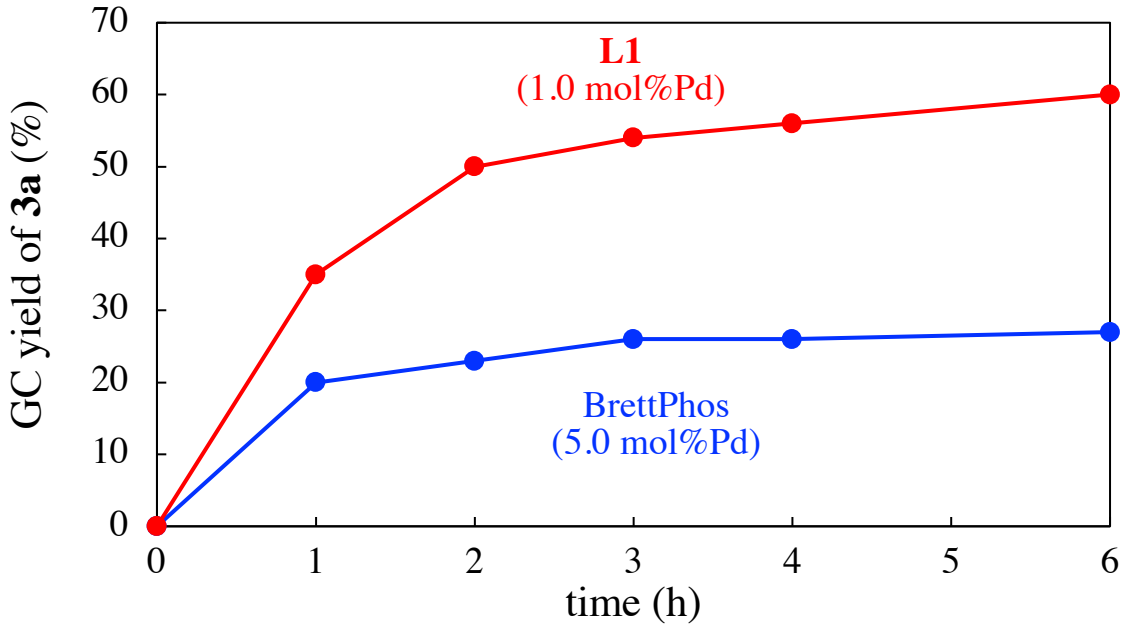


Figure 4-2. Time-courses of the coupling of 4-nitroanisole (**1a**) and phenylboronic acid (**2a**).

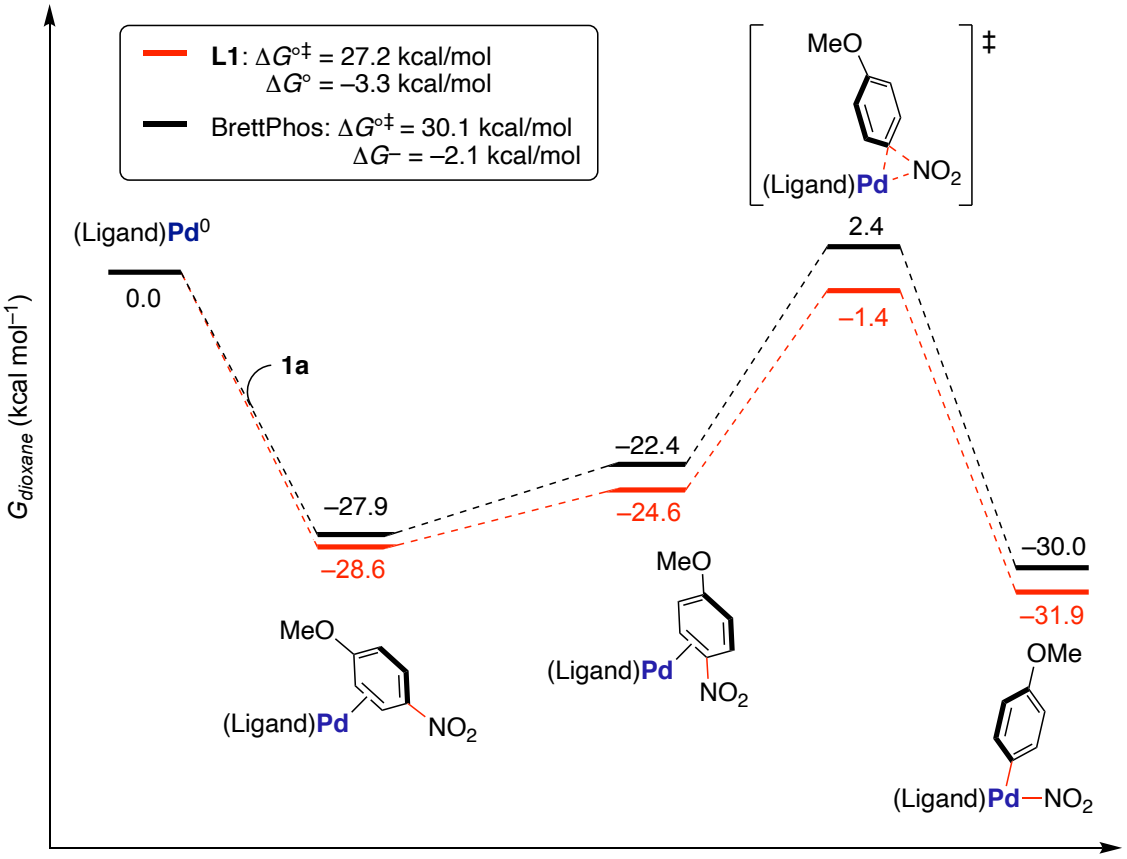


Figure 4-3. Calculated Gibbs energy profile of oxidative addition of **1a** to (**L1**)Pd^0 and (BrettPhos)Pd^0.

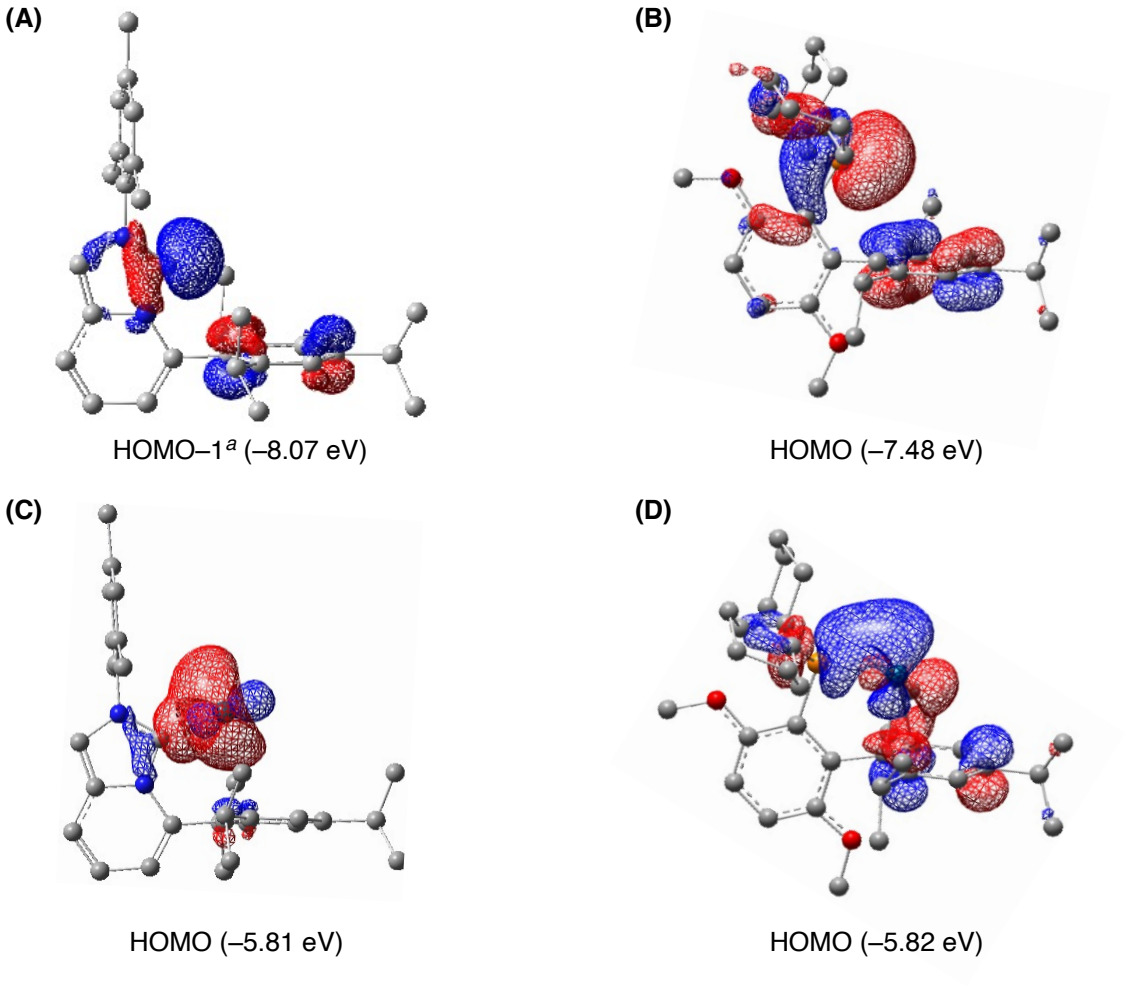


Figure 4-4. HOMOs of (A) **L1**, (B) BrettPhos, (C) (**L1**)Pd^0 and (D) (BrettPhos)Pd^0.

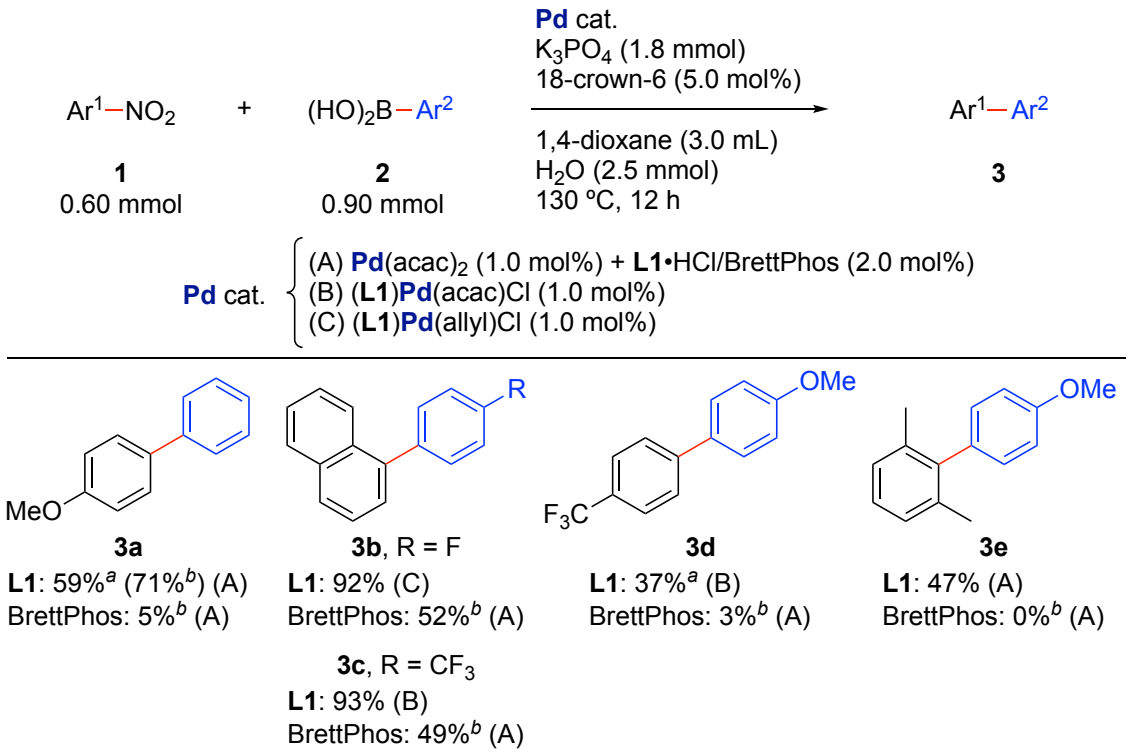
[a] The HOMO of **L1** is π MO of imidazopyridinylidene ring (–7.03 eV).

The author also checked the reactivity of the new catalyst to several other substrate sets (Scheme 4-2). The use of boronic acid neopentylglycol ester in combination with a catalyst derived from $Pd(acac)_2$ and **L1**•HCl slightly improved the yield of **3a**. Couplings of nitronaphthalene and F-containing arylboronic acids proceeded very smoothly to give **3b** and **3c**. A nitroarene bearing an electron-withdrawing trifluoromethyl group could be reacted, though the yield of biaryl **3d** was relatively low as observed in the author's original report.[7a] In all the cases, the new catalytic system performed much

better than 1 mol% Pd/BrettPhos. Moreover, 2,6-dimethylnitrobenzene, which was too sterically demanding to cross-couple under the previous conditions, afforded biaryl **3e** by the Pd/**L1** catalyst, possibly due to the reduced $\%V_{Bur}$ of **L1** compared with BrettPhos.

The Pd/NHC system developed herein catalyzed not only the Suzuki–Miyaura coupling, but also the Buchwald–Hartwig amination and reductive denitration of nitroarenes (Scheme 4-3). Aniline (**4**) could be coupled with **1a** to afford diarylamine **5** by using 1.0 mol% (**L1**)Pd(acac)Cl as a catalyst precursor. Denitration of **1a** proceeded well with (**L9**)Pd(acac)Cl, delivering anisole (**7**) in 62% yield. Both reactions again afforded the products in yields much higher than those catalyzed by 1 mol% Pd/BrettPhos.

Scheme 4-2. Scope of the Suzuki–Miyaura coupling of nitroarenes.



3a
L1: 59%[a] (71%[b]) (A)
BrettPhos: 5%[b] (A)

3b, R = F
L1: 92% (C)
BrettPhos: 52%[b] (A)

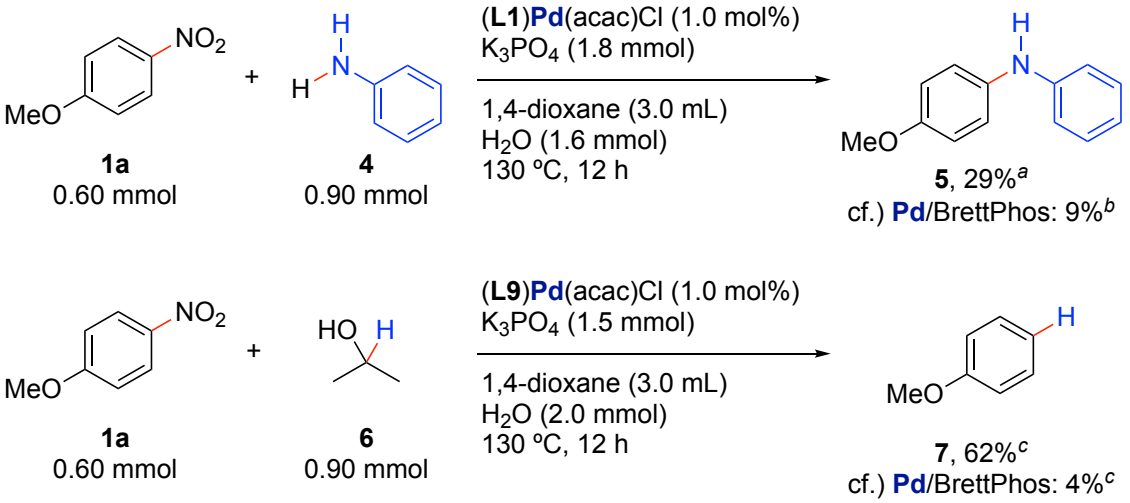
3c, R = CF_3
L1: 93% (B)
BrettPhos: 49%[b] (A)

3d
L1: 37%[a] (B)
BrettPhos: 3%[b] (A)

3e
L1: 47% (A)
BrettPhos: 0%[b] (A)

[a] Ar^2–B(nep)$_2$ was used instead of Ar^2–B(OH)$_2$.
[b] NMR yields determined using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 4-3. The Buchwald–Hartwig amination and reductive denitration of **1a**.



[a] Isolated yield.
[b] NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard.
[c] GC yields determined using *n*-$C_{13}H_{28}$ as an internal standard.

Conclusion

In conclusion, the author has developed new reaction conditions employing imidazo[1,5-a]pyridinylidene as NHC ligands for the cross-coupling reactions of nitroarenes. The Pd/NHC catalysts showed much higher activity than the Pd/BrettPhos system. Some insights into the reasons for the improved performance by the Pd/NHC catalyst are shown in terms of experimental and theoretical studies.

Experimental section

Chemicals

L1 and **L4** were prepared according to the literature procedures.[9i]

Preparation of L2•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde[9i] (155 mg, 0.50 mmol), 3,5-bis(trifluoromethyl)aniline (77 μL, 0.50 mmol), and EtOH (1 mL). After the mixture was stirred for 12 h at 90 ºC under air, the resulting dark brown solution was cooled to rt and the solvent was removed under reduced pressure. The residue was washed with hexane to afford *N*-[3,5-bis(trifluoromethyl)phenyl][6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a pale green solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.91 (t, *J* = 7.8 Hz, 1H), 7.77 (s, 1H), 7.70 (s, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.10 (s, 2H), 2.94 (sept, *J* = 6.9 Hz, 1H), 2.50 (sept, *J* = 6.9 Hz, 2H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H), 1.11 (d, *J* = 6.9 Hz, 6H).

A 15-mL vial was charged with *N*-[3,5-bis(trifluoromethyl)phenyl][6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (93 mg, 0.18 mmol), paraformaldehyde (5.2 mg, 0.18 mmol), TMSCl (45 μL, 0.36 mmol), and toluene (1.4 mL). After the mixture was stirred for 12 h at rt under air, volatile compounds were removed under reduced pressure. The residue was washed with hexane and Et_2O to afford the title compound (89 mg, 0.16 mmol, 87%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.35 (s, 1H), 8.61 (d, *J* = 9.2 Hz, 1H), 8.36 (s, 1H), 8.31 (s, 2H), 8.11 (s, 1H), 7.48 (dd, *J* = 8.9 Hz, 7.1 Hz, 1H), 7.25 (s, 2H) (overlaps with signal of $CHCl_3$), 7.10 (d, *J* = 6.4 Hz, 1H), 3.02 (sept, *J* = 6.9 Hz, 1H), 2.32 (sept, *J* = 6.9 Hz, 2H), 1.34 (d, *J* = 6.9

Hz, 6H), 1.17 (d, J = 5.6 Hz, 6H), 1.15 (d, J = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.3, 148.1, 136.0, 134.3 (q, J = 34.5 Hz), 133.4, 132.5, 126.0, 125.1 (q, J = 4.3 Hz), 124.9, 123.8, 122.7, 122.0 (q, J = 273.7 Hz), 121.6, 120.0, 119.7, 118.7, 34.5, 31.3, 25.3, 24.0, 23.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ –63.1. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{30}H_{31}N_2F_6$, 533.2386; found, 533.2395.

Preparation of L3•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (155 mg, 0.50 mmol), aniline (46 μL, 0.50 mmol), and MeOH (5 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-phenyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.87 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.34–7.26 (m, 3H), 7.11 (s, 2H), 2.95 (sept, J = 6.9 Hz, 1H), 2.55 (sept, J = 6.9 Hz, 2H), 1.30 (d, J = 6.9 Hz, 6H), 1.15 (d, J = 6.9 Hz, 6H), 1.12 (d, J = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-phenyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (90 mg, 0.24 mmol) and MOMCl (0.36 mL, 4.7 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was washed with Et_2O to afford the title compound (24 mg, 0.056 mmol, 24%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.2 (s, 1H), 8.70 (d, J = 9.2 Hz, 1H), 8.16 (s, 1H), 7.78 (d, J = 7.3 Hz, 2H), 7.65–7.56 (m, 3H), 7.41 (dd, J = 9.4 Hz, 6.6 Hz, 1H), 7.24 (s, 2H), 7.02 (d, J = 6.4 Hz, 1H), 3.01 (sept, J = 6.9 Hz, 1H), 2.32 (sept, J = 6.9 Hz, 2H), 1.34 (d, J = 6.9 Hz, 6H), 1.16 (d, J = 6.9 Hz, 6H), 1.12 (d, J = 6.9 Hz,

6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0, 148.1, 134.6, 133.1, 132.3, 131.2, 130.8, 125.3, 124.1, 123.1, 122.6, 120.8, 120.2, 118.6, 117.7, 34.5, 31.1, 25.1, 24.1, 23.8. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{28}H_{33}N_2$, 397.2638; found, 397.2647.

Preparation of L5•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (155 mg, 0.50 mmol), 2,6-dimethoxyaniline (77 mg, 0.50 mmol), and EtOH (1 mL). After the mixture was stirred for 12 h at 90 ºC under air, resulting dark red solution was cooled to rt and the solvent was removed under reduced pressure. The residue was washed with hexane to afford *N*-(2,6-dimethoxyphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a yellow solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 8.7 Hz, 1H), 7.08 (s, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 6H), 2.93 (sept, *J* = 6.9 Hz, 1H), 2.55 (sept, *J* = 6.9 Hz, 2H), 1.28 (d, *J* = 7.3 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H), 1.10 (d, *J* = 6.9 Hz, 6H).

A 15-mL vial was charged with *N*-(2,6-dimethoxyphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (184 mg, 0.41 mmol), paraformaldehyde (12.0 mg, 0.41 mmol), TMSCl (104 μL, 0.83 mmol), and toluene (3 mL). After the mixture was stirred for 24 h at rt under air, volatile compounds were removed under reduced pressure. The residue was purified by recrystallization from DCM and EtOAc to afford the title compound (127 mg, 0.26 mmol, 62%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.65 (d, *J* = 9.2 Hz, 1H), 7.92 (s, 1H), 7.44 (t, *J* = 8.5 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.14 (s, 2H), 6.93 (d, *J* = 6.9 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 2H), 3.72 (s, 6H), 2.92 (sept, *J* = 6.9 Hz, 1H), 2.33 (sept, *J* = 6.9 Hz, 2H),

1.25 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H), 1.02 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.5, 152.7, 148.0, 132.9, 132.6, 131.2, 124.6, 124.3, 123.0, 122.4, 120.2, 120.1, 119.5, 112.2, 104.5, 56.4, 34.3, 31.0, 24.8, 23.9, 23.7. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{30}H_{37}N_2O_2$, 457.2850; found, 457.2859.

Preparation of L6•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.62 g, 2.0 mmol), cyclopropylamine (140 μL, 2.0 mmol), and EtOH (6.5 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-cyclopropyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, C_6D_6): δ 8.68 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.24 (s, 2H), 7.12 (t, J = 7.8 Hz, 2H), 6.99 (d, J = 7.3 Hz, 1H), 2.89 (sept, J = 6.9 Hz, 1H), , 2.77 (sept, J = 6.9 Hz, 2H), 2.73–2.67 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H), 1.23 (d, J = 6.9 Hz, 6H), 1.18 (d, J = 6.9 Hz, 6H), 1.08–1.03 (m, 2H), 0.70–0.64 (m, 2H).

A 4-mL vial was charged with *N*-cyclopropyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (174 mg, 0.50 mmol) and MOMCl (0.76 mL, 10 mmol). After the mixture was stirred for 48 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and EtOAc to afford the title compound (110 mg, 0.28 mmol, 55%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.18 (d, J = 9.2 Hz, 1H), 8.14 (s, 1H), 7.33 (dd, J = 9.2 Hz, 6.9 Hz, 1H), 7.22 (s, 2H), 6.92 (d, J = 6.9 Hz, 1H), 4.42–4.35 (m, 1H), 3.01 (sept, J = 6.9 Hz, 1H), 2.21 (sept, J = 6.9 Hz, 2H), 1.42–1.36 (m, 2H), 1.34 (d, J = 6.9 Hz, 6H), 1.32–1.26 (m, 2H), 1.12 (d, J = 6.9 Hz, 6H), 1.09 (d, J = 6.9 Hz, 6H). ^{13}C

NMR (101 MHz, $CDCl_3$): δ 152.7, 147.8, 133.1, 131.0, 124.9, 124.1, 122.4, 122.0, 119.8, 118.8, 117.1, 34.3, 33.3, 31.0, 25.1, 23.8, 23.7, 8.1. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{25}H_{33}N_2$, 361.2638; found, 361.2649.

Preparation of L7•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.46 g, 1.5 mmol), cyclobutylamine (127 μL, 1.5 mmol), and EtOH (10 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-cyclobutyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.07 (s, 2H), 4.26 (quint, *J* = 7.9 Hz, 1H), 2.93 (sept, *J* = 6.9 Hz, 1H), 2.50 (sept, *J* = 6.9 Hz, 2H), 2.40–2.31 (m, 2H), 2.20 (quint, *J* = 9.6Hz, 2H), 1.89–1.79 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.4 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-cyclobutyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (181 mg, 0.50 mmol) and MOMCl (0.76 mL, 10 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O to afford the title compound (130 mg, 0.32 mmol, 63%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.13 (s, 1H), 8.12 (d, *J* = 10.1 Hz, 1H), 7.33 (dd, *J* = 9.2 Hz, 6.9 Hz, 1H), 7.22 (s, 2H), 6.92 (d, *J* = 7.8 Hz, 1H), 5.50 (quint, *J* = 8.2 Hz, 1H), 3.01 (sept, *J* = 6.9 Hz, 1H), 2.81–2.71 (m, 2H), 2.48 (dquint, *J* = 9.6Hz, 2.3 Hz, 2H), 2.23 (sept, *J* = 6.9 Hz, 2H), 2.01 (sept, *J* = 5.0 Hz, 2H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.9, 148.0,

133.5, 131.2, 124.7, 124.3, 122.6, 119.8, 119.6, 119.1, 116.8, 54.8, 34.5, 31.4, 31.2, 25.1, 24.1, 23.9, 14.8. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{26}H_{35}N_2$, 375.2795; found, 375.2806.

Preparation of L8•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.46 g, 1.5 mmol), cyclopentylamine (148 μL, 1.5 mmol), and EtOH (10 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-cyclopentyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 0.9 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.08 (s, 2H), 3.86 (quint, *J* = 6.3 Hz, 1H), 2.94 (sept, *J* = 6.9 Hz, 1H), 2.51 (sept, *J* = 6.9 Hz, 2H), 1.98–1.82 (m, 4H), 1.82–1.63 (m, 4H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-cyclopentyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (188 mg, 0.50 mmol) and MOMCl (0.76 mL, 10 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O to afford the title compound (123 mg, 0.29 mmol, 58%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.16 (d, *J* = 9.2 Hz, 1H), 8.04 (s, 1H), 7.31 (t, *J* = 8.0 Hz, 6.9 Hz, 1H), 7.21 (s, 2H), 6.90 (d, *J* = 6.9 Hz, 1H), 5.52 (quint, *J* = 6.9 Hz, 1H), 3.01 (sept, *J* = 6.9 Hz, 1H), 2.55–2.44 (m, 2H), 2.22 (sept, *J* = 6.9 Hz, 2H), 1.97–1.80 (m, 6H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.07 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7, 147.8, 133.2, 131.1, 124.7, 124.1, 122.4, 120.0, 119.6, 118.8,

116.3, 63.0, 34.3, 34.0, 31.0, 24.9, 23.9, 23.7, 23.5. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{27}H_{37}N_2$, 389.2951; found, 389.2963.

Preparation of L9•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.97 g, 3.2 mmol), cyclohexylamine (0.36 mL, 3.2 mmol), and MeOH (8 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-cyclohexyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.07 (s, 2H), 3.33–3.24 (m, 1H), 2.93 (sept, *J* = 6.9 Hz, 1H), 2.50 (sept, *J* = 6.9 Hz, 2H), 1.82 (t, *J* = 16.3 Hz, 4H), 1.72–1.55 (m, 4H), 1.45–1.30 (m, 2 H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.4 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 6H).

A 15-mL vial was charged with *N*-cyclohexyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.54 g, 1.4 mmol) and MOMCl (2.2 mL, 28 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was washed with Et_2O to afford the title compound (0.57 g, 1.3 mmol, 94%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.21 (d, *J* = 9.2 Hz, 1H), 8.01 (s, 1H), 8.31 (dd, *J* = 8.7 Hz, 7.3 Hz, 1H), 7.21 (s, 2H), 6.90 (d, *J* = 6.9 Hz, 1H), 5.01 (tt, *J* = 11.7 Hz, 3.7 Hz, 1H), 3.01 (sept, *J* = 6.9 Hz, 1H), 2.28 (d, *J* = 12.7 Hz, 2H), 2.23 (sept, *J* = 6.9 Hz, 2H), 1.91 (d, *J* = 13.3 Hz, 2H), 1.79–1.66 (m, 3H), 1.58 (q, 12.8 Hz, 2H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.31–1.18 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.06 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7, 147.9, 133.3, 131.1, 124.7, 124.2, 122.5, 119.6, 119.5, 118.9, 116.0, 61.4, 34.4, 34.1, 31.1,

25.0, 24.8, 24.5, 24.0, 23.8. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{28}H_{39}N_2$, 403.3108; found, 403.3118.

Preparation of L10•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.46 g, 1.5 mmol), cycloheptylamine (190 μL, 1.5 mmol), and EtOH (10 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-cycloheptyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.08 (s, 2H), 3.46 (quint, *J* = 5.5 Hz, 1H), 2.94 (sept, *J* = 6.9 Hz, 1H), 2.51 (sept, *J* = 6.9 Hz, 2H), 1.86–1.74 (m, 6H), 1.71–1.49 (m, 6H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-cycloheptyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.20 g, 0.50 mmol) and MOMCl (0.76 mL, 10 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O to afford the title compound (111 mg, 0.25 mmol, 49%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.01 (s, 1H), 7.31 (dd, *J* = 8.2 Hz, 7.3 Hz, 1H), 7.22 (s, 2H), 6.89 (d, *J* = 6.4 Hz, 1H), 5.25–5.15 (m, 1H), 3.01 (sept, *J* = 6.9 Hz, 1H), 2.30–2.17 (m, 4H), 2.03–1.53 (m, 10H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.06 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7, 147.9, 133.2, 131.0, 124.6, 124.3, 122.4, 119.6, 119.4, 119.1, 116.3, 63.8, 36.4, 34.3, 31.0, 26.9, 24.9, 24.0, 23.9, 23.7. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{29}H_{41}N_2$, 417.3264;

found, 417.3275.

Preparation of L11•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.46 g, 1.5 mmol), cyclododecylamine (0.30 mL, 1.5 mmol), and EtOH (10 mL). After the mixture was stirred for 8 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-cyclododecyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.08 (s, 2H), 3.50 (br s, 1H), 2.93 (sept, *J* = 6.9 Hz, 1H), 2.51 (sept, *J* = 6.9 Hz, 2H), 1.95–1.79 (m, 2H), 1.60–1.26 (m, 20H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-cyclododecyl[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.38 g, 0.81 mmol) and MOMCl (1.22 mL, 16 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O and MPLC (Kanto Chemical silica gel 60, DCM:MeOH = 100:0 to 95:5) to afford the title compound (170 mg, 0.33 mmol, 40%) as a colorless solid. R_f 0.33 (DCM:MeOH = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.36 (d, *J* = 9.2 Hz, 1H), 7.92 (s, 1H), 7.31 (dd, *J* = 9.6 Hz, 6.9 Hz, 1H), 7.23 (s, 2H), 6.90 (d, *J* = 6.4 Hz, 1H), 5.05–4.96 (m, 1H), 3.03 (sept, *J* = 6.9 Hz, 1H), 2.21 (m, 4H), 1.92–1.81 (m, 2H), 1.52–1.28 (m, 22H), 1.25–1.16 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.05 (d, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7, 147.8, 132.9, 131.3, 124.6, 124.1, 122.4, 119.8, 119.3, 117.1, 117.0, 60.5, 34.2, 31.0, 30.6, 24.8, 23.9, 23.7, 23.6, 23.3, 23.0, 22.9, 21.1. HRMS–

ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{34}H_{51}N_2$, 487.4047; found, 487.4060.

Preparation of L12•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.62 g, 2.0 mmol), 1-adamantylamine (0.30 g, 2.0 mmol), and EtOH (12 mL). After the mixture was stirred for 14 h at 90 ºC under air, the resulting gray dispersion was cooled to rt and passed through glass filter, eluted with DCM. The filtrate was dried under reduced pressure to afford *N*-(1-adamantyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.07 (s, 2H), 2.92 (sept, *J* = 6.9 Hz, 1H), 2.51 (sept, *J* = 6.9 Hz, 2H), 2.17 (br s, 3H), 1.83 (br s, 6H), 1.72 (q, *J* = 11.9 Hz, 6H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-(1-adamantyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.83 g, 1.9 mmol) and MOMCl (2.8 mL, 37 mmol). After the mixture was stirred for 12 h at 80 ºC under air, the resulting brown solution was cooled to rt and volatiles were removed under reduced pressure. The residue was purified by MPLC (Kanto Chemical silica gel 60, DCM:MeOH = 95:5) and recrystallization from DCM and EtOAc to afford the title compound (0.23 g, 0.46 mmol, 25%) as a colorless solid. R_f 0.33 (DCM:MeOH = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.52 (d, *J* = 9.2 Hz, 1H), 7.82 (s, 1H), 7.30 (t, *J* = 8.2 Hz, 1H), 7.22 (s, 2H), 6.89 (d, *J* = 6.9 Hz, 1H), 3.02 (sept, *J* = 6.9 Hz, 1H), 2.33 (br s, 3H), 2.30–2.20 (m, 8H), 1.80 (t, *J* = 14.4 Hz, 6H), 1.35 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H), 1.05 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7, 148.0, 132.9, 131.6, 124.5, 124.3,

122.5, 120.0, 119.9, 117.4, 115.9, 62.3, 43.1, 35.1, 34.4, 31.0, 29.5, 24.9, 24.3, 23.8. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{32}H_{43}N_2$, 455.3421; found, 455.3430.

Preparation of L13•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.62 g, 2.0 mmol), 2-adamantylamine (0.30 g, 2.0 mmol), and EtOH (6.5 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with MeOH to afford *N*-(2-adamantyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.07 (s, 2H), 3.53 (br s, 1H), 2.93 (sept, *J* = 6.9 Hz, 1H), 2.51 (sept, *J* = 6.9 Hz, 2H), 2.43 (d, *J* = 12.8 Hz, 2H), 1.97–1.88 (m, 4H), 1.88–1.79 (m, 6H) 1.60 (s, 2H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-(2-adamantyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.22 g, 0.50 mmol) and chloromethyl methyl ether (0.76 mL, 10 mmol). After the mixture was stirred for 72 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O to afford the title compound (152 mg, 0.31 mmol, 62%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 8.32 (d, *J* = 9.6 Hz, 1H), 8.01 (s, 1H), 7.31 (dd, *J* = 9.2 Hz, 6.9 Hz, 1H), 7.21 (s, 2H), 6.90 (d, *J* = 6.9 Hz, 1H), 5.01 (br s, 1H), 3.00 (sept, *J* = 6.9 Hz, 1H), 2.74 (br s, 2H), 2.25 (sept, *J* = 6.9 Hz, 2H), 2.13–1.98 (m, 5H), 1.86–1.70 (m, 5H), 1.53 (d, *J* = 12.8 Hz, 2H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7, 148.0, 133.1, 131.1, 124.5, 124.3, 122.4, 120.0, 119.8, 119.3, 116.3, 65.1, 36.7,

36.5, 34.4, 31.3, 31.0, 30.9, 26.4$_5$, 26.4$_0$, 25.1, 23.9, 23.8. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{32}H_{43}N_2$, 455.3421; found, 455.3429.

Preparation of L14•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.46 g, 1.5 mmol), 3,5-di-*tert*-butyl-4-methoxyaniline (0.35 g, 1.5 mmol), and EtOH (5 mL). After the mixture was stirred for 7 h at rt under air, the resulting yellow precipitate was collected by filtration. The residue was washed with MeOH to afford *N*-(3,5-di-*tert*-butyl-4-methoxyphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a yellow solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, C_6D_6): δ 9.02 (s, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 7.47 (s, 2H), 7.24 (s, 2H), 7.23–7.18 (m, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 3.38 (s, 3H), 2.90 (sept, *J* = 6.9 Hz, 1H), 2.78 (sept, *J* = 6.9 Hz, 2H), 1.43 (s, 18H), 1.31 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 7.3 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-(3,5-di-*tert*-butyl-4-methoxyphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.26 g, 0.50 mmol) and MOMCl (0.76 mL, 10 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O to afford the title compound (0.20 g, 0.35 mmol, 70%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.87 (d, *J* = 9.2 Hz, 1H), 8.05 (s, 1H), 7.40 (dd, *J* = 9.2 Hz, 6.9 Hz 1H), 7.31 (s, 2H), 7.20 (s, 2H), 7.00 (d, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 2.97 (sept, *J* = 6.9 Hz, 1H), 2.33 (sept, *J* = 6.9 Hz, 2H), 1.40 (s, 18H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.0, 152.9, 148.1, 146.9, 132.6, 132.2, 129.7, 124.9, 124.3, 122.5$_5$, 122.4$_5$, 121.0, 120.7, 119.2, 119.1, 64.8, 36.2, 34.5, 31.6, 31.1, 25.1, 24.0,

23.8. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{37}H_{51}N_2O$, 539.3996; found, 539.4004.

Preparation of L15•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.46 g, 1.5 mmol), 4-methoxy-2,6-dimethylaniline (0.23 g, 1.5 mmol), and MeOH (5 mL). After the mixture was stirred for 12 h at rt under air, the solvent was removed under reduced pressure. The residue was washed with cold MeOH to afford *N*-(4-methoxy-2,6-dimethylphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a yellow solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.10 (s, 2H), 6.65 (s, 2H), 3.79 (s, 3H), 2.94 (sept, *J* = 6.9 Hz, 1H), 2.54 (sept, *J* = 6.9 Hz, 2H), 2.21 (s, 6H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 7.3 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-(4-methoxy-2,6-dimethylphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.22 g, 0.50 mmol) and MOMCl (1.52 mL, 20 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O to afford the title compound (0.24 g, 0.48 mmol, 96%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.86 (d, *J* = 9.6 Hz, 1H), 7.91 (s, 1H), 7.48 (dd, *J* = 8.9 Hz, 7.1 Hz, 1H), 7.19 (s, 2H), 7.05 (d, *J* = 6.9 Hz, 1H), 6.69 (s, 2H), 3.81 (s, 3H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.33 (sept, *J* = 6.9 Hz, 2H), 1.97 (s, 6H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.05 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.1, 153.0, 147.9, 135.8, 132.8, 132.3, 126.2, 125.6, 124.2, 122.5, 121.4, 120.8, 120.5, 119.3, 114.2, 55.6, 34.4, 31.2, 24.8, 24.0, 23.8, 17.5. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{31}H_{39}N_2O$, 455.3057; found, 455.3066.

Preparation of L16•HCl. A 15-mL vial was charged with 6-(2,4,6-triisopropylphenyl)-2-pyridinecarboxaldehyde (0.46 g, 1.5 mmol), 4-dimethylamino-2,6-dimethylaniline (0.25 g, 1.5 mmol), and MeOH (5 mL). After the mixture was stirred for 12 h at rt under air, the resulting yellow precipitate was collected by filtration, and washed with cold MeOH to afford *N*-(4-dimethylamino-2,6-dimethylphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine as a yellow solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.09 (s, 2H), 6.50 (s, 2H), 2.93 (sept, *J* = 6.9 Hz, 1H), 2.92 (s, 6H), 2.54 (sept, *J* = 6.9 Hz, 2H), 2.24 (s, 6H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 7.3 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-(4-dimethylamino-2,6-dimethylphenyl)[6-(2,4,6-triisopropylphenyl)pyridin-2-ylmethylidene]amine (0.23 g, 0.50 mmol) and MOMCl (2.3 mL, 30 mmol). After the mixture was stirred for 12 h at rt under air, volatiles were removed under reduced pressure. The residue was purified by recrystallization from DCM and Et_2O to afford the title compound (0.25 g, 0.50 mmol, quant.) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.94 (d, *J* = 8.7 Hz, 1H), 7.88 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.19 (s, 2H), 7.04 (d, *J* = 6.4 Hz, 1H), 6.72 (s, 2H), 3.04 (s, 6H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.31 (sept, *J* = 6.9 Hz, 2H), 1.95 (s, 6H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.16 (d, *J* = 6.4 Hz, 6H), 1.04 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.4, 147.8, 145.8, 137.2, 133.6, 133.5, 132.3, 126.1, 123.7, 122.7, 122.5, 121.2, 121.1, 119.8, 118.8, 46.2, 34.5, 31.3, 24.8, 24.1, 23.8, 17.5. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{32}H_{42}N_3$, 468.3373; found, 468.3382.

Preparation of L17•HCl. In a glovebox, an 80 mL Schlenk flask was charged with 1-(6-

bromopyridin-2-yl)ethan-1-one (1.20 g, 6.0 mmol), 2,4,6-triisopropylphenylboronic acid (1.71 g, 6.9 mmol), $Pd_2(dba)_3$(110 mg, 0.12 mmol), PPh_3 (0.24 g, 0.90 mmol), K_3PO_4 (3.2 g, 15 mmol), and toluene (32 mL). The mixture was stirred for 72 h at 110 ºC. The resulting brown dispersion was passed through Celite® and eluted with Et_2O. The solvent was removed under reduced pressure and the residue was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 100:0 to 97:3) to afford 1-[6-(2,4,6-triisopropylphenyl)pyridin-2-yl]ethan-1-one (0.26 g, 0.80 mmol) as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.10 (s, 2H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.68 (s, 3H), 2.46 (sept, *J* = 6.9 Hz, 2H), 1.31 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 12H).

A 15-mL vial was charged with 1-[6-(2,4,6-triisopropylphenyl)pyridin-2-yl]ethan-1-one (0.26 g, 0.80 mmol), 2,4,6-trimethyaniline (1.12 mL, 8.0 mmol), MeOH (8 mL), and H_2SO_4 (2 drops). After the mixture was stirred for 12 h at 40 ºC under air, the resulting pink dispersion was cooled to rt and the solvent was removed under reduce pressure. The residue was washed with MeOH to afford *N*-(2,4,6-trimethylphenyl)-1-[6-(2,4,6-triisopropylphenyl)pyridin-2-ylethan]-1-imine as a colorless solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.10 (s, 2H), 6.88 (s, 2H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.56 (sept, *J* = 6.9 Hz, 2H), 2.28 (s, 3H), 2.11 (s, 3H), 2.02 (s, 6H), 1.31 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 6H).

A 4-mL vial was charged with *N*-(2,4,6-trimethylphenyl)-1-[6-(2,4,6-triisopropylphenyl)pyridin-2-ylethan]-1-imine (0.22 g, 0.50 mmol) and MOMCl (0.76 mL, 10 mmol). After the mixture was stirred for 12 h at 80 ºC under air, the resulting

brown solution was cooled to rt and volatiles were removed under reduced pressure. The residue was purified by MPLC (Kanto Chemical silica gel 60, DCM:MeOH = 95:5) and recrystallization from DCM and EtOAc to afford the title compound (51 mg, 0.11 mmol, 21%) as a gray solid. R_f 0.32 (DCM:MeOH = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (d, *J* = 9.2 Hz, 1H), 7.90 (s, 1H), 7.64 (dd, *J* = 9.2 Hz, 7.3 Hz, 1H), 7.18 (s, 2H), 7.06_4 (s, 2H), 7.05_6 (d, *J* = 6.4 Hz, 1H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.73 (s, 3H), 2.36 (s, 3H), 2.33 (sept, *J* = 6.9 Hz, 2H), 1.86 (s, 6H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.16 (d, *J* = 6.4 Hz, 6H), 1.04 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0, 147.8, 142.3, 134.0, 132.6, 130.1, 129.5, 128.6, 125.5, 125.4, 124.0, 122.5, 121.2, 119.8, 119.7, 34.4, 31.1, 24.7, 24.0, 23.7, 21.0, 16.9, 9.3. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{32}H_{41}N_2$, 453.3264; found, 453.3272.

Preparation of L18•HCl. A 15-mL vial was charged with 6-(2,6-dimethoxyphenyl)-2-pyridinecarboxaldehyde[16] (0.97 g, 4.0 mmol), 2,4,6-trimethylaniline (0.56 mL, 4.0 mmol), and EtOH (10 mL). After the mixture was stirred for 24 h at 90 ºC under air, the resulting yellow dispersion was cooled to rt and the solid was collected by filtration. The solid was washed with MeOH and hexane to afford *N*-(2,4,6-trimethylphenyl)[6-(2,6-dimethoxyphenyl)pyridin-2-ylmethylidene]amine as a yellow solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 8.2 Hz, 1H), 6.88 (s, 2H), 6.67 (d, *J* = 8.2 Hz, 2H), 3.75 (s, 6H), 2.28 (s, 3H), 2.15 (s, 6H).

A 15-mL vial was charged with *N*-(2,4,6-trimethylphenyl)[6-(2,6-dimethoxyphenyl)pyridin-2-ylmethylidene]amine (1.32 g, 3.7 mmol) and MOMCl (5.5

mL, 73 mmol). After the mixture was stirred for 12 h at 60 ºC under air, the resulting brown solution was cooled to rt and volatiles were removed under reduced pressure. The residue was purified by MPLC (Kanto Chemical silica gel 60, DCM:MeOH = 95:5) to afford the title compound (1.48 g, 3.6 mmol, 99%) as a yellow solid. R_f 0.29 (DCM:MeOH = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.56 (d, *J* = 9.2 Hz, 1H), 8.39 (s, 1H), 7.52 (t, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 6.9 Hz, 1H), 7.01 (s, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 6H), 2.34 (s, 3H), 2.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 141.3, 133.7, 133.5, 131.8, 131.0, 129.5, 128.7, 125.3, 123.0, 121.5, 119.0, 116.6, 106.9, 104.4, 56.0, 20.9, 17.1. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{24}H_{25}N_2O_2$, 373.1911; found, 373.1921.

Preparation of L19•HCl. In a glovebox, an 80 mL Schlenk flask was charged with 6-bromopyridinecarboxaldehyde (0.93 g, 5.0 mmol), 2,6-diisopropoxyphenylboronic acid (1.37 g, 5.8 mmol), $Pd_2(dba)_3$ (92 mg, 0.10 mmol), PPh_3 (197 mg, 0.75 mmol), K_3PO_4 (2.7 g, 13 mmol), and toluene (28 mL). The mixture was stirred for 36 h at 110 ºC. The resulting brown dispersion was passed through Celite® and eluted with Et_2O. The solvent was removed under reduced pressure and the residue was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 100:0 to 95:5) to afford 6-(2,6-diisopropoxyphenyl)-2-pyridinecarboxaldehyde as a yellow solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.1 (s, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.86 (t, *J* = 7.3 Hz, 1H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.30–7.24 (m, 1H), 6.64 (d, *J* = 8.7 Hz, 2H), 4.45 (sept, *J* = 6.0 Hz, 2H), 1.15 (d, *J* = 6.0 Hz, 12H).

A 15-mL vial was charged with 6-(2,6-diisopropoxyphenyl)-2-

pyridinecarboxaldehyde (0.23 g, 0.76 mmol), 2,4,6-trimethyaniline (2.1 mL, 15 mmol), and MeOH (5 mL). After the mixture was stirred for 12 h at rt, volatiles were removed under reduced pressure at 90 ºC to afford *N*-(2,4,6-trimethylphenyl)[6-(2,6-diisopropoxyphenyl)pyridin-2-ylmethylidene]amine as a yellow solid, which was used directly in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 2H), 6.64 (d, *J* = 8.2 Hz, 2H), 4.45 (sept, *J* = 6.0 Hz, 2H), 2.29 (s, 3H), 2.16 (s, 6H), 1.18 (d, *J* = 6.0 Hz, 12H).

A 15-mL vial was charged with *N*-(2,4,6-trimethylphenyl)[6-(2,6-diisopropoxyphenyl)pyridin-2-ylmethylidene]amine (0.42 g, 1.0 mmol) and MOMCl (1.51 mL, 20 mmol). After the mixture was stirred for 11 h at 40 ºC under air, the resulting solution was cooled to rt and volatiles were removed under reduced pressure. The residue was purified by MPLC (Kanto Chemical silica gel 60, DCM:MeOH = 98:2 to 96:4) and recrystallization from DCM and EtOAc to afford the title compound (0.38 g, 0.82 mmol, 63%) as a colorless solid. R_f 0.37 (DCM:MeOH = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.86 (d, *J* = 9.2 Hz, 1H), 8.04 (s, 1H), 7.43 (t, *J* = 8.2 Hz, 1H), 7.39 (dd, *J* = 9.2 Hz, 6.9 Hz, 1H), 7.03 (d, *J* = 6.9 Hz, 1H), 7.00 (s, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 4.52 (sept, *J* = 6.0 Hz, 2H), 2.34 (s, 3H), 2.00 (s, 6H), 1.15 (d, *J* = 6.0 Hz, 6H), 1.10 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.0, 141.3, 133.7, 133.1, 132.0, 131.0, 129.5, 129.2, 125.0, 121.8, 121.1, 119.7, 117.6, 110.0, 106.9, 71.6, 21.8, 21.6, 20.9, 17.1. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{28}H_{33}N_2O_2$, 429.2537; found, 429.2548.

Preparation of L20•HCl. A 15-mL vial was charged with *N*-(2,4,6-trimethylphenyl)[6-(2,6-diisopropoxyphenyl)pyridin-2-ylmethylidene]amine (0.89 g, 2.1 mmol) and

MOMCl (3.2 mL, 20 mmol). After the mixture was stirred for 16 h at 80 ºC under air, the resulting solution was cooled to rt and volatile compounds were removed under reduced pressure. The residue was washed with Et_2O and EtOAc and purified by recrystallization from DCM and EtOAc to afford the title compound (0.86 g, 1.7 mmol, 82%) as a brown crystal. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (m, 1H), 8.98 (dd, *J* = 11.5 Hz, 9.6 Hz, 1H), 8.16 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 8.9 Hz, 7.1 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.01 (s, 2H), 6.88 (d, *J* = 9.2 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.62–4.53 (m, 2H), 3.87 (sept, *J* = 6.0 Hz, 1H), 2.35 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.9, 155.2, 141.5, 135.1, 133.7$_4$, 133.6$_5$, 131.8, 131.0, 129.6$_4$, 129.6$_0$, 128.7, 124.7, 124.6, 122.5, 122.0, 120.7, 118.1, 114.5, 110.3, 77.8, 71.9, 40.7, 22.1, 22.0, 21.8, 21.6, 21.0, 17.3, 17.1. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{29}H_{35}N_2O_3$, 459.2642; found, 459.2652.

Preparation of (L1)Pd(acac)Cl. A 15-mL vial was charged with $Pd(acac)_2$ (0.91 g, 3.0 mmol), **L1**•HCl (1.42 g, 3.0 mmol), and 1,4-dioxane (15 mL). After the mixture was stirred for 36 h at 80 ºC, the resulting dispersion was cooled to rt and filtered through Celite® and eluted with EtOAc. The solvent was removed under reduced pressure and purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 95:5 to 85:15) to afford the title compound (0.63 g, 0.93 mmol, 31%) as a yellow solid. R_f 0.20 (hexane:EtOAc = 85:15). mp. 150 ºC (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.31 (d, *J* = 6.4 Hz, 1H), 7.30 (s, 1 H), 7.02 (s, 1H), 6.93 (t, *J* = 6.9 Hz, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 6.66 (d, *J* = 6.4 Hz, 1H), 4.86 (s, 1H), 3.56 (sept, *J* = 6.9 Hz, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 2.34 (s, 3H), 2.29 (s, 3H), 1.94 (s, 3H), 1.85 (sept, *J* = 6.9 Hz, 1H),

1.71 (s, 3H), 1.67 (s, 3H), 1.57 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 7.3 Hz, 6H) 1.09 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.0, 182.3, 150.1, 149.3, 147.5, 142.5, 139.0, 138.0, 136.1, 135.8, 135.6, 133.7, 130.5, 130.1, 128.4, 122.0, 121.2, 120.1, 118.3, 116.8, 114.7, 99.4, 34.3, 32.3, 30.6, 27.5, 26.6, 26.0, 25.7, 23.9, 23.7, 23.1, 21.9, 21.1, 19.1, 17.5. HRMS–ESI (+) (*m/z*): [M–Cl]$^+$ calcd for $C_{36}H_{45}N_2O_2Pd$, 643.2510; found, 643.2532. Anal. Calcd for $C_{36}H_{45}N_2O_2ClPd$: C, 63.62; H, 6.67; N, 4.12. Found: C, 63.54; H, 6.61; N, 4.13.

Preparation of (L1)Pd(allyl)Cl. In a glovebox, a 15-mL was charged with **L1**•HCl (0.48 g, 1.0 mmol), LiHMDS (184 mg, 1.1 mmol), and THF (10 mL). After stirred for 2 h at rt, the mixture was added with $[(ally)PdCl]_2$ (183 mg, 0.50 mmol) and stirred for 3 h. The resulting dispersion was taken out from glovebox and filtered through Celite®, eluted with DCM, and the solvent was removed under reduced pressure. The residue was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 80:20 to 70:30) and recrystallization from DCM and hexane to afford the title compound (0.39 g, 0.63 mmol, 63%) as a yellow solid. R_f 0.14 (hexane:EtOAc = 75:25). mp. 130 ºC (decomp.). NMR profiles were too complicated to analyze. HRMS–ESI (+) (*m/z*): [M–Cl]$^+$ calcd for $C_{34}H_{43}N_2Pd$, 585.2456; found, 585.2478. Anal. Calcd for $C_{34}H_{43}N_2ClPd$: C, 65.70; H, 6.97; N, 4.51. Found: C, 65.55; H, 6.89; N, 4.40. Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a saturated DCM solution.

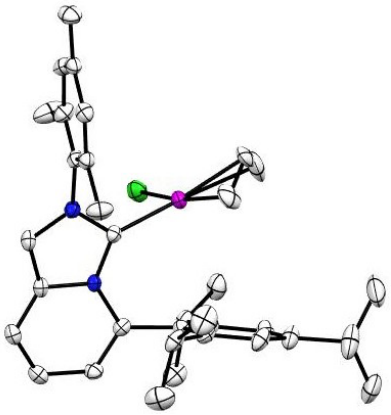


Figure S4-1. Single-crystal X-ray diffraction structure of (**L1**)Pd(allyl)Cl. (atomic displacement parameters set at 30% probability; hydrogen atoms omitted for clarity)

Preparation of (L9)Pd(acac)Cl. A 15-mL vial was charged with $Pd(acac)_2$ (0.66 g, 1.5 mmol), **L9**•HCl (0.46 g, 1.5 mmol), and 1,4-dioxane (7.5 mL). After the mixture was stirred for 48 h at 100 ºC, it was cooled to rt, filtered by Celite®, and eluted with DCM. The solvent was removed under reduced pressure and purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 90:10 to 85:15) to afford the title compound (164 mg, 0.26 mmol, 17%) as a yellow solid. R_f 0.33 (hexane:EtOAc = 75:25). mp. 150 ºC (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.23 (d, *J* = 9.6 Hz, 2H), 6.93 (s, 1H), 6.85 (dd, *J* = 8.7 Hz, 6.9 Hz, 1H), 6.56 (s, 1H), 6.09–6.00 (m, 1H), 5.00 (s, 1H), 3.29 (sept, *J* = 6.9 Hz, 1H), 2.87 (sept, *J* = 6.9 Hz, 1H), 2.53–2.46 (m. 1H), 2.19–2.13 (m, 1H), 1.95–1.76 (m, 4H), 1.83 (s, 3H), 1.75–1.68 (m, 2H), 1.69 (s, 3H), 1.61–1.51 (m, 5H), 1.31–1.24 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.6, 183.1, 150.1, 149.1, 147.6, 139.4, 137.4, 133.7, 130.3, 121.4, 121.2, 120.5, 117.5, 116.8, 109.0, 99.5, 62.1, 35.8, 34.3, 32.7, 32.2, 30.9, 27.3, 26.8, 25.9, 25.5, 25.4, 25.3, 23.9, 23.8, 22.9, 22.4. HRMS–ESI (+) (*m/z*): $[M–Cl]^+$ calcd for $C_{33}H_{45}N_2O_2Pd$, 607.2510; found, 607.2534.

General procedure for Scheme 4-1. A 4-mL vial was charged with 4-nitroanisole (**1a**) (31 mg, 0.20 mmol), phenylboronic acid (**2a**) (37 mg, 0.30 mmol), $Pd(acac)_2$ (0.61 mg, 2.0 μmol), and ligand precursor (4.0 μmol). In a glovebox, K_3PO_4 (127 mg, 0.60 mmol), 18-crown-6 (2.6 mg, 0.010 mmol), and 1,4-dioxane (1.0 mL) were added to the vial. The vial and a cap were put in a Ziploc® bag which was attached with a septum by packing tape. The whole bag was closed and taken out of glovebox. H_2O (15.1 μL, 0.84 mmol) was added to the vial through the septum using a microsyringe. The resulting mixture was stirred for 12 h at 130 ºC. After the reaction, it was cooled to rt and passed through a short pad of Celite® with EtOAc and the solvent was removed under reduced pressure. The yield of the product was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

For the reactions with (NHC)Pd complexes, 2.0 μmol of (NHC)Pd complex was used instead of $Pd(acac)_2$ and ligand precursor.

Time-course study of Suzuki–Miyaura coupling (Figure 4-2). In a glovebox, a 15-mL vial was charged with 4-nitroanisole (**1a**) (92 mg, 0.60 mmol), phenylboronic acid (**2a**) (110 mg, 0.90 mmol), $Pd(acac)_2$ (1.83 mg, 6.0 μmol for **L1**; 9.1 mg, 0.030 mmol for BrettPhos), **L1**•HCl (5.7 mg, 0.012 mmol) or BrettPhos (32 mg, 0.060 mmol) K_3PO_4•nH_2O (0.42 g, 1.8 mmol, assumed n = 1.1), 18-crown-6 (15.9 mg, 0.060 mmol), 1,4-dioxane (3.0 mL), and *n*-$C_{13}H_{28}$ (60 μL, 0.25 mmol) as an internal standard. The resulting mixture was taken outside and stirred at 130 ºC. At 1 h, 2h, 3 h, 4 h, 6 h, the vial was soaked into an ice-cooled acetone bath to stop the reaction immediately. The cooled vial was then brought into a glovebox and small aliquots (~40 μL) of the reaction mixture were taken for GC analysis. It was returned to a hot stirrer and stirred at 130 ºC till the

time for the next sampling. The yield of 4-methoxybiphenyl (**3a**) at each time interval were determined by GC analysis.

After the reaction with Pd/BrettPhos, the reaction mixture was filtered through Celite® and the filtrate was concentrated. 15.0 mg (0.054 mmol) of triphenylphosphine oxide was added as an internal standard and the combined mixture was analyzed by ^{31}P NMR spectroscopy (Figure S4-2).

Table S4-1. Results of time-course study.

time	0 h	1 h	2 h	3 h	4 h	6 h
L1	0%	35%	50%	54%	56%	60%
BrettPhos	0%	20%	23%	26%	26%	27%

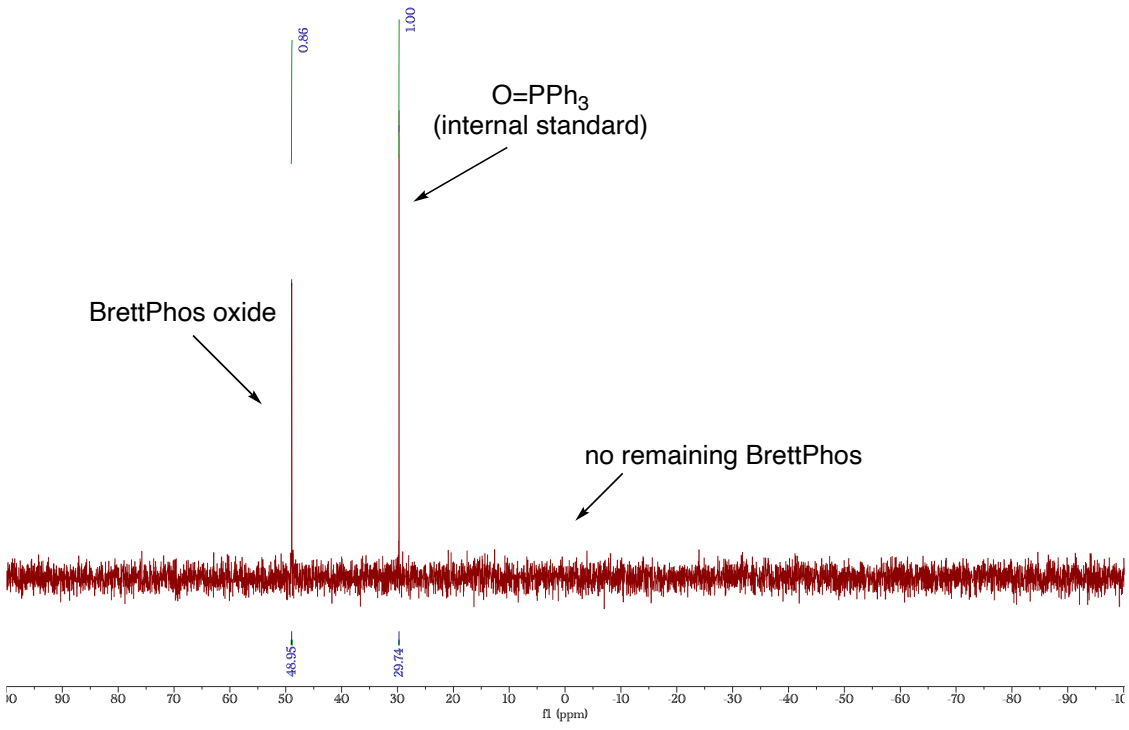


Figure S4-2. A ^{31}P NMR spectrum of the crude mixture after the reaction with Pd/BrettPhos system.

Computational details. All geometry optimizations were performed by the ωB97XD[17] functional, where the Stuttgart-Dresden-Bonn (SDB) basis sets were used for Pd atom with the ECPs employed for representing core electrons[18,19] and the 6-31G(d) basis sets were used for all other atoms. To evaluate better potential energy, the author performed single-point calculations using the above-optimized geometries with two f polarization functions added to Pd[20,21] and usual 6-311G(d) basis sets for other atoms,[22,23] where a set of diffuse functions was added to anionic O and N atoms and NO_2 group.[24] Solvation effects of dioxane were evaluated with the PCM method.[25–28] The Gibbs energy was employed for discussion, where the translation entropy in solution was corrected by the method of Whiteside et al.[29] All these calculations were carried out with Gaussian09 program.[30]

Cartesian coordinates for calculated structures.

1a

C	–1.297377	–1.724007	0.000388
C	–1.230497	–0.336433	0.000365
C	0.007128	0.288106	0.000082
C	1.192577	–0.445170	–0.000178
C	1.127602	–1.824040	–0.000160
C	–0.115805	–2.473986	0.000091
H	–2.268102	–2.204300	0.000681
H	–2.132256	0.263319	0.000593
H	2.143012	0.073884	–0.000376
H	2.028147	–2.428036	–0.000354
N	0.069974	1.746878	0.000093
O	1.175709	2.268734	–0.000147
O	–0.985946	2.363878	0.000372
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C	–1.284626	–4.539257	–0.000318
H	–1.008630	–5.593669	–0.000336
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(L1)Pd^0

Pd	–0.376946	–0.421888	–0.091292
C	–1.357528	1.255075	0.290377
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C	3.315207	3.273928	0.394634

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H	–5.150288	0.068461	–3.903448
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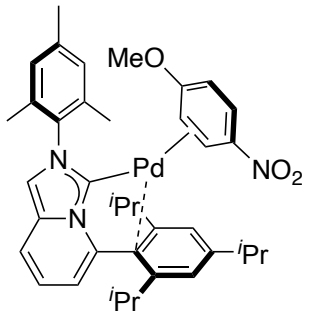

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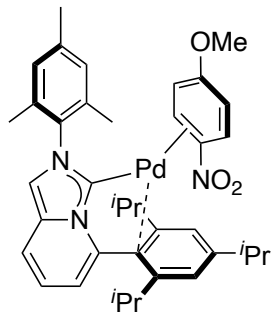

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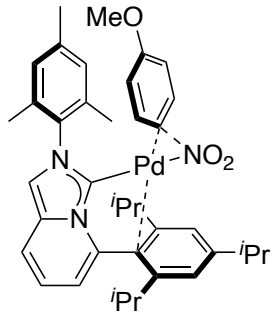

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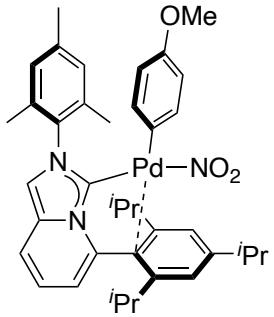

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C	1.746797	–0.085493	–1.606023
C	2.083627	–0.225009	0.760763
O	–0.135044	–3.065589	–1.499628
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C	6.214352	0.178002	0.065043
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X-ray analysis of (BrettPhos)AuCl. (BrettPhos)AuCl was synthesized according to literature procedure.[31] Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a saturated DCM solution.

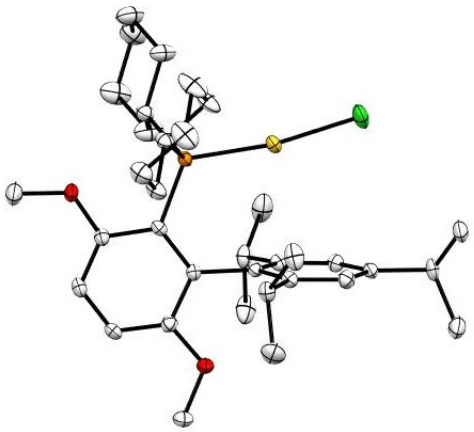
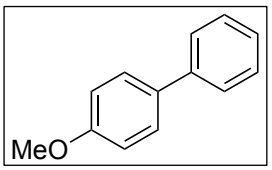


Figure S4-3. Single-crystal X-ray diffraction structure of (BrettPhos)AuCl. (atomic displacement parameters set at 30% probability; hydrogen atoms and DCM solvate molecule omitted for clarity)

$\%V_{Bur}$ was calculated *via* Samb*V*ca 2.0[15b,32] to be 57.5% with following parameters: Radius of sphere = 3.5 Å; Distance from sphere 2.0 Å; Mesh step 0.05 Å; H atoms omitted; Bondi radii scaled by 1.17.

General procedure for Schemes 4-2 and 4-3. In a glovebox, a 15-mL vial was charged with nitroarene (**1**) (0.60 mmol), corresponding nucleophiles (**2** or **4**) (0.90 mmol), catalyst (6.0 μmolPd), K_3PO_4 (0.38 g, 1.8 mmol), 18-crown-6 (7.9 mg, 0.030 mmol, only for Suzuki–Miyaura coupling), and 1,4-dioxane (3.0 mL). The vial and a cap were put in a Ziploc® bag which was attached with a septum by packing tape. The whole bag was closed and taken out of glovebox. H_2O (45 μL, 2.5 mmol for Suzuki–Miyaura coupling; 29 μL, 1.6 mmol for Buchwald–Hartwig amination) was added to the vial through the septum using a microsyringe. The resulting mixture was stirred for 12 h at 130 ºC. After the reaction, it was cooled to rt and passed through a short pad of Celite® with EtOAc and the solvent was removed under reduced pressure. The residue was purified by MPLC on silica gel to give the corresponding products.

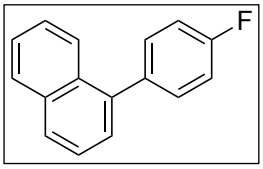
For the comparison, reactions using $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and BrettPhos (10.7 mg, 0.012 mmol) were conducted under similar conditions. The yields of the product were determined by ^1H NMR or ^{19}F NMR analysis of the crudes using 1,3,5-trimethoxybenzene or hexafluorobenzene respectively as an internal standard.



4-Methoxybiphenyl (3a). The reaction of 4-nitroanisole (**1a**) (92 mg, 0.60 mmol) with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**2a'**) (PhB(nep), 146 mg, 0.90 mmol) under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and **L1**•HCl (5.7 mg, 0.012 mmol) followed by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 100:0 to 99:1) afforded the title compound (65 mg, 0.35 mmol, 59%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (t, J = 8.7 Hz, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 140.8, 133.8, 128.7, 128.1,

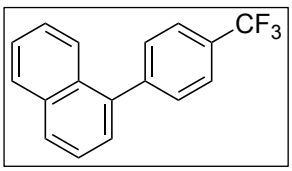
126.7, 126.6, 114.2, 56.3. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[7a]

In contrast, the reaction under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and BrettPhos (6.4 mg, 0.012 mmol) afforded the title compound in 5%.



1-(4-Fluorophenyl)naphthalene (3b). The reaction of 1-nitronaphthalene (**1b**) (104 mg, 0.60 mmol) with 4-fluorophenylboronic acid (**2b**) (126 mg, 0.90 mmol) under the catalysis of (**L1**)Pd(ally)Cl (3.7 mg, 6.0 μmol) followed by MPLC (25 g Biotage® SNAP Ultra column (25 μm size), hexane) afforded the title compound (123 mg, 0.55 mmol, 92%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 7.8 Hz, 1H), 7.86 (t, J = 9.2 Hz, 2H), 7.56–7.38 (m, 6H), 7.18 (t, J = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2 (d, J = 246.2 Hz), 139.1, 136.6, (d, J = 3.5 Hz), 133.8, 131.6$_1$ 131.5$_6$, 131.5, 128.3, 127.8, 127.0, 126.1, 125.8 (d, J = 9.3 Hz), 125.3, 115.1 (d, J = 22.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ –115.8. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[33]

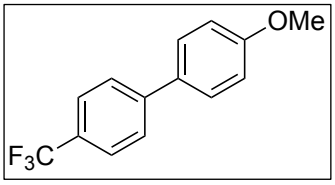
In contrast, the reaction under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and BrettPhos (6.4 mg, 0.012 mmol) afforded the title compound in 52%.



1-(4-Trifluoromethylphenyl)naphthalene (3c). The reaction of 1-nitronaphthalene (**1b**) (104 mg, 0.60 mmol) with 5,5-dimethyl-2-(4-trifluoromethylphenyl)-1,3,2-dioxaborinane (**2c'**) (4-F_3C-C_6H_4B(nep), 0.23 g, 0.90 mmol) under the catalysis of (**L1**)Pd(acac)Cl (4.1 mg, 6.0 μmol) followed by MPLC (25 g Biotage® SNAP Ultra column (25 μm size), hexane) afforded

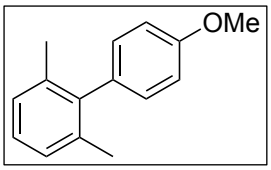
the title compound (153 mg, 0.56 mmol, 93%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (t, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.49–7.40 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.5, 138.7, 133.8, 131.2, 130.4, 129.5 (q, *J* = 32.4 Hz), 128.4_2, 128.3_7, 127.0, 126.4, 126.0, 125.5, 125.3, 125.2 (q, *J* = 3.5 Hz), 124.3 (q, *J* = 272.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.7. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[33]

In contrast, the reaction under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and BrettPhos (6.4 mg, 0.012 mmol) afforded the title compound in 49%.



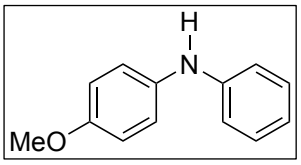
4-Methoxy-4'-trifluoromethylbiphenyl (3d). The reaction of 1-nitro-4-trifluoromethybenzene (**1c**) (115 mg, 0.60 mmol) with 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**2d'**) (4-MeO-C_6H_4B(nep), 198 mg, 0.90 mmol) under the catalysis of (**L1**)Pd(acac)Cl (4.1 mg, 6.0 μmol) followed by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 99:1 to 98:2) afforded the title compound 56 mg, 0.22 mmol, 37%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 4H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.8, 144.3, 132.2, 128.7 (q, *J* = 31.2 Hz), 128.3, 126.8, 125.7 (q, *J* = 3.5 Hz), 124.4 (q, *J* = 270.5 Hz), 114.4, 55.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.6. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[7a]

In contrast, the reaction under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and BrettPhos (6.4 mg, 0.012 mmol) afforded the title compound in 3%.



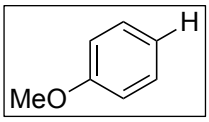
2,6-Dimethyl-4'-methoxybiphenyl (3e). The reaction of 2,6-dimethylnitrobezene (**1d**) (82 μL, 0.60 mmol) with 4-methoxyphenylboronic acid (**2d**) (137 mg, 0.90 mmol) under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and **L1**•HCl (5.7 mg, 0.012 mmol) followed by MPLC (25 g Biotage® SNAP Ultra column (25 μm size), hexane) afforded the title compound (60 mg, 0.28 mmol, 47%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (dd, J = 8.7 Hz, 6.0 Hz, 1H), 7.12–7.04 (m, 4H), 6.96 (J = 8.7 Hz, 2H), 3.86 (s, 3H), 2.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2, 141.5, 136.5, 133.3, 130.0, 127.2, 126.8, 113.8, 55.2, 20.9. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[34]

In contrast, the reaction under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and BrettPhos (6.4 mg, 0.012 mmol) did not afford the title compound at all.



4-Methoxy-*N*-phenylaniline (5). The reaction of 4-nitroanisole (**1a**) (92 mg, 0.60 mmol) with aniline (**4**) (82 μL, 0.90 mmol) under the catalysis of (**L1**)Pd(acac)Cl (4.1 mg, 6.0 μmol) followed by MPLC (Kanto Chemical silica gel 60, hexane:DCM:Et_3N = 98:5:2) afforded the title compound (35 mg, 0.17 mmol, 29%) as a brown solid.. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (t, J =7.8 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 6.89–6.81 (m, 3H), 5.49 (br s, 1H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 145.1, 135.7, 129.3, 122.2, 119.5, 115.6, 114.6, 55.5. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[7b]

In contrast, the reaction under the catalysis of $Pd(acac)_2$ (1.83 mg, 6.0 μmol) and BrettPhos (6.4 mg, 0.012 mmol) in DMF afforded the title compound in 9%.



Anisole (7). In a glovebox, a 4-mL vial was charged with nitroanisole (**1a**) (31 mg, 0.20 mmol), 2-propanol (**6**) (23 μL, 0.30 mmol), (**L9**)Pd(acac)Cl (1.29 mg, 2.0 μmol), K_3PO_4 (107 mg, 0.50 mmol), 1,4-dioxane (1.0 mL), and *n*-$C_{13}H_{28}$ (20 μL, 0.084 mmol) as an internal standard. The vial and a cap were put in a Ziploc® bag which was attached with a septum by packing tape. The whole bag was closed and taken out of glovebox. H_2O (11.7 μL, 0.65 mmol) was added to the vial through the septum using a microsyringe. The resulting mixture was stirred for 12 h at 130 ºC. The yield of the title compound (62%) was determined by GC analysis.

In contrast, the reaction under the catalysis of $Pd(acac)_2$ (0.61 mg, 2.0 μmol) and BrettPhos (2.1 mg, 4.0 μmol) afforded the title compound in 4%.

X-ray crystallographic analysis. Crystallographic data of (**L1**)Pd(allyl)Cl and (BrettPhos)AuCl were summarized in Table S4-2. CCDC 1937349 ((**L1**)Pd(allyl)Cl) and 1937350 ((BrettPhos)AuCl) (Deposition Number) contain the supplementary crystallographic data. These data can be obtained from The Cambridge Crystallographic Data Centre.

Table S4-2. Crystallographic data for (**L1**)Pd(allyl)Cl and (BrettPhos)AuCl.

compound	(**L1**)Pd(allyl)Cl	(BrettPhos)AuCl
empirical formula	$C_{34}H_{43}ClN_2Pd$	$C_{35}H_{53}AuClO_2P \cdot CH_2Cl_2$
formula weight	621.55	854.13
crystal system	Triclinic	Monoclinic
space group	*P* –1 (#2)	*P* 1 2_1/c 1 (#14)
a, Å	9.9673(2)	8.9157(9)
b, Å	11.8168(2)	17.5878(17)
c, Å	13.9447(2)	23.819(3)
α, deg.	99.7160(10)	90
β, deg.	102.4070(10)	96.3829(13)
γ, deg.	100.7430(10)	90
V, Å^3	1538.19(5)	3711.8(6)
Z	2	4
D_{calcd}, g/cm^3	1.342	1.528
μ [Mo-Kα], mm^{-1}	0.711	0.711
T, K	293	143
crystal size, mm	0.238×0.203×0.144	0.225×0.164×0.125
θ range, deg.	2.30 to 25.35	3.02 to 27.51
reflections measured	10827	29808
unique data	5493	8502
restraints	0	0
parameters	362	374
*R*1 ($I > 2.0\sigma(I)$)	0.0289	0.0392
*wR*2 ($I > 2.0\sigma(I)$)	0.0719	0.1001
*R*1 (all data)	0.0310	0.0438
*wR*2 (all data)	0.0737	0.1032
GOF on F^2	1.055	1.039

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(13) BrettPhos was completely consumed to give BrettPhos oxide (~80%) and a certain amount of biaryl *via* C(sp^2)–P bond cleavage.

(14) The energy value for (BrettPhos)Pd is different from that in ref 7a because the author applied a different functional.

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Chapter 5

Catalytic Generation of Radicals from Nitroalkanes

A new protocol for denitrative radical generation from nitroalkanes has been developed. 9-Fluorenol turned out to act as an efficient catalyst to reduce nitroalkanes to the corresponding radical anions, whose C–N bonds are cleaved to form alkyl radicals. The thus obtained radicals were demonstrated to participate in hydrogenation, the Giese addition, and the Minisci reactions. The present system outperforms conventional method using tin hydride in terms of cost, toxicity, and experimental manipulation.

Introduction

Organic radicals have been regarded as an important intermediate to construct complex carbon frameworks and to introduce substituents to them for the synthesis of functional molecules found in materials and pharmaceuticals.[1] Since radicals have an unpaired electron, they are typically characterized by high reactivity, which especially helps to connect sterically congested groups under relatively mild conditions. Meanwhile, radicals exhibit unique chemo-, regio-, or stereoselectivity distinct from ionic species. These advantages motivated synthetic chemists to develop diverse methods to generate radical species. Especially, recent prosperity of photochemistry[1b,2] and electrochemistry[3] in organic synthesis has enabled a wide variety of compounds to act as radical precursors, which offers facile access to highly functionalized molecules *via* radical intermediates.

Nitroalkanes have also been utilized as potential radical precursors, though such examples are less common.[4] Denitrative radical generation is typically mediated by a stoichiometric amount of tin hydride (Bu_3SnH in most cases) in the presence of a radical initiator like AIBN or $(BzO)_2$. An organotin radical generated *in situ* efficiently removes a nitro group to yield the corresponding alkyl radicals, which generally abstract hydrogen atom of tin hydride to form C–H bond (Scheme 5-1). Although this is a highly reliable method of reductive denitration, the use of tin hydride causes some drawbacks: 1) The bio- and ecotoxicity of organotin compounds limit their practicality.[5] 2) Inevitable formation of tin-containing byproducts sometimes brings about a trouble in separation. 3) It is necessary to prepare fresh tin hydride to secure high experimental reproducibility. 4) Reduction of other functional groups by tin hydride can compete with the denitrative radical generation. Several improvements to reduce or avoid the loading of tin hydride could be found in the literature, but alternative reductants therein were expensive and

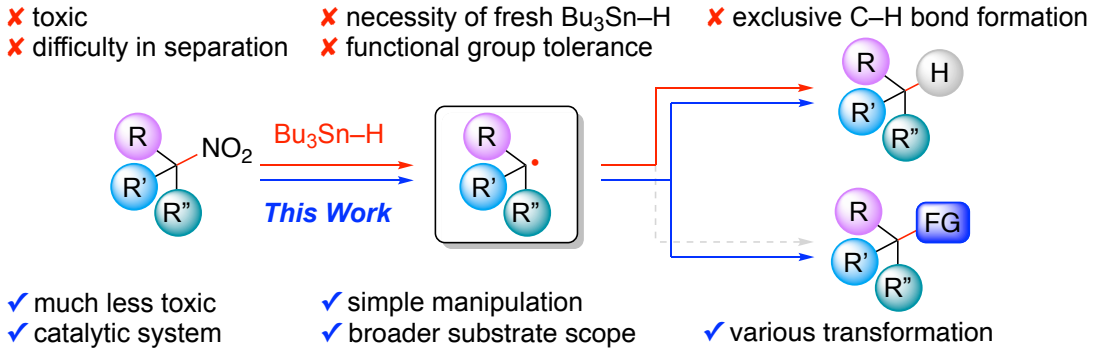
devoid of atom-economy.[6] In this context, a less toxic, inexpensive, easy-to-handle, and ideally catalytic substitute for tin hydride is of high demand to make the most of synthetic utility of nitroalkanes.[7]

Despite obvious benefits of denitrative transformations, reductive removal of a NO_2 group from nitroalkanes is still difficult because of competitive reduction of the NO_2 group itself to give nitroso compounds, hydroxylamines, and amines. This contrasts with haloalkanes, which predominantly undergo C–X bond scission when reduced by an electron (Scheme 5-2).[8] The corresponding radical anions of nitroalkanes could potentially undergo desired C–N bond cleavage to afford alkyl radicals or undesired N–O bond cleavage to afford nitroso compounds, which would be further reduced to hydroxylamines or amines.[9] Typical electron donors contain oxophilic metals or ligands, which are more likely to facilitate the latter process by abstracting oxygen atoms. Some organic reductants are known to directly abstract oxygen atoms from NO_2 group in a manner transferring two-electrons.[10] It is thus essential to use non-oxophilic one-electron organic reductants to facilitate the radical generation from nitroalkanes. Such organic single-electron donors have recently been extensively studied,[11] but their catalytic use in combination with terminal reductants is still in its infancy and suffers from preparation of specific electron donors or use of strong bases to attain sufficient redox potential.[12]

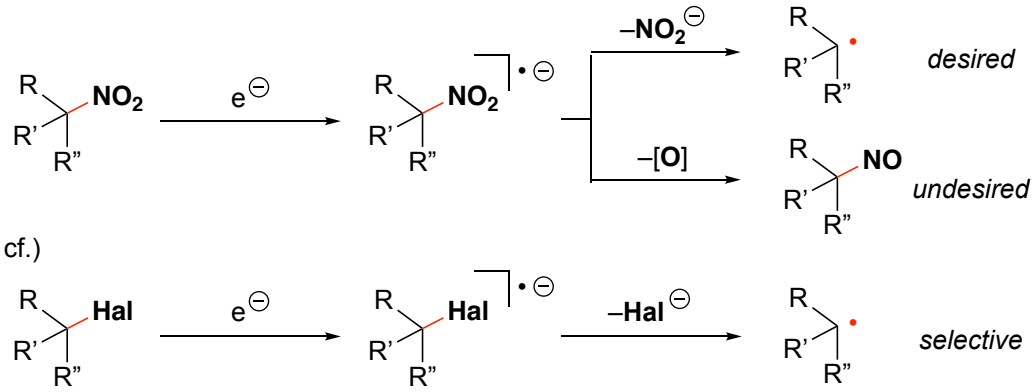
Presented herein is a catalytic protocol to generate alkyl radicals from tertiary nitroalkanes. The author hypothesized that readily available and less toxic 9-fluorenol[13] would be a suitable reductant because its carbanion can act as a non-oxophilic electron donor[14] and catalyst regeneration could be achieved by exploiting an alcohol–ketone redox cycle (Scheme 5-3).[15] Thanks to relatively low p*K*a of fluorenylic proton, a strong base was not necessary. In addition, alcohol solvents turned out to be consumed as

terminal reductant, which makes the whole system very simple and cost-effective.

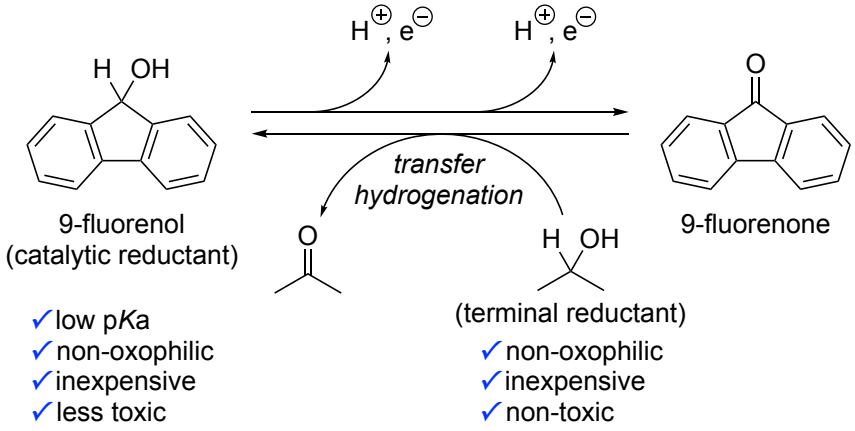
Scheme 5-1. Denitrative radical generation from nitroalkanes: a conventional method (red) and the present study (blue).



Scheme 5-2. Possible pathways of one-electron reduction of nitroalkanes and haloalkanes.



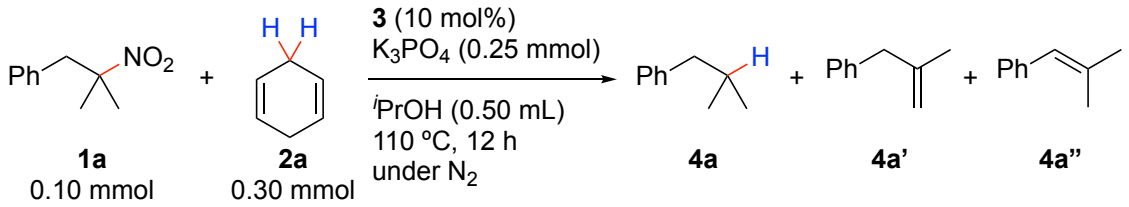
Scheme 5-3. Design of organic one-electron donor.



Results and discussion

To verify the working hypothesis above, the author conducted the reductive denitration of (2-methyl-2-nitropropyl)benzene (**1a**) as a model substrate (Table 5-1). As a result, the combination of 9-fluorenol (**3a**) as a catalyst, K_3PO_4 as a base, and ^{i}PrOH as a solvent turned out to be effective to generate alkyl radical from **1a**, affording the corresponding alkane **4a** in 76% yield through abstraction of hydrogen atom from 1,4-cyclohexadiene (**2a**) (entry 1). It is notable that no nitro-reduction products (amines, hydroxylamines) were observed in this reaction. The reaction proceeded gradually even in the absence of **3a** (entry 2), where *in situ* formed isopropoxide seemed to act as an electron donor.[16] The addition of benzhydrol (**3b**) or xanthydrol (**3c**) as a catalyst did not improve the efficiency (entries 3 and 4), indicating the importance of a planar fluorene skeleton. The necessity of fluorenylic proton was revealed by the results of 9-methyl-9-fluorenol (**3d**) and 9-methoxyfluorene (**3e**) (entries 5 and 6), the latter of which provided satisfactory yield of desired alkane **4a** accompanied by a substantial amount of undesired alkene **4a"**. A comparable result brought by 9-fluorenone (**3f**) implies its involvement in the catalytic cycle, and further highlights cost-efficiency of the new methodology (**3a**: ¥ 7,800/25 g, **3f**: ¥ 1,800/25 g@TCI) (entry 7). The choice of a base did not affect the result so much as long as its basicity is above a certain level (entries 8 and 9), whereas no activity was obtained by a weaker base such as K_2CO_3 (entry 10). The solvent was the key to control alkane/alkene ratio by affecting the solubility of bases and catalyst regeneration, where ^{i}PrOH brought the best result (entries 1, 11–15). Notably, the new denitration protocol is still operative in the presence of oxygen and water (entry 16). It is hence not necessary to use freshly purified catalysts (like Bu_3SnH), dry K_3PO_4, nor degassed ^{i}PrOH.

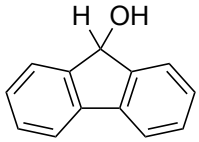
Table 5-1. Optimization study for reductive denitration of **1a**.



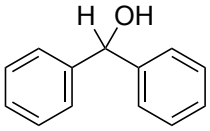
1a 0.10 mmol

2a 0.30 mmol

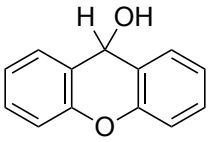
4a **4a'** **4a"**



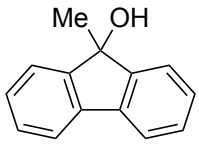
3a



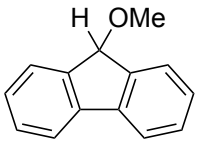
3b



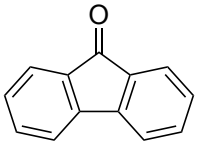
3c



3d



3e



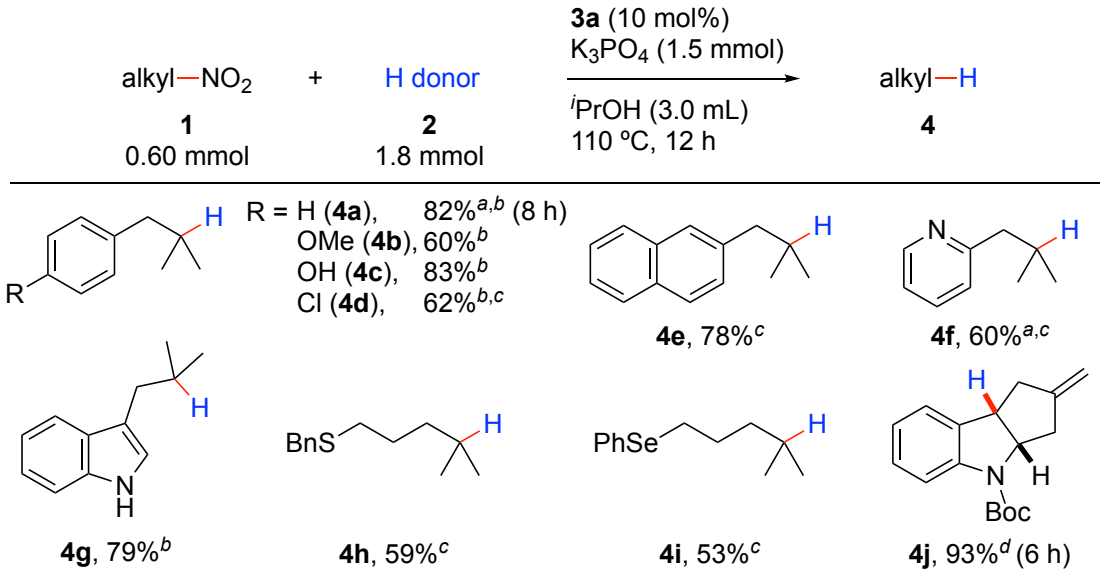
3f

entry	catalyst	base	solvent	yield (%)[a]		
				4a	**4a'**	**4a"**
1	**3a**	K_3PO_4	^{i}PrOH	76	1	1
2	—	K_3PO_4	^{i}PrOH	50	2	25
3	**3b**	K_3PO_4	^{i}PrOH	43	1	26
4	**3c**	K_3PO_4	^{i}PrOH	47	2	16
5	**3d**	K_3PO_4	^{i}PrOH	54	1	21
6	**3e**	K_3PO_4	^{i}PrOH	72	1	9
7	**3f**	K_3PO_4	^{i}PrOH	79	1	1
8	**3a**	KO^{t}Bu	^{i}PrOH	67	1	1
9	**3a**	Cs_2CO_3	^{i}PrOH	78	2	3
10	**3a**	K_2CO_3	^{i}PrOH	1	3	2
11	**3a**	K_3PO_4	MeOH	12	1	11
12	**3a**	K_3PO_4	EtOH	39	1	3
13	**3a**	K_3PO_4	^{t}BuOH	8	2	2
14	**3a**	K_3PO_4	toluene	<1	2	1
15	**3a**	K_3PO_4	DMSO	19	3	23
16[b]	**3a**	K_3PO_4•nH_2O	^{i}PrOH	81	3	2
17[c]	**3a**	K_3PO_4	^{i}PrOH	41	8	7

[a] GC yields determined using *n*-$C_{13}H_{28}$ as an internal standard.
[b] The reaction was performed in air using ^{i}PrOH stored outside the glovebox.
[c] The reaction was performed in the absence of **2a**.

With established reaction conditions above, the author tested several nitroalkanes to verify the applicability of the reductive denitration (Scheme 5-4). In some cases, cheaper γ-terpinene (**2b**) was used as a hydrogen atom donor because it showed similar activity as **2a**. Scaling-up the denitration of model substrate **1a** smoothly delivered **4a** in 82% yield. Not only methoxy but also acidic hydroxyl groups did not interfere the reaction, affording **4b** and **4c** in high yields. A chloro substituent on the phenyl ring was also tolerated (**4d**). π-Extended and heterocyclic substrates **1e**, **1f**, and **1g** were denitrated without losing efficiency. It was worth noting that benzylsulfanyl and phenylselanyl moieties, which are usually cleaved by tin hydride, were compatible with the new denitrative protocol (**4h** and **4i**). Substrate **1j**, synthesized *via* dearomative [2+3] cyclization of 3-nitroindole,[7h] also underwent reductive denitration in high yield by using phenylmethanethiol (**2c**) as a hydrogen atom donor to facilitate HAT.[17]

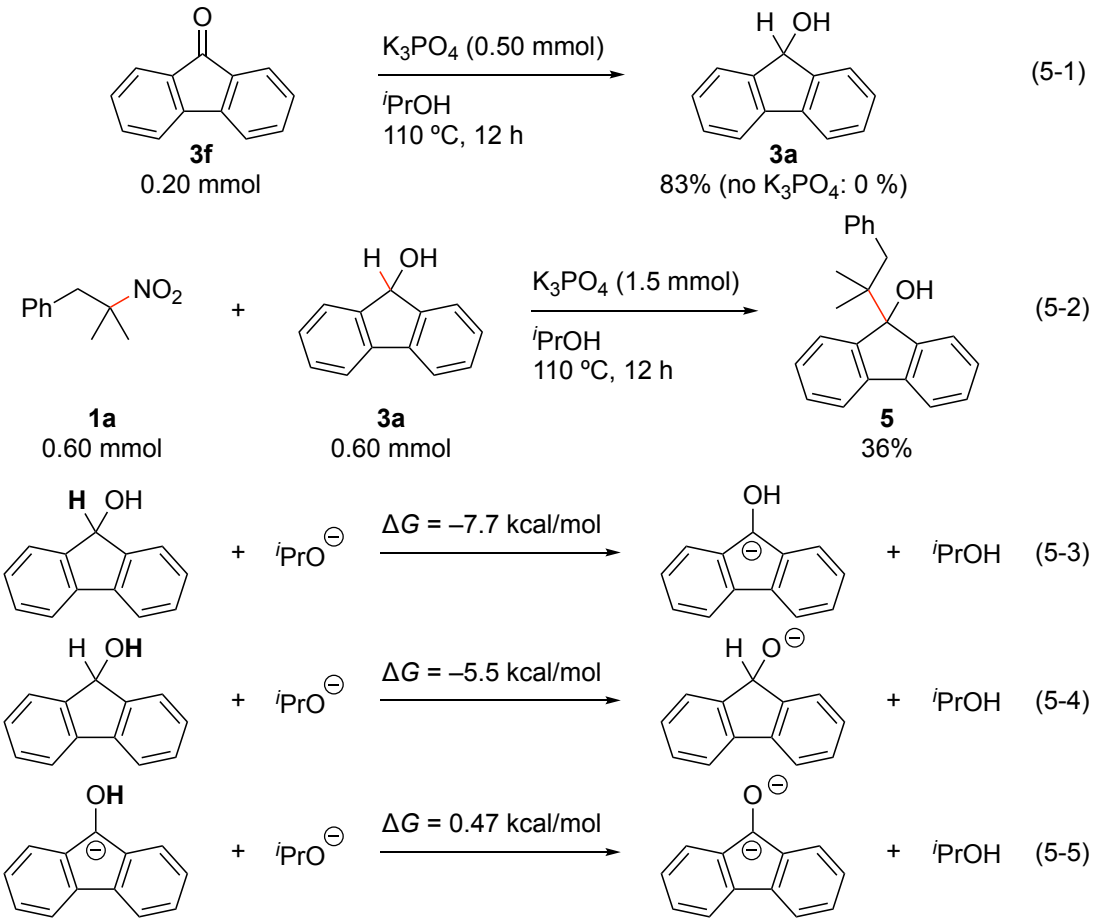
Scheme 5-4. Substrate scope for the reductive denitration of nitroalkanes.



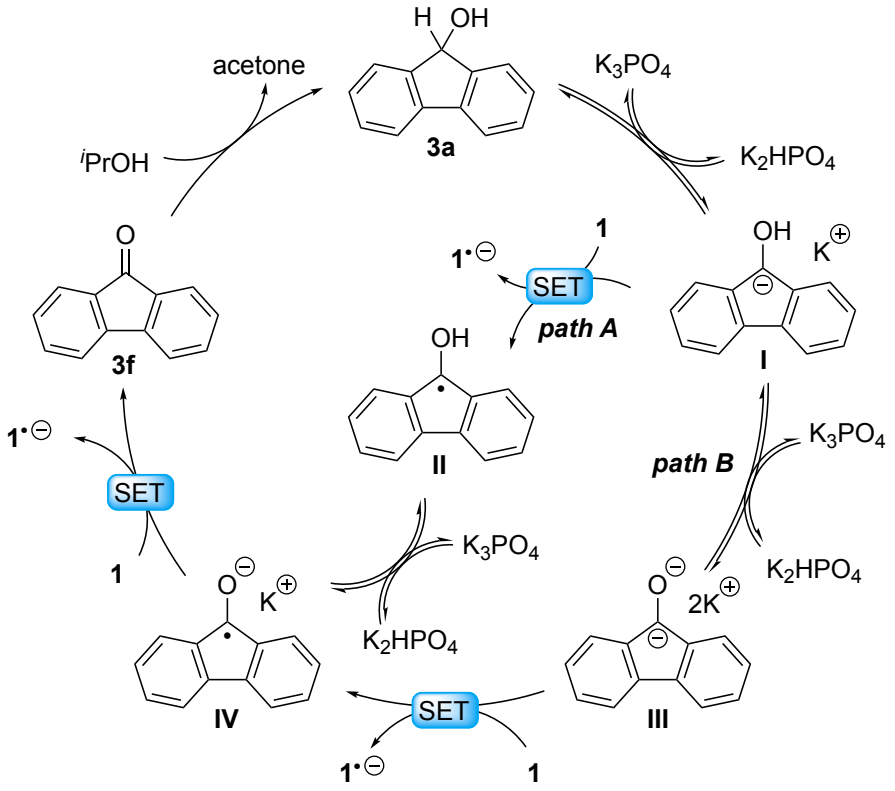
[a] GC yields determined using *n*-$C_{13}H_{28}$ as an internal standard.
[b] **2b** was used as a hydrogen atom donor.
[c] **2a** was used as a hydrogen atom donor.
[d] The reaction was performed using **2c** as a hydrogen atom donor, 20 mol% **3f** instead of **3a**, and K_3PO_4•nH_2O instead of K_3PO_4 in air.

The author performed stoichiometric reactions to gain insights into the catalysis of 9-fluorenol (**3a**). As expected, the transfer hydrogenation between 9-fluorenone (**3f**) and solvent ^{i}PrOH proceeded smoothly only in the presence of K_3PO_4 to generate **3a** (Eq. 5-1). Besides, the reaction of **1a** with one equivalent of **3a** afforded **5** in 36% yield (Eq. 5-2). **5** presumably formed *via* the coupling of a transient tertiary alkyl radical from **1a** and a persistent fluorenyl radical from **3a**,[18] indicating the involvement of such radical species in the catalytic cycle.

Based on these results and DFT calculations as well as the literature precedents,[14] the author proposes the reaction mechanism as shown in Scheme 5-5. **3a** has two acidic protons: less acidic one at the hydroxyl group and more acidic one at the benzylic C9 position (Eq. 5-3 and 5-4). The benzylic position of **3a** is first deprotonated by K_3PO_4 to give aromatic monoanion **I**. Nitroalkane **1** is reduced by intermediate **I** through SET to form the key radical anion species (**1**$^{\bullet-}$) with concomitant formation of fluorenyl radical **II** (path A). Alternatively, **I** would be further deprotonated to afford dianion **III** (path B) (Eq. 5-5).[19] **II** and **III** are then converted to ketyl radical **IV** *via* deprotonation and SET, respectively. **IV** would donate another electron to the substrate, and resulting **3f** is transformed into **3a** by ^{i}PrOH and K_3PO_4.



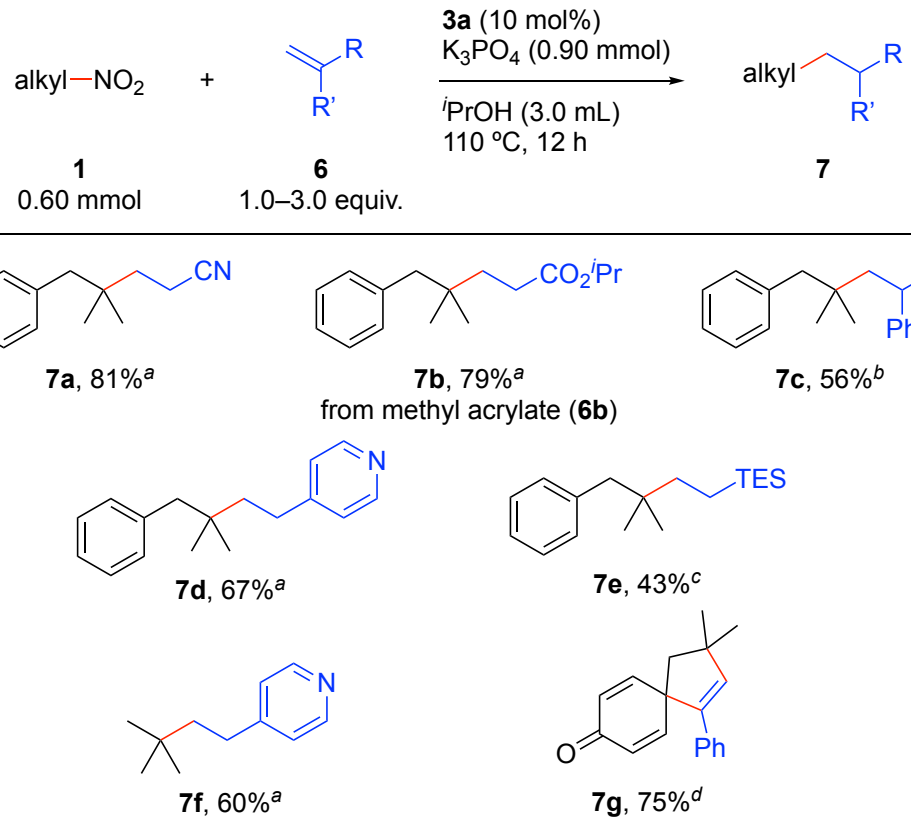
Scheme 5-5. Plausible catalytic cycle of **3a** as an electron donor.



Alkyl radicals can generally participate in various transformations. To demonstrate the versatility of the new denitrative radical generation, the author next investigated the Giese addition reaction.[20] Although Ono has already reported the Giese addition starting from nitroalkanes and electron-deficient olefins (Michael acceptors) by using tin hydride as a reductant, it requires a large excess of alkenes to overcome undesired side reactions such as hydrogenation of alkyl radical and hydrostannylation of alkenes.[21] The present system, where tin hydride is absent, is not expected to waste alkenes in vain.

In accordance with the hypothesis above, the reaction of nitroalkane **1a** and one equivalent of acrylonitrile (**6a**) under the fluorenol-catalyzed conditions successfully delivered alkanenitrile **7a** in 81% yield (Scheme 5-6). The product from **1a** and methyl acrylate (**6b**) was obtained in 79% yield as an isopropoxy ester. Vinylarenes such as 1,1-diphenylethylene (**6c**) and 4-vinylpyridine (**6d**) were suitable Michael acceptors, providing the corresponding products **7c** and **7d** in 56% and 67% yield, respectively. Electron-rich vinylsilane **6e** also participated in the reaction with **1a** to afford tetraalkylsilane **7e** in moderate yield. *tert*-Butyl radical generated from the corresponding nitroalkane (**1k**) coupled with **6d**, resulting in 60% yield of alkylated pyridine **7f**. Substrate **1c** bearing an aromatic ring underwent consecutive addition across phenylacetylene (**6f**) followed by dearomative spirocyclization, yielding spiro compound **7g** in 75%.[22]

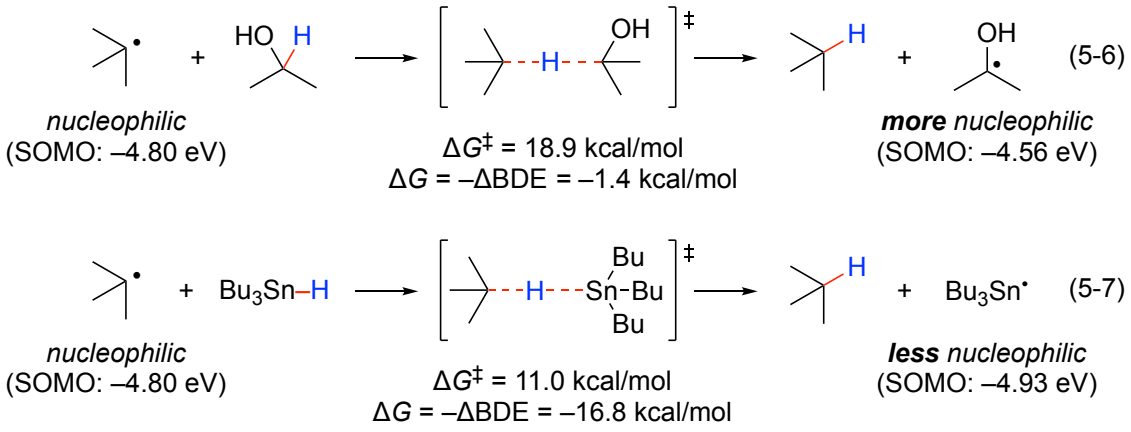
Scheme 5-6. Substrate scope for the Giese addition of nitroalkanes.



[a] 1.0 equiv. of **6** was used.
[b] 1.5 equiv. of **6** was used.
[c] 3.0 equiv. of **6** was used.
[d] 0.72 mmol of **1c** and 0.60 mmol of **6f** was used.

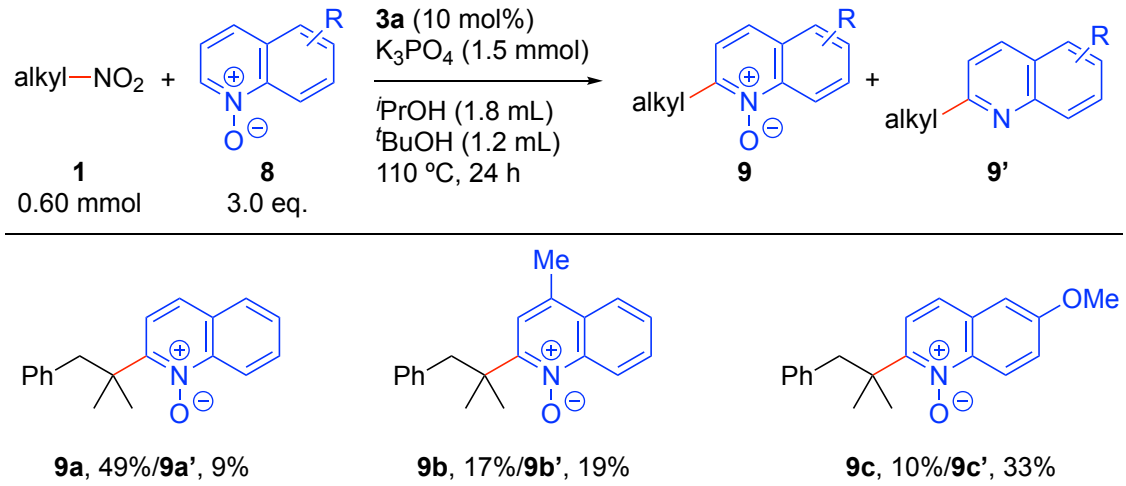
In this newly developed fluorenol-catalyzed system, alkyl radical formed *in situ* can also be hydrogenated even in the absence of hydrogen atom donor (**2a**) *via* HAT from solvent ^{i}PrOH (Table 5-1, entry 17), but this process was assumed to be both thermodynamically and kinetically disfavored than HAT from tin hydride: 1) Thermodynamically, BDE of α-C–H bond of ^{i}PrOH would be much higher than that of the Sn–H bond of Bu_3SnH. 2) Kinetically, the resulting α-alkoxy radical would be more nucleophilic than the tin radical, which induces larger polarity mismatch in the transition state of the HAT to a ^{t}Bu radical.[23] This was proved by DFT calculations (Eq. 3 and 4). The reaction of a ^{t}Bu radical with ^{i}PrOH is only slightly downhill (ΔG = –1.4 kcal/mol)

with a relatively high activation barrier ($\Delta G^{\ddagger}$ = 18.9 kcal/mol), while the reaction with Bu_3SnH is highly downhill (ΔG = –16.8 kcal/mol) with a lower activation barrier ($\Delta G^{\ddagger}$ = 11.0 kcal/mol).[24] Accordingly, the alkyl radical generated in the current system can more likely react with Michael acceptors.



The author also made an effort to develop another important radical-based transformation, namely the Minisci reaction using nitroalkanes and electron-deficient heteroarenes.[25] Tin hydride is seldom used as a radical generator in the Minisci reaction because of its incompatibility with activated (protonated or oxidized) heteroarenes.[26] It was proved that some oxidized heteroarenes, especially quinoline *N*-oxides coupled with alkyl radical under the reductive conditions for the denitration (Scheme 5-7). The reaction of **1a** and quinoline *N*-oxide (**8a**) provided the corresponding alkylated heterocycle *N*-oxide **9a** in 49% yield accompanied by 9% of reduced product **9a'**.[27] The use of 4-methylquinoline *N*-oxide (**8b**) resulted in the formation of almost an equal amount of **9b** and **9b'** (17% and 19%, respectively), while 6-methoxyquinoline *N*-oxide (**8c**) delivered reduced product **9c'** preferentially in 33% with *N*-oxide **9c** in 10% yield. Although the yields are relatively low, these are the first examples of the Minisci reaction using nitroalkanes as alkylating reagents.

Scheme 5-7. Substrate scope for the Minisci reaction of nitroalkanes.



Conclusion

In summary, the author has succeeded in generating organic radicals from nitroalkanes by using 9-fluorenol as a catalyst. Compared to conventional methods using tin hydride, this new catalytic protocol represents cost-efficiency, environmental compatibility, simple and safe experimental operation, and substrate generality. Furthermore, alkyl radicals formed *in situ* can be applied to some of important radical reactions including hydrogenation, the Giese addition, and the Minisci reactions. The remarkable catalytic activity of fluorene derivatives was proved to derive from their planar aromatic framework, which effectively stabilizes both anionic and radical species by charge/spin delocalization.

Experimental section

Chemicals

1a,[7f] **1c**,[28] **1g**,[29] **1j**,[7g] **3a**,[30] **3c**,[31] and **3e**[32] were prepared according to the literature procedures.

Preparation of 1b. A 100-mL recovery flask was charged with 4-(2-methyl-2-nitropropyl)phenol (**1c**) (0.98 g, 5.0 mmol), K_2CO_3 (1.38 g, 10 mmol), and a magnetic stir bar. THF (12.5 mL), DMF (12.5 mL), and MeI (0.47 mL, 7.5 mmol) were added *via* syringe and the reaction mixture was heated to reflux and stirred for 12 h under argon atmosphere. After cooling to room temperature, the reaction mixture was quenched with 1 M HCl aq. (10 mL) and extracted with EtOAc (20 mL, three times). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 90:10) to afford the title compound (0.87 g, 4.2 mmol, 84%) as a yellow oil. R_f 0.44 (hexane:EtOAc = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 6.9 Hz, 2H), 6.82 (d, *J* = 6.9 Hz, 2H), 3.78 (s, 3H), 3.13 (s, 2H), 1.56 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9, 131.0, 126.9, 113.8, 88.7, 55.2, 46.0, 25.4. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{15}NO_3Na$, 232.0944; found, 232.0944.

General procedure for the synthesis of 1d–1f.[7f] A Schlenk flask was charged with a magnetic stir bar, CuBr (20 mol%), 2,4-bis(2,6-diisopropylphenylimino)pentane (20 mol%). In a glovebox, NaO^{t}Bu (1.2 equiv.) was added to the flask. Anhydrous hexane (0.20 M) was added to a flask and the resulting solution was stirred for 1 h at 60 ºC. The

mixture was then added with 2-nitropropane (1.15 equiv.) and arylmethylbromide (1.0 equiv.) sequentially *via* syringe and the resulting suspension was stirred vigorously for 48 h at 60 ºC. After cooling to room temperature, the reaction mixture was diluted with Et_2O. The solution was washed with saturated NH_4Cl aq. and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by MPLC using Kanto Chemical silica gel 60 and distillation or recrystallization.

Preparation of 1d. The reaction of 4-chlorobenzyl bromide (2.1 g, 10 mmol) followed by purification by MPLC (hexane:EtOAc = 95:5) and distillation (1 torr, 175 ºC) afforded the title compound (1.07 g, 5.0 mmol, 50%) as a yellow oil. R_f 0.46 (hexane:EtOAc = 90:10). ^{1}H NMR (400 MHz, C_6D_6): δ 6.96 (d, *J* = 7.3 Hz, 2H), 6.51 (d, *J* = 7.5 Hz, 2H), 2.56 (s, 2H), 1.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.5, 133.3, 131.3, 128.7, 88.4, 46.0, 25.5. HRMS–EI (+) (*m/z*): $[M]^+$ calcd for $C_{10}H_{12}NO_2Cl$, 213.0557; found, 213.0552.

Preparation of 1e. The reaction of 2-(bromomethyl)naphthalene (2.2 g, 10 mmol) and 2-nitropropane (1.32 mL, 15 mmol) followed by purification by MPLC (hexane:EtOAc = 95:5) and recrystallization (hexane, 70 ºC to –15 ºC) afforded the title compound (2.4 g, 10 mmol, 17%, total 6 batches were combined) as a beige solid. R_f 0.30 (hexane:EtOAc = 95:5). mp. 90.7–91.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.75 (m, 3H), 7.59 (s, 1H), 7.54–7.42 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 3.37 (s, 2H), 1.62 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.2, 132.5, 132.4, 129.0, 128.1, 128.0, 127.7, 127.6, 126.2, 126.0, 88.7, 46.8, 25.6. HRMS–EI (+) (*m/z*): $[M]^+$ calcd for $C_{14}H_{15}NO_2$, 229.1103; found, 229.1100.

Preparation of 1f. The reaction of 2-(bromomethyl)pyridine hydrochloride (2.5 g, 10 mmol) using NaO^{t}Bu (2.1 g, 22 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 90:10) and distillation (1 torr, 150 ºC) afforded the title compound (0.61 g, 3.4 mmol, 34%) as a yellow oil. R_f 0.21 (hexane:EtOAc = 70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.57 (t, *J* = 7.5Hz, 1H), 7.18–7.10 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 3.36 (s, 2H), 1.59 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.6, 149.3, 136.5, 124.3, 122.2, 88.3, 48.2, 25.9. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_9H_{12}N_2O_2Na$, 203.0791; found, 203.0791.

Preparation of 1h. A 50-mL recovery flask was charged with 4-methyl-4-nitropentyl methanesulfonate[33] (1.13 g, 5.0 mmol), BnSH (0.70 mL, 6.0 mmol), DBU (1.12 mL, 7.5 mmol), C_6H_6 (6.0 mL), and a magnetic stir bar. The reaction mixture was stirred for 12 h at rt. After the reaction completion, the mixture was diluted with Et_2O and washed with 0.20 M NaOH aq. and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound (1.09 g, 4.3 mmol, 86%) as a yellow oil. R_f 0.28 (hexane:EtOAc = 95:5). ^{1}H NMR (400 MHz, C_6D_6): δ 7.22–7.00 (m, 5H), 3.39 (s, 2H), 2.03 (t, *J* = 5.7 Hz, 2H), 1.55–1.44 (m, 2H), 1.24–1.11 (m, 2H), 1.06 (s, 6H). ^{13}C NMR (101 MHz, C_6D_6): δ 138.9, 129.2, 128.7, 127.1, 87.4, 39.7, 36.2, 30.9, 25.4, 23.8. HRMS–EI (+) (*m/z*): $[M]^+$ calcd. for $C_{13}H_{19}NO_2S$, 253.1136; found, 253.1133.

Preparation of 1i. A 50-mL recovery flask was charged with $(PhSe)_2$ (0.77 g, 2.5 mmol), $NaBH_4$ (0.31 g, 8.1 mmol), EtOH (15 mL), and a magnetic stir bar. The reaction mixture was stirred for 30 min at rt and then added with 4-methyl-4-nitropentyl

methanesulfonate[33] (0.45 g, 2.0 mmol) in EtOH (15 mL). The reaction mixture was stirred for 1 h at 60 ºC and the volatiles were evaporated under reduced pressure. The residual yellow solid was dissolved in EtOAc and washed with H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by MPLC (Kanto Chemical silica gel 60, hexane:EtOAc = 100:0 to 95:5) to afford the title compound (0.38 g, 1.3 mmol, 67%) as a brown oil. R_f 0.31 (hexane:EtOAc = 95:5). ^{1}H NMR (400 MHz, C_6D_6): δ 7.39 (d, *J* = 5.8 Hz, 2H), 7.07–6.91 (m, 3H), 2.44 (t, *J* = 6.0 Hz, 2H), 1.64–1.52 (m, 2H), 1.36–1.23 (m, 2H), 1.04 (s, 6H). ^{13}C NMR (101 MHz, C_6D_6): δ 133.0, 130.5, 129.3, 127.1, 87.4, 40.5, 27.3, 25.3, 24.6. HRMS–EI (+) (*m/z*): [M+] calcd. for $C_{12}H_{17}NO_2Se$, 287.0425; found, 287.0426.

General Procedure for Table 5-1. A 4-mL vial was charged with reductant (0.010 mmol) and a magnetic stir bar. In a grove box, (2-methyl-2-nitropropyl)benzene (**1a**) (17.9 mg, 0.10 mmol), base (0.25 mmol), solvent (0.50 mL), and 1,4-cyclohexadiene (**2a**) (28 μL, 0.30 mmol) were added to the vial. The resulting mixture was taken outside and stirred for 12 h at 110 ºC. After the completion of reaction, the yield of isobutylbenzene (**4a**), (2-methyl-1-propen-1-yl)benzene (**4a'**), and (2-methylallyl)benzene (**4a"**) were determined by GC analysis using calibration curves drawn based on data from authentic samples of **4a**, **4a'**, and **4a"** (Figures S5-1–3).

Table S5-1. Data for the GC calibration curve obtained using authentic sample of **4a**.

entry	mass (mg)		x = mass of **4a** / mass of $C_{13}H_{28}$	GC area		y = GC area of **4a** / GC area of $C_{13}H_{28}$
	4a	$C_{13}H_{28}$		**4a**	$C_{13}H_{28}$	
1	9.5	7.5	1.266667	9511341	6890136	1.380429
2	11.9	7.3	1.630137	12795814	7331690	1.745275
3	13.0	7.7	1.688312	14774991	7734032	1.910387
4	15.9	7.5	2.120000	16782892	7202486	2.330153
5	20.0	7.4	2.702703	22541172	7531922	2.992752
6	23.4	7.6	3.078947	26380531	7764995	3.397366
7	26.4	7.5	3.520000	32330295	8343410	3.874950

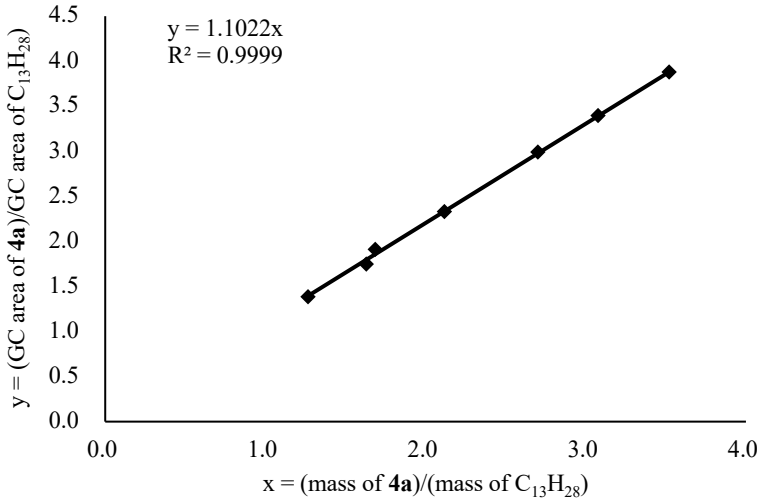


Figure S5-1. GC calibration curve to determine the yield of **4a**.

Table S5-2. Data for the GC calibration curve obtained using authentic sample of **4a'**.

entry	mass (mg)		x = mass of **4a'** / mass of $C_{13}H_{28}$	GC area		y = GC area of **4a'** / GC area of $C_{13}H_{28}$
	4a'	$C_{13}H_{28}$		**4a'**	$C_{13}H_{28}$	
1	6.6	7.7	0.857143	7063793	7690922	0.918459
2	8.6	7.6	1.131579	11015996	8671127	1.270423
3	11.1	7.6	1.460526	13825724	8431263	1.639817
4	12.9	7.2	1.791667	16254917	8463806	1.920521
5	15.5	7.5	2.066667	17482724	7871969	2.220883
6	19.4	7.5	2.586667	22349229	8009507	2.790338

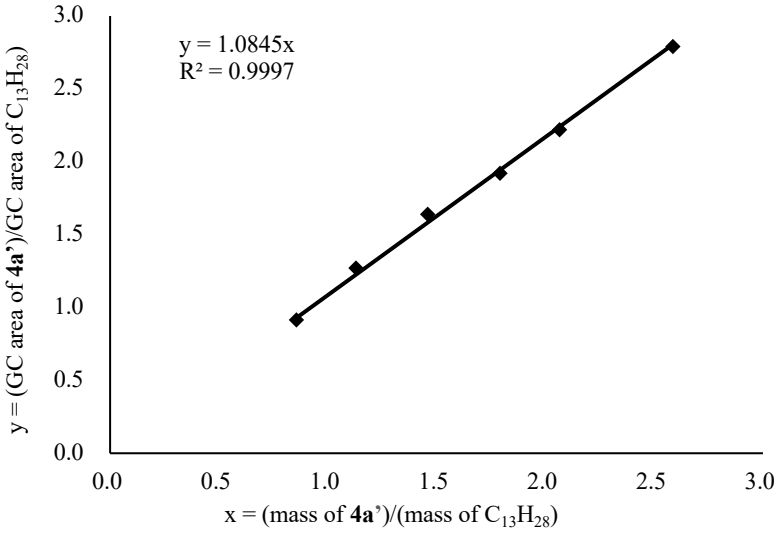


Figure S5-2. GC calibration curve to determine the yield of **4a'**.

Table S5-3. Data for the GC calibration curve obtained using authentic sample of **4a"**.

entry	mass (mg)		$x = \frac{\text{mass of 4a"}}{\text{mass of } C_{13}H_{28}}$	GC area		$y = \frac{\text{GC area of 4a"}}{\text{GC area of } C_{13}H_{28}}$
	4a"	$C_{13}H_{28}$		**4a"**	$C_{13}H_{28}$	
1	6.6	7.4	0.891892	6891941	8065023	0.854547
2	8.7	7.3	1.191781	9187761	7785362	1.180133
3	12.0	7.3	1.643836	14994002	9198830	1.629990
4	13.4	7.3	1.835616	12829931	6938428	1.849112
5	16.3	7.7	2.116883	18646336	8537321	2.184097
6	19.2	7.3	2.630137	22299351	8440775	2.641861
7	23.7	7.6	3.118421	28880444	9141822	3.159156

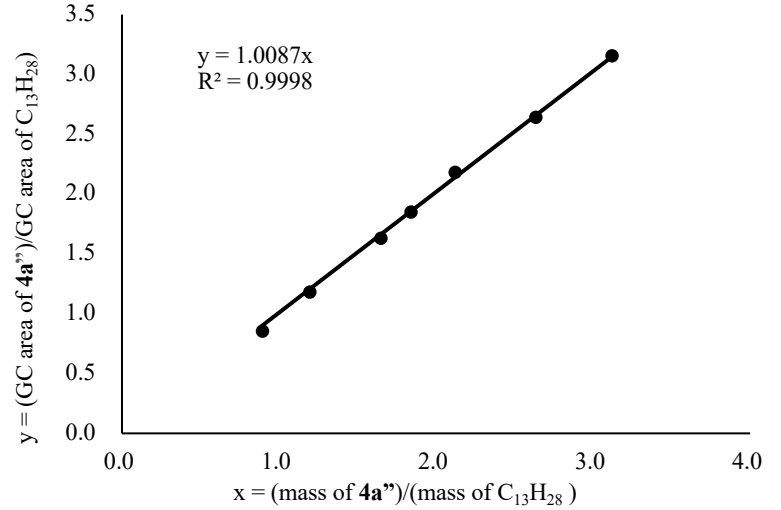
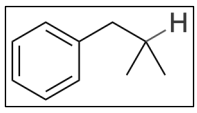
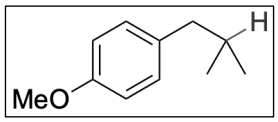


Figure S5-3. GC calibration curve to determine the yield of **4a"**.

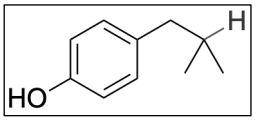
General Procedure for Scheme 5-4. A 15-mL vial was charged with nitroalkane (0.60 mmol), 9-fluorenol (10.9 mg, 0.060 mmol), and a magnetic stir bar. In a glovebox, 1,4-cyclohexadiene (**2a**) (170 μL, 1.8 mmol) or γ-terpinene (**2b**) (0.29 mL, 1.8 mmol), K_3PO_4 (318 mg, 1.5 mmol) and 2-propanol (3.0 mL) were added to the vial (liquid nitroalkane was added in a glovebox). For the reactions whose yield was determined by GC analysis, *n*-$C_{13}H_{28}$ (60 μL, 45 mg, 0.25 mmol) was also added. The resulting mixture was taken outside and stirred for 12 h at 110 ºC. After completion of the reaction, the mixture was filtered through a short pad of Celite® and eluted with DCM. All volatiles were removed in vacuo and the residue was purified by MPLC using Biotage® Sfär Silica HC D to afford the corresponding product.



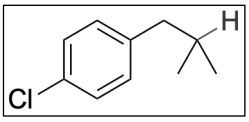
Isobutylbenzene (4a). The reaction of (2-methyl-2-nitropropyl)benzene (**1a**) (108 mg, 0.60 mmol) with **2b** was stirred for 8 h. The yield of **4a** (82%) was determined by GC analysis using calibration curve (Figure S5-1).



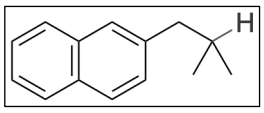
1-Isobutyl-4-methoxybenzene (4b). The reaction of 1-methoxy-4-(2-methyl-2-nitropropyl)benzene (**1b**) (126 mg, 0.60 mmol) with **2b** followed by purification by MPLC. (hexane:EtOAc = 99:1 to 97:3) afforded the title compound (59 mg, 0.36 mmol, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 6.9 Hz, 2H), 6.82 (d, *J* = 6.8 Hz, 2H), 3.79 (s, 3H), 2.41 (d, *J* = 5.8 Hz, 1H), 1.90–1.73 (m, 1H), 0.89 (d, *J* = 4.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.6, 133.8, 129.9, 113.4, 55.2, 44.5, 30.3, 22.3. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[34]



4-Isobutylphenol (4c). The reaction of 4-(2-methyl-2-nitropropyl)phenol (**1c**) (117 mg, 0.60 mmol) with **2b** followed by purification by MPLC (hexane:EtOAc = 95:5 to 90:10) afforded the title compound (75 mg, 0.50 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, *J* = 6.0 Hz, 2H), 6.74 (d, *J* = 6.4 Hz, 2H), 4.69 (s, 1H), 2.40 (d, *J* = 6.8 Hz, 2H), 1.90–1.72 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.4, 134.0, 130.1, 114.9, 44.5, 30.3, 22.3. All resonances of ^{1}H NMR spectra were consistent with the reported values.[35] HRMS–ESI (–) (*m/z*): $[M–H]^-$ calcd for $C_{10}H_{13}O$, 149.0972; found, 149.0971.

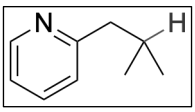


1-Chloro-4-isobutylbenzene (4d). The reaction of 1-chloro-4-(2-methyl-2-nitropropyl)benzene (**1d**) (128 mg, 0.60 mmol) with **2a** followed by purification by MPLC (hexane) afforded the title compound (62 mg, 0.37 mmol, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 6.6 Hz, 2H), 7.06 (d, *J* = 6.9 Hz, 2H), 2.44 (d, *J* = 6.2 Hz, 2H), 1.91–1.74 (m, 1H), 0.89 (d, *J* = 5.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.1, 131.3, 130.4, 128.1, 44.7, 30.2, 22.2. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[36]



2-Isobutylnaphthalene (**4e**). The reaction of 2-(2-methyl-2-nitropropyl)naphthalene (**1e**) (138 mg, 0.60 mmol) with **2a** followed by purification by MPLC (hexane) afforded the title compound (86 mg, 0.47 mmol, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.72 (m, 3H), 7.59 (s, 1H), 7.49–7.37 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 2.65 (d, *J* = 6.1 Hz, 2H), 2.07–1.90 (m, 1H), 0.95 (d, *J* = 5.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.3, 133.5, 131.9, 127.9, 127.6, 127.5, 127.4, 127.2, 125.7, 125.0, 45.6, 30.2, 22.4. All resonances of ^{1}H and

^{13}C NMR spectra were consistent with the reported values.[34]



2-Isobutylpyridine (4f). The reaction of 2-(2-methyl-2-nitropropyl)pyridine (**1f**) (108 mg, 0.60 mmol) with **2a** was stirred for 12 h. The yield of **4f** (60%) was determined by GC analysis using calibration curve (Figure S5-4).

Table S5-4. Data for the GC calibration curve obtained using an authentic sample of **4f**.

entry	mass (mg)		x = mass of **4f** / mass of $C_{13}H_{28}$	GC area		y = GC area of **4f** / GC area of $C_{13}H_{28}$
	4f	$C_{13}H_{28}$		**4f**	$C_{13}H_{28}$	
1	6.1	6.7	0.910448	7775329	8430013	0.922339
2	9.7	6.4	1.515625	8585372	6168729	1.391757
3	11.7	6.6	1.772727	9559766	5754192	1.661357
4	12.9	6.6	1.954545	11086203	6299367	1.759892
5	16.3	6.5	2.507692	14850931	6719845	2.210011
6	20.5	6.7	3.059701	16889016	6100746	2.768353
7	24.2	6.9	3.507246	20171772	6361341	3.170994

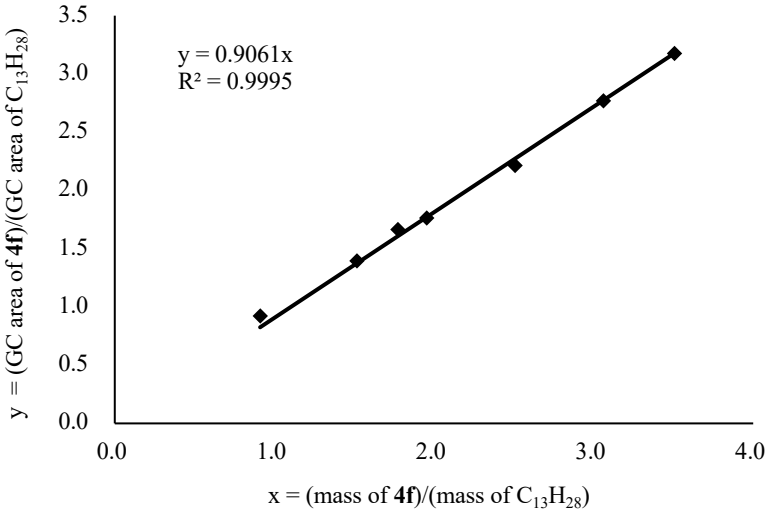
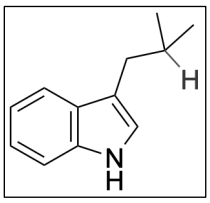
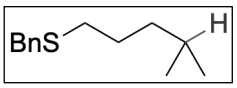


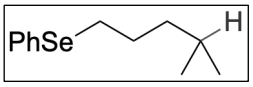
Figure S5-4. GC calibration curve to determine the yield of **4f**.



3-Isobutyl-1*H*-indole (4g). The reaction of 3-(2-methyl-2-nitropropyl)-1*H*-indole (**1g**) (131 mg, 0.60 mmol) with **2b** followed by purification by MPLC (hexane:EtOAc = 90:10) afforded the title compound (81 mg, 0.47 mmol, 79%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 6.9 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 2.63 (d, *J* = 4.9 Hz, 2H), 2.09–1.91 (m, 1H), 0.96 (d, *J* = 4.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.2, 127.9, 121.8, 121.7, 119.2, 119.0, 115.9, 110.9, 34.5, 29.1, 22.7. All resonances of ^{1}H and ^{13}C NMR spectra were consistent with the reported values.[37]

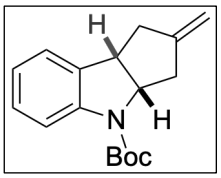


Benzyl(4-methylpentyl)sulfane (4h). The reaction of benzyl(4-methyl-4-nitropentyl)sulfane (**1h**) (152 mg, 0.60 mmol) with **2a** followed by purification by MPLC. (hexane:EtOAc = 100:0 to 95:5) afforded the title compound (74 mg, 0.36 mmol, 59%) as a yellow oil. R_f 0.68 (hexane:EtOAc = 95:5). ^{1}H NMR (400 MHz, C_6D_6): δ 7.22 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.08–7.02 (m, 1H), 3.48 (s, 2H), 2.23 (t, *J* = 8.0 Hz, 2H), 1.48–1.36 (m, 2H), 1.37–1.31 (m, 1H), 1.13–1.02 (m, 2H), 0.78 (d, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, C_6D_6): δ 139.3, 129.2, 128.6, 127.0, 38.3, 36.5, 31.7, 27.9, 27.4, 22.6. HRMS–EI (+) (*m/z*): [M+] calcd. for $C_{13}H_{20}S$, 208.1286; found, 208.1281.



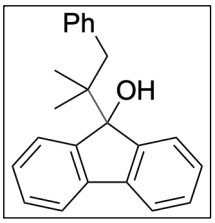
(4-Methypentyl)(phenyl)selane (4i). The reaction of (4-methyl-4-nitropentyl)(phenyl)selane (**1i**) (145 mg, 0.60 mmol) with **2a** followed by purification by MPLC. (hexane:EtOAc = 100:0 to 95:5) afforded the title compound (77 mg, 0.32 mmol, 53%) as a yellow oil. R_f 0.76 (hexane:EtOAc = 95:5). ^{1}H

NMR (400 MHz, C_6D_6): δ 7.46 (d, *J* = 6.9 Hz, 2H), 7.06–6.93 (m, 3H), 2.65 (t, *J* = 6.0 Hz, 2H), 1.63–1.49 (m, 2H), 1.42–1.25 (m, 1H), 1.16–1.05 (m, 2H), 0.76 (d, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, C_6D_6): δ 132.7, 131.4, 129.2, 126.7, 39.2, 28.3, 28.1, 27.8, 22.6. HRMS–EI (+) (*m/z*): [M+] calcd. for $C_{12}H_{18}Se$, 242.0574; found, 242.0571.



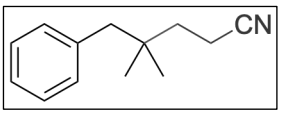
***tert*-Butyl 2-methylene-2,3,3a,8b-tetrahydrocyclopenta[*b*]indole-4(1*H*)-carboxylate (4j).** A 15-mL vial was charged with *tert*-butyl 2-methylene-8b-nitro-2,3,3a,8b-tetrahydrocyclopenta[*b*]indole-4(1*H*)-carboxylate (**1j**) (190 mg, 0.60 mmol), **3f** (22 mg, 0.12 mmol), K_3PO_4•nH_2O (0.21 g, 0.90 mmol), 2-propanol (stored outside, 3.0 mL), BnSH (**2c**) (0.21 mL, 1.8 mmol), and a magnetic stir bar. The resulting mixture was stirred for 6 h at 110 ºC under air. After completion of the reaction, the mixture was filtered through a glass fiber filter and eluted with DCM. All volatiles were removed in vacuo and the residue was purified by MPLC (hexane:EtOAc = 98:2 to 95:5) using Biotage® Sfär Silica HC D to afford the title compound (152 mg, 0.56 mmol, 93%) as a colorless oil. R_f 0.34 (hexane:EtOAc = 95:5). Because of two rotamers in equilibrium at rt, some NMR peaks were split. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (br s, 1H, isomer A), 7.41 (br s, 1H, isomer B), 7.14 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 4.74 (br s, 1H), 3.87 (t, *J* = 9.0 Hz, 1H), 2.94–2.77 (m, 1H), 2.47 (d, *J* = 14.4 Hz, 2H), 1.58 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4 (B), 152.1 (A), 148.5, 142.4 (A), 141.7 (B), 135.0 (B), 134.2 (A), 127.6, 124.5 (B), 124.1 (A), 122.5, 114.5, 107.4, 81.4 (B), 80.3 (A), 63.9, 44.2 (A), 43.6 (B), 41.3 (A), 40.7 (B), 40.0, 28.4. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{21}NO_2Na$, 294.1465; found, 294.1469.

Procedure for Eq. 5-1. A 4-mL vial was charged with **3f** (36.0 mg, 0.20 mmol) and a magnetic stir bar. In a glovebox, K_3PO_4 (106 mg, 0.50 mmol) and 2-propanol (1.0 mL) were added to the vial. The resulting mixture was taken outside and stirred for 1 h at 110 ºC. After cooling the reaction mixture to rt, 1.0 M HCl aq. (1.0 mL) was added quickly, and the crude mixture was extracted with EtOAc (1.0 mL, 2 times). The combined organic layer was concentrated under reduced pressure, and added with 1,3,5-trimethoxybenzene (5.7 mg, 34 μmol). ^{1}H NMR analysis (DMSO-d_6) revealed the formation of **3a** in 83% yield.

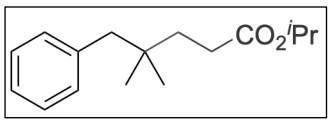


Procedure for Eq. 5-2. A 15-mL vial was charged with (2-methyl-2-nitropropyl)benzene (**1a**) (107 mg, 0.60 mmol), 9-fluroenol (**3a**) (109 mg, 0.60 mmol), and a magnetic stir bar. In a glovebox, K_3PO_4 (0.32 g, 1.5 mmol) and 2-propanol (3.0 mL) were added to the vial. The resulting mixture was taken outside and stirred for 12 h at 110 ºC. After completion of the reaction, the mixture was filtered through a short pad of Celite® and eluted with DCM. All volatiles were removed in vacuo and the residue was purified by MPLC (hexane:EtOAc = 97:3 to 95:5) using Biotage® Sfär Silica HC D to afford 9-(2-methyl-1-phenylpropan-2-yl)-9*H*-fluoren-9-ol (**5**) (68 mg, 0.22 mmol, 36%) as a colorless solid. R_f 0.21 (hexane:EtOAc = 95:5). mp. 114.6–115.0 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (t, J = 7.5 Hz, 4H), 7.38 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.23–7.15 (m, 3H), 7.01 (d, J = 7.1 Hz, 2H), 2.68 (s, 2H), 2.12 (s, 1H), 0.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 140.7, 139.0, 131.1, 128.7, 127.5, 126.8, 125.7, 125.7, 119.7, 88.3, 42.0, 41.9, 21.3. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{22}ONa$, 337.1563; found, 337.1569.

General Procedure for Scheme 5-6. A 15-mL vial was charged with 9-fluorenol (**3a**) (10.9 mg, 0.060 mmol) and a magnetic stir bar. In a glovebox, nitroalkane **1** (0.60 mmol), alkene or alkyne **6** (0.60–1.8 mmol), K_3PO_4 (191 mg, 0.90 mmol) and 2-propanol (3.0 mL) were added to the vial. The resulting mixture was taken outside and stirred for 12 h at 110 ºC. After completion of the reaction, the mixture was filtered through a short pad of Celite®. All volatiles were removed in vacuo and the residue was purified by MPLC using Biotage® Sfär Silica HC D to afford the corresponding product.

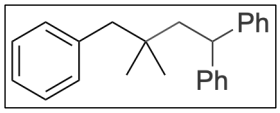


4,4-Dimethyl-5-phenylpentanenitrile (7a). The reaction of (2-methyl-2-nitropropyl)benzene (**1a**) (108 g, 0.60 mmol) with acrylonitrile (**6a**) (39 µL, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 95:5 to 90:10) afforded the title compound (91 mg, 0.49 mmol, 81%) as a yellow oil. R_f 0.22 (hexane:EtOAc = 95:5). ^{1}H NMR (400 MHz, C_6D_6): δ 7.14–7.06 (m, 3H), 6.84 (d, *J* = 8.7 Hz, 2H), 2.03 (s, 2H), 1.42 (t, *J* = 5.5 Hz, 2H), 1.09 (t, *J* = 6.4 Hz, 2H), 0.44 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.8, 130.4, 127.9, 126.2, 120.4, 48.1, 37.1, 33.9, 25.9, 12.4. HRMS–ESI (+) (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{18}N$, 188.1434; found, 188.1432.

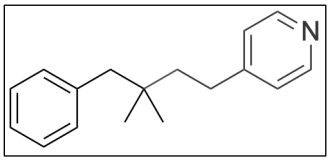


Isopropyl 4,4-dimethyl-5-phenylpentanoate (7b). The reaction of (2-methyl-2-nitropropyl)benzene (**1a**) (108 mg, 0.60 mmol) with methyl acrylate (**6b**) (57 µL, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 97:3 to 90:10) afforded the title compound (91 mg, 0.49 mmol, 81%) as an colorless oil. R_f 0.47 (hexane:EtOAc = 97:3).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.16 (m, 3H), 7.12 (d, *J* = 5.8 Hz, 2H), 5.00 (m, 1H), 2.51 (s, 2H), 2.30 (t, *J* = 6.1

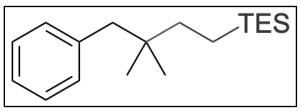
Hz, 2H), 1.58 (t, *J* = 6.1 Hz, 2H), 0.85 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 138.8, 130.6, 127.7, 125.9, 67.5, 48.2, 36.7, 33.9, 30.1, 26.3, 21.8. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{24}O_2Na$, 271.1669; found, 271.1668.



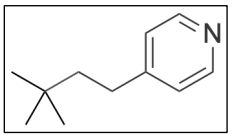
(3,3-Dimethylbutane-1,1,4-triyl)tribenzene (7c). The reaction of (2-methyl-2-nitropropyl)benzene (**1a**) (108 mg, 0.60 mmol) with 1,1-diphenylethylene (**6c**) (158 μL, 0.90 mmol) followed by purification by MPLC (hexane) and HPLC (COSMOSIL, hexane, λ = 206 nm) afforded the title compound (59 mg, 0.36 mmol, 60%) as a colorless oil. R_f 0.43 (hexane) ^{1}H NMR (400 MHz, acetone-*d*$_6$): δ 7.42 (d, *J* = 6.8 Hz, 4H), 7.29–7.07 (m, 11H), 4.26 (t, *J* = 5.5 Hz, 1H), 2.56 (s, 2H), 2.22 (d, *J* = 4.8 Hz, 2H), 0.78 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.7, 139.0, 130.7, 128.4, 127.7, 127.6, 125.9, 125.8, 49.5, 48.1, 47.9, 35.3, 27.1. HRMS–ESI (+) (*m/z*): $[M]^+$ calcd for $C_{24}H_{26}$, 314.2035; found, 314.2034.



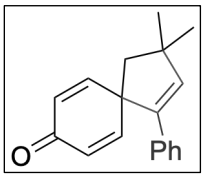
4-(3,3-Dimethyl-4-phenylbutyl)pyridine (7d). The reaction of (2-methyl-2-nitropropyl)benzene (**1a**) (108 mg, 0.60 mmol) with 4-vinylpyridine (**6d**) (64 μL, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 95:5 to 0:100) afforded the title compound (95 mg, 0.40 mmol, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.47 (s, 2H), 7.32–7.18 (m, 3H), 7.17–7.05 (m, 4H), 2.62 (t, *J* = 7.0Hz, 2H), 2.58 (s, 2H), 1.52 (t, *J* = 6.9 Hz, 2H), 0.95 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$): δ 152.2, 149.6, 138.8, 130.5, 127.7, 125.9, 123.8, 48.3, 42.9, 34.3, 30.2, 26.6. HRMS–ESI (+) (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{22}N$, 240.1747; found, 240.1744.



(3,3-Dimethyl-4-phenylbutyl)triethylsilane (7e). The reaction of (2-methyl-2-nitropropyl)benzene (**1a**) (108 mg, 0.60 mmol) with triethylvinylsilane (**6e**) (0.33 mL, 1.8 mmol) followed by purification by MPLC (hexane) afforded the title compound (59 mg, 0.36 mmol, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 6.9 Hz, 2H), 2.49 (s, 2H), 1.24–1.17 (m, 2H), 0.94 (t, J = 7.9 Hz, 9H), 0.81 (s, 6H), 0.58–0.46 (m, 2H), 0.52 (q, J = 8.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.7, 130.5, 127.5, 125.6, 47.5, 36.1, 35.0, 26.2, 7.5, 4.8, 3.2. HRMS–EI (+) (*m/z*): $[M–Et]^+$ calcd for $C_{16}H_{27}Si$, 247.1887; found, 247.1875.



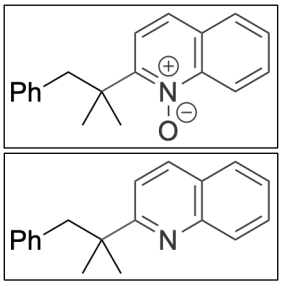
4-(3,3-Dimethylbutyl)pyridine (7f). The reaction of 2-methyl-2-nitropropane (**1k**) (65 μL, 0.60 mmol) with 4-vinylpyridine (**6d**) (64 μL, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 90:10 to 50:50) afforded the title compound (59 mg, 0.36 mmol, 60%) as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 2H), 7.08 (s, 2H), 2.61–2.46 (m, 2H), 1.56–1.38 (m, 2H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4, 149.5, 123.8, 45.0, 30.6, 30.5, 29.2. All resonances of ^{1}H NMR spectra were consistent with the reported values.



3,3-Dimethyl-1-phenylspiro[4.5]deca-1,6,9-trien-8-one (7g). The reaction of 4-(2-methyl-2-nitropropyl)phenol (**1c**) (141 mg, 0.72 mmol) with phenylacetylene (**6f**) (66 μL, 0.60 mmol) followed by purification by MPLC (hexane:EtOAc = 92:8 to 90:10) afforded the title compound (112 mg, 0.45 mmol, 75%) as a colorless solid. R_f 0.31 (hexane:EtOAc = 92:8). mp. 143.0–143.2 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.34 (d, J = 5.8 Hz, 2H), 7.29–7.18 (m, 3H), 7.14 (d, J =

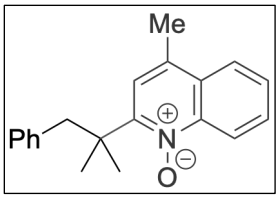
9.3 Hz, 2H), 6.30 (s, 1H), 6.20 (d, *J* = 8.9 Hz, 2H), 2.17 (s, 2H), 1.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.9, 156.0, 142.1, 140.4, 135.2, 128.3, 128.1, 127.8, 125.9, 56.7, 51.5, 44.5, 30.0. HRMS–ESI (+) (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{19}O$, 251.1430; found, 251.1423.

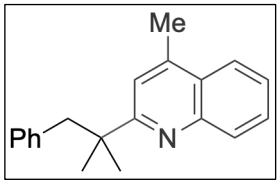
General Procedure for Scheme 5-7. A 15-mL vial was charged with 9-fluorenol (**3a**) (10.9 mg, 0.060 mmol) and a magnetic stir bar. In a glovebox, (2-methyl-2-nitropropyl)benzene (**1a**) (108 mg, 0.60 mmol), quinoline *N*-oxide derivative **8** (1.8 mmol), K_3PO_4 (382 mg, 1.8 mmol), 2-propanol (1.8 mL), and *tert*-butyl alcohol (1.2 mL) were added to the vial. The resulting mixture was taken outside and stirred for 24 h at 110 ºC. After completion of the reaction, the mixture was filtered through a short pad of Celite®. All volatiles were removed in vacuo and the residue was purified by MPLC using Biotage® Sfär Silica HC D followed by PTLC to afford the corresponding product.



2-(1,1-Dimethyl-2-phenylethyl)quinoline-*N*-oxide (9a) and 2-(1,1-dimethyl-2-phenylethyl)quinoline (9a'). The reaction of **1a** with quinoline-*N*-oxide (**8a**) (0.26 g, 1.8 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 90:10) and PTLC (for **9a**, hexane:EtOAc = 60:40) afforded the title compounds (**9a**: 81 mg, 0.29 mmol, 49%, **9a'**: 14 mg, 0.054 mmol, 8.9%). **9a**: brown oil. R_f 0.40 (hexane:EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, *J* = 8.9 Hz, 1H), 7.84–7.74 (m, 2H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.06–6.94 (m, 3H), 6.90–6.81 (m, 2H), 3.60 (s, 2H), 1.61 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4, 142.8, 139.2, 130.2, 129.7, 129.0, 127.8, 127.7, 127.5, 125.7, 124.4, 121.1, 119.8, 41.9,

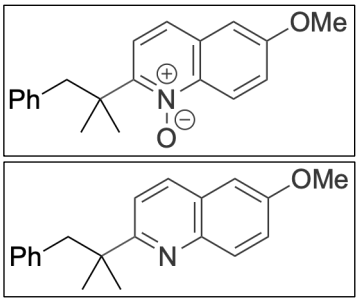
41.2, 26.1. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{19}NONa$, 300.1359; found, 300.1359. **9a'**: yellow oil. R_f 0.63 (hexane:EtOAc = 90:10). ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 6.9 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.16–7.07 (m, 3H), 6.95–6.85 (m, 2H), 3.16 (s, 2H), 1.47 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 147.5, 139.1, 135.6, 130.4, 129.4, 129.0, 127.5, 127.3, 126.4, 125.8, 125.7, 118.9, 49.2, 42.3, 27.5. HRMS–ESI (+) (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{20}N$, 262.1590; found, 262.1591.





2-(1,1-Dimethyl-2-phenylethyl)-4-methylquinoline-*N*-oxide (9b) and 2-(1,1-dimethyl-2-phenylethyl)-4-methylquinoline (9b'). The reaction of **1a** with 4-methylquinoline-*N*-oxide (**8b**) (0.29 g, 1.8 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 55:45) and PTLC (for **9b**: hexane:EtOAc = 50:50, for **9b'**: hexane:EtOAc = 90:10) afforded the title compounds (**9b**: 29 mg, 0.10 mmol, 17%, **9b'**: 31 mg, 0.11 mmol, 19%). **9b**: colorless solid. R_f 0.59 (hexane:EtOAc = 50:50). mp. 146.6–147.0 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.09–6.99 (m, 3H), 6.96–6.85 (m, 3H), 3.61 (s, 2H), 2.53 (s, 3H), 1.60 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.8, 142.4, 139.3, 132.5, 129.9_3, 129.9_1, 128.6, 127.7 127.6, 125.7, 124.4, 121.7, 120.4, 42.1, 41.2, 26.2, 18.5. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{21}NONa$, 314.1515; found, 314.1516. **9b'**: yellow oil. R_f 0.60 (hexane:EtOAc = 90:10). ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.97 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.69 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.52 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.22 (s, 1H), 7.16–7.11 (m, 3H), 6.97–6.91 (m, 2H), 3.16 (s, 2H), 2.66 (s,

3H), 1.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 147.3, 143.4, 139.2, 130.5, 130.0, 128.7, 127.5, 126.5, 125.8, 125.4, 123.4, 119.6, 49.0, 42.1, 27.4, 18.9. HRMS–ESI (+) (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{22}N$, 276.1747; found, 276.1747.



2-(1,1-Dimethyl-2-phenylethyl)-4-methylquinoline-*N*-oxide (9c) and 2-(1,1-dimethyl-2-phenylethyl)-4-methylquinoline (9c'). The reaction of **1a** with 6-methoxyquinoline-*N*-oxide (**8c**) (0.32 g, 1.8 mmol) followed by purification by MPLC (hexane:EtOAc = 100:0 to 70:30) and PTLC (for **9c'**: hexane:EtOAc = 90:10) afforded the title compounds (**9c**: 18 mg, 0.058 mmol, 9.7%, **9c'**: 58 mg, 0.20 mmol, 33%). **9c**: brown oil. R_f 0.32 (hexane:EtOAc = 70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 9.6 Hz, 1H), 7.39 (dd, *J* = 9.6, 2.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.07–6.99 (m, 5H), 6.87–6.82 (m, 2H), 3.93 (s, 3H), 3.57 (s, 2H), 1.59 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9, 150.5, 139.4, 138.6, 130.4, 129.8, 127.6, 125.7, 123.6, 122.4, 121.8, 121.7, 105.5, 55.6, 42.1, 41.1, 26.3. HRMS–ESI (+) (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{21}NO_2Na$, 330.1465; found, 330.1466. **9c'**: orange oil. R_f 0.44 (hexane:EtOAc = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.35 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.14–7.08 (m, 3H), 7.05 (d, *J* = 2.8 Hz, 1H), 6.90–6.83 (m, 2H), 3.93 (s, 3H), 3.12 (s, 2H), 1.44 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 157.1, 143.5, 139.1, 134.4, 130.8, 130.4, 127.5, 127.2, 125.7, 121.6, 119.1, 104.8, 55.4, 49.2, 41.9, 27.5. HRMS–ESI (+) (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{22}NO$, 292.1696; found, 292.1695.

Computational Details

All geometry optimizations were performed by the density functional theory (DFT) with B3LYP[39]-D3 functional.[40] Solvation effects of 2-propanol were evaluated with the PCM method.[41] The Stuttgart-Dresden-Bonn (SDB) basis sets were used for Sn atoms with the effective core potentials (ECPs).[42] The 6-311++G(d,p) basis sets were used for all other atoms.[43] All DFT calculations were performed using Gaussian 16.[44] The Gibbs energy change was evaluated at 298.15 K and 1 atm.

Cartesian coordinates for calculated structures.

E = –158.411381 Hartree

C	0.000000	–0.000011	0.376933
C	–0.000063	1.459201	–0.096546
H	0.000000	–0.000035	1.474796
C	1.263770	–0.729539	–0.096548
C	–1.263707	–0.729648	–0.096548
H	2.168448	–0.230188	0.262801
H	1.306566	–0.753867	–1.191225
H	1.283520	–1.762883	0.262253
H	0.884825	1.993017	0.262514
H	–0.884997	1.992940	0.262514
H	–0.000065	1.508349	–1.191224
H	–2.168429	–0.230375	0.262801
H	–1.283368	–1.762994	0.262253
H	–1.306501	–0.753979	–1.191225

E = –157.765595 Hartree

C	–0.000002	–0.000003	–0.174263
C	–1.327345	–0.661861	0.016715
C	0.090475	1.480425	0.016714
C	1.236867	–0.818567	0.016717
H	–1.566182	–0.780821	1.089550
H	–1.349191	–1.665308	–0.420553
H	–2.141868	–0.075525	–0.420734
H	0.107307	1.746724	1.089545
H	–0.767864	2.000953	–0.420186
H	1.005284	1.892756	–0.421124
H	1.136370	–1.817158	–0.420672
H	1.459427	–0.965836	1.089535
H	2.116743	–0.335753	–0.420655

E = –194.356238 Hartree

C	–1.269390	–0.668132	0.101164
C	0.000000	0.033320	–0.375963
H	–1.305804	–1.696519	–0.268883
H	–2.157134	–0.139471	–0.253310
H	–1.299136	–0.701330	1.195795
C	1.269391	–0.668131	0.101164
H	1.305806	–1.696518	–0.268883
H	1.299137	–0.701328	1.195795
H	2.157134	–0.139468	–0.253310
O	–0.000001	1.420286	0.022147
H	0.000000	0.073489	–1.469091
H	–0.000004	1.456520	0.986518

E = –193.712662 Hartree

C	–1.220865	–0.779554	0.032182
C	0.008522	0.026972	–0.232403
H	–1.120240	–1.783039	–0.386877
H	–2.111646	–0.317562	–0.407318
H	–1.408123	–0.888142	1.115175
C	1.364050	–0.533819	0.027236
H	1.453958	–1.536953	–0.394971
H	1.569202	–0.609571	1.109553
H	2.142199	0.099299	–0.407964
O	–0.058429	1.383008	0.055765
H	–0.968158	1.690312	–0.035813

E = –193.853785 Hartree

C	1.258554	–0.638497	–0.087800
C	–0.000001	0.159692	0.335765
H	2.161841	–0.106041	0.226910
H	1.285453	–0.730974	–1.181029
H	1.284377	–1.647593	0.345157
C	–1.258546	–0.638509	–0.087800
H	–1.285454	–0.730959	–1.181031
H	–2.161841	–0.106078	0.226932
H	–1.284345	–1.647616	0.345132
O	–0.000009	1.442208	–0.150221
H	–0.000003	0.135483	1.458716

$^{n}Bu_3Sn–H$

E = –477.379711 Hartree

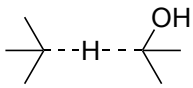
Sn	0.001058	–0.000318	–0.363944
C	–1.376394	1.548152	0.332048
C	–0.653033	–1.968530	0.327347
C	2.030343	0.415624	0.335026
H	0.046330	–2.710708	–0.072022
C	–2.093027	–2.337708	–0.056431
H	–0.536885	–1.984107	1.416501
H	–2.210322	–2.311739	–1.147632
H	–2.791869	–1.589646	0.339509
C	–2.519675	–3.722834	0.449540
H	–1.829726	–4.476406	0.050452

C	–3.957712	–4.084734	0.065645
H	–2.409800	–3.753220	1.540523
H	–4.083861	–4.089540	–1.021984
H	–4.667756	–3.360304	0.477893
H	–4.236406	–5.074574	0.438454
H	2.321637	1.397023	–0.054141
C	3.073228	–0.640483	–0.057507
H	1.983530	0.513083	1.425126
H	3.111447	–0.744107	–1.149722
H	2.776640	–1.624370	0.328218
C	4.484439	–0.318966	0.454074
H	4.790422	0.659903	0.065014
C	5.520078	–1.377169	0.061709
H	4.453596	–0.219272	1.546020
H	5.589670	–1.473109	–1.026788
H	5.249118	–2.358936	0.463730
H	6.515347	–1.125075	0.438969
H	–2.370304	1.310550	–0.061770
C	–0.981068	2.979822	–0.056674
H	–1.442139	1.457303	1.421745
H	–0.905128	3.066171	–1.148433
H	0.017493	3.214101	0.334228
C	–1.967304	4.040916	0.451268
H	–2.966158	3.817188	0.057047
C	–1.566318	5.467155	0.062214
H	–2.043585	3.963317	1.542774
H	–1.512129	5.576236	–1.025925
H	–0.582741	5.722867	0.469754
H	–2.284177	6.202867	0.436172
H	0.003536	0.002930	–2.096061

$^{n}Bu_3Sn^{\bullet}$

E = –476.760725 Hartree

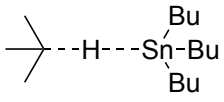
Sn	0.000951	0.001234	–0.663687
C	0.412740	–2.012666	0.169350
C	1.539029	1.362534	0.173014
C	–1.947792	0.649745	0.173354
H	1.397603	2.354048	–0.267511
C	2.986408	0.892181	–0.005705
H	1.290764	1.447971	1.238697
H	3.221032	0.797498	–1.073766
H	3.112160	–0.111501	0.420373
C	4.015098	1.831022	0.641547
H	3.900583	2.834682	0.214201
C	5.459490	1.353836	0.459363
H	3.789408	1.925052	1.710814
H	5.716997	1.280139	–0.602292
H	5.604232	0.363966	0.904435
H	6.171631	2.038496	0.929049
H	–2.734619	0.030327	–0.267604
C	–2.266869	2.137906	–0.004819
H	–1.897658	0.391608	1.238936
H	–2.300472	2.389249	–1.072746
H	–1.462835	2.750136	0.423491
C	–3.596555	2.555994	0.639921
H	–4.406231	1.953447	0.210472
C	–3.908451	4.044880	0.457951
H	–3.566905	2.312937	1.709106
H	–3.971781	4.305193	–0.603694
H	–3.125889	4.666701	0.904959
H	–4.859031	4.316896	0.925831
H	1.339408	–2.386734	–0.276230
C	–0.720464	–3.029363	–0.004970
H	0.616544	–1.842014	1.234230
H	–0.925684	–3.183141	–1.072220
H	–1.649865	–2.636260	0.426793
C	–0.420036	–4.391262	0.638174
H	0.503721	–4.794239	0.205332
C	–1.557671	–5.401742	0.459761
H	–0.220151	–4.245165	1.706734
H	–1.755862	–5.585529	–0.601271
H	–2.484562	–5.031845	0.910233
H	–1.319670	–6.362032	0.926350



E = –352.272782

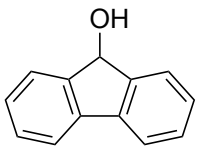
C	1.367547	–0.004244	0.014007
C	1.725960	1.181497	–0.859015
C	1.751724	–1.344653	–0.578520
H	–0.005205	–0.014492	0.019049
C	1.753640	0.162146	1.470010
H	1.345873	–1.467001	–1.587503
H	1.387954	–2.173301	0.036688
H	2.845941	–1.443332	–0.649528
H	1.340006	1.061305	–1.876325
H	2.817930	1.297843	–0.935735
H	1.326835	2.115422	–0.450608
H	2.848120	0.178384	1.586806
H	1.372248	–0.661431	2.081835
H	1.367204	1.099236	1.882672
C	–1.355308	–0.008461	–0.025935
C	–1.787359	1.201452	0.772566
O	–1.715996	0.064826	–1.396005
C	–1.793137	–1.343131	0.519380
H	–1.432583	–1.471996	1.542513

H	–1.398070	–2.158209	–0.091753
H	–2.888846	–1.421582	0.529432
H	–1.380995	2.123788	0.345183
H	–1.430485	1.124608	1.802506
H	–2.882334	1.286991	0.791747
H	–1.484021	0.937526	–1.733888



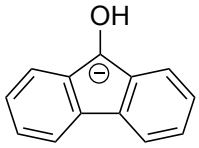
E = –635.546515

Sn	–0.366256	0.002805	–0.530822
C	–2.348446	0.183387	–1.457407
C	1.212580	0.653088	–1.916644
C	–0.008156	–2.111334	–0.042001
H	1.409682	–0.176788	–2.604791
C	2.512113	1.084147	–1.221555
H	0.817386	1.477004	–2.520636
H	2.897308	0.266054	–0.599547
H	2.308710	1.912035	–0.530200
C	3.614925	1.517867	–2.196601
H	3.829607	0.690501	–2.884164
C	4.903554	1.948263	–1.488691
H	3.240060	2.342099	–2.815951
H	5.311286	1.130032	–0.885930
H	4.718149	2.792894	–0.816924
H	5.673891	2.252639	–2.203218
H	–0.754385	–2.417326	0.699308
C	1.405607	–2.404716	0.478286
H	–0.206411	–2.696407	–0.947528
H	1.612774	–1.795912	1.368027
H	2.150269	–2.103625	–0.269907
C	1.636438	–3.880574	0.831072
H	0.899931	–4.186437	1.584384
C	3.050954	–4.158138	1.349694
H	1.440740	–4.494970	–0.056405
H	3.258147	–3.575408	2.253339
H	3.802943	–3.886235	0.601585
H	3.190585	–5.215101	1.594574
H	–2.461696	1.214091	–1.810239
C	–3.510304	–0.189495	–0.526229
H	–2.355638	–0.457031	–2.346761
H	–3.489881	0.443770	0.370535
H	–3.389891	–1.220473	–0.168504
C	–4.889764	–0.059340	–1.186949
H	–5.019135	0.970447	–1.542155
C	–6.041684	–0.429726	–0.247483
H	–4.920187	–0.697600	–2.078558
H	–6.048696	0.215336	0.637305
H	–5.948148	–1.464435	0.098432
H	–7.012511	–0.329445	–0.741478
H	–0.228101	0.984329	0.989156
C	0.087454	1.848353	2.458590
C	0.194705	3.250474	1.932891
C	1.365676	1.188982	2.890142
C	–1.149070	1.507242	3.238652
H	2.153289	1.312470	2.139867
H	1.225254	0.116944	3.061955
H	1.740110	1.623470	3.831467
H	1.009353	3.344746	1.207433
H	0.399639	3.966318	2.745940
H	–0.733589	3.569693	1.447963
H	–2.053352	1.857770	2.730459
H	–1.133729	1.976541	4.236176
H	–1.240464	0.426886	3.391496



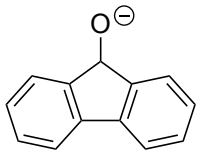
E = –576.653759 Hartree

C	–0.120027	0.040730	3.457559
C	–1.439522	–0.094513	3.015538
C	–1.740795	–0.099291	1.650687
C	0.926180	0.183566	2.538043
C	0.627175	0.179559	1.184231
C	–0.697514	0.032416	0.736263
C	1.570315	0.328397	0.000000
C	0.627175	0.179559	–1.184231
C	–0.697514	0.032416	–0.736263
C	–1.740795	–0.099291	–1.650687
C	–1.439522	–0.094513	–3.015538
C	0.926180	0.183566	–2.538043
C	–0.120027	0.040730	–3.457559
H	0.093285	0.038053	4.520419
H	–2.238685	–0.199218	3.740752
H	–2.766254	–0.207835	1.315727
H	1.950009	0.291175	2.878973
O	2.683938	–0.571851	0.000000
H	2.023970	1.324482	0.000000
H	–2.766254	–0.207835	–1.315727
H	–2.238685	–0.199218	–3.740752
H	1.950009	0.291175	–2.878973
H	0.093285	0.038053	–4.520419
H	2.339973	–1.474022	0.000000



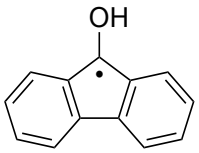
E = –576.163526 Hartree

C	3.452387	–0.093820	–0.003565
C	3.031836	–1.447379	0.004171
C	1.673014	–1.756296	0.006893
C	2.537676	0.948641	–0.008992
C	1.149760	0.660135	–0.006168
C	0.720615	–0.729746	0.001443
C	–0.000860	1.475328	–0.010088
C	–1.149455	0.656565	–0.011168
C	–0.716365	–0.731953	0.001929
C	–1.666261	–1.760640	0.010973
C	–3.025995	–1.454926	0.006904
C	–2.537856	0.941948	–0.015530
C	–3.450220	–0.102790	–0.006847
H	4.515586	0.128806	–0.005774
H	3.771749	–2.240806	0.007962
H	1.352752	–2.795186	0.012681
H	2.880362	1.979123	–0.015613
O	0.005004	2.877759	–0.077114
H	–1.343683	–2.798768	0.020639
H	–3.763847	–2.250237	0.013996
H	–2.883823	1.971456	–0.027018
H	–4.513939	0.117175	–0.011439
H	–0.164850	3.235959	0.801743



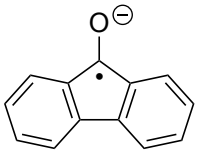
E = –576.160101 Hartree

C	0.107497	–0.009707	3.457066
C	1.432601	–0.080570	3.012162
C	1.723453	–0.055406	1.645360
C	–0.945169	0.100231	2.539923
C	–0.662537	0.135537	1.181379
C	0.669180	0.044792	0.735644
C	–1.645874	0.271431	0.000000
C	–0.662537	0.135537	–1.181379
C	0.669180	0.044792	–0.735644
C	1.723453	–0.055406	–1.645360
C	1.432601	–0.080570	–3.012162
C	–0.945169	0.100231	–2.539923
C	0.107497	–0.009707	–3.457066
H	–0.102576	–0.041561	4.521179
H	2.238515	–0.163913	3.733465
H	2.751426	–0.121971	1.303589
H	–1.973261	0.149927	2.884774
H	–1.912301	1.366922	0.000000
O	–2.742620	–0.532375	0.000000
H	2.751426	–0.121971	–1.303589
H	2.238515	–0.163913	–3.733465
H	–1.973261	0.149927	–2.884774
H	–0.102576	–0.041561	–4.521179



E = –576.040824 Hartree

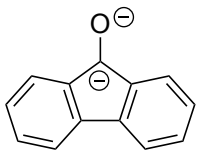
C	3.456965	–0.081956	0.000196
C	3.033837	–1.420492	0.000096
C	1.671219	–1.745031	–0.000083
C	2.532484	0.960944	0.000104
C	1.168052	0.643455	–0.000092
C	0.735830	–0.718631	–0.000180
C	0.001045	1.470866	–0.000069
C	–1.167611	0.641413	–0.000113
C	–0.727474	–0.721196	–0.000170
C	–1.656098	–1.752782	–0.000080
C	–3.021463	–1.439492	0.000079
C	–2.536662	0.944874	0.000099
C	–3.453674	–0.104548	0.000187
H	4.517752	0.141684	0.000353
H	3.772581	–2.213781	0.000168
H	1.357072	–2.783005	–0.000138
H	2.859488	1.994207	0.000196
O	0.072067	2.816024	–0.000227
H	–1.333635	–2.788206	–0.000138
H	–3.754317	–2.238085	0.000110
H	–2.889291	1.971006	0.000217
H	–4.515553	0.113079	0.000341
H	–0.809333	3.210369	0.000864



E = –575.587341 Hartree

C	–0.066425	–0.000014	3.455154
C	–1.409477	0.000002	3.025168
C	–1.717222	0.000012	1.661269
C	0.978004	–0.000027	2.534523

C	0.683460	–0.000015	1.161957
C	–0.681516	0.000012	0.727879
C	1.568903	–0.000002	0.000000
C	0.683460	–0.000015	–1.161957
C	–0.681516	0.000012	–0.727879
C	–1.717222	0.000012	–1.661269
C	–1.409477	0.000002	–3.025168
C	0.978004	–0.000027	–2.534523
C	–0.066425	–0.000014	–3.455154
H	0.151622	–0.000010	4.518404
H	–2.208112	0.000011	3.759163
H	–2.753604	0.000020	1.336766
H	2.010581	–0.000027	2.869597
O	2.842965	0.000049	0.000000
H	–2.753604	0.000020	–1.336766
H	–2.208112	0.000011	–3.759163
H	2.010581	–0.000027	–2.869597
H	0.151622	–0.000010	–4.518404



E = –575.660317 Hartree

C	–3.453492	–0.059013	0.000000
C	–3.033057	–1.422096	0.000000
C	–1.670849	–1.728655	0.000000
C	–2.532224	0.976794	0.000000
C	–1.138305	0.697028	0.000000
C	–0.714252	–0.706285	0.000000
C	–0.000001	1.565015	0.000000
C	1.138304	0.697029	0.000000
C	0.714253	–0.706284	0.000000
C	1.670851	–1.728654	0.000000
C	3.033059	–1.422095	0.000000
C	2.532223	0.976796	0.000000
C	3.453492	–0.059012	0.000000
H	–4.517342	0.166093	0.000000
H	–3.773501	–2.216217	0.000000
H	–1.352885	–2.770078	0.000000
H	–2.875142	2.009253	0.000000
O	–0.000002	2.892310	0.000000
H	1.352888	–2.770077	0.000000
H	3.773503	–2.216215	0.000000
H	2.875142	2.009254	0.000000
H	4.517342	0.166096	0.000000

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List of Publications

All the present Thesis have been published in the following journals.
The following parts of the accepted materials were modified:

(a) A word ‘we’ is replaced to ‘the author’.
(b) Words ‘see supporting information’ and similar expressions are deleted and corresponding materials (text, figures, and/or schemes) are moved from supporting information of accepted works to the main text of the Thesis or the Experimental section.
(c) Subtitles are inserted to the section heads.
(d) Parts of the introduction, results and discussion, and conclusion are modified according to the context of the Thesis.
(e) Words listed in Abbreviations are replaced to the corresponding abbreviations.

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Chapter 2

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Chapter 3

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Chapter 4

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Chapter 5

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