

Copper-Catalyzed Enantioselective Alkylation of Heteroarene *N*-oxides with Azadienes

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Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science
in the Department of
Chemistry in the Graduate School
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ABSTRACT

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Abstract

Heteroarenes bearing nitrogen centers such as pyridines and quinolines are ubiquitous in pharmaceuticals, agrochemicals, and other small molecules of medicinal interest. Among them, quinoline derivatives belong to a significant class of bioactive molecules in the field of drugs and pharmaceuticals and they also display significant activity against numerous viruses and bacterium. Previous studies on enantioselective synthesis of α -heterocyclic amine derivatives include diastereoselective addition of organometallics to enantiopure pyridyl imines derived from Ellman auxiliary, and enantioselective reduction of a pyridyl ketone, conversion to a leaving group, and azide displacement followed by the reduction to obtain the amine. In addition, numerous other methods have been developed to prepare alkylated *N*-heteroarenes. However, protocols for enantioselective synthesis are rather limited and these stereospecific transformations require stoichiometric amounts of optically pure reagents and do not create new stereogenic centers. Considering the aforementioned limitations, the Ge group investigated addition of a chiral Cu-alkyl species, generated by insertion of alkenes into a chiral Cu-H complex to quinoline *N*-oxides to produce chiral 2-alkylated quinolines. This strategy that utilizes quinoline *N*-oxide as an electrophile inspired us to expand the methodology to afford enantioenriched chiral 2-aminoalkyl quinolines from quinoline *N*-oxide and 2-azadienes via a copper-catalyzed process. However, there are possible challenges to this reaction including a reductive dimerization of 2-azadiene,

reduction of quinoline *N*-oxides to quinolines, and potential catalyst deactivation. If these challenges can be overcome, this strategy could represent a practical protocol to prepare chiral aminoalkylated quinolines from readily available quinoline *N*-oxides and alkenes.

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Introduction

Heteroarenes bearing nitrogen centers, such as pyridines and quinolines, are ubiquitous in pharmaceuticals, agrochemicals, and other small molecules of medicinal interest. Among them, heteroarenes bearing adjacent stereogenic centers are of increasing interest in the pharmaceutical industry. For this reason, various methods to synthesize α -alkylated *N*-heteroarenes have been studied. One of the methods is a direct addition of α -amino alkyl radicals to the 2-position of basic heteroarenes. However, due to the limitations of these methods for enantioselective synthesis, there have been further studies to synthesize chiral alkylated *N*-heteroaromatics with high enantioselectivity. I aimed to expand the methodology to afford enantioenriched α -alkylated chiral quinolines. Herein, we will discuss the highlighted method of preparing amines by a copper-catalyzed enantioselective aminoalkylation of heteroaryl *N*-oxides with azadienes and summarize the challenges that I have encountered during this research.

1. Copper-Catalyzed Enantioselective Alkylation of Heteroarene *N*-oxides with Azadienes

1.1 Introduction

Over the years, *N*-heterocycles have captured the interest of organic chemists due to their versatility as intermediates in organic synthesis and their prevalence as structural components in natural and synthetic compounds with a variety of biological functions.^{1,2} The fact that heterocycles make up more than 85% of all biologically active chemicals emphasizes the significance of these substances in organic and medicinal chemistry.¹ Among them, *N*-heteroarenes, such as pyridines and quinolines with adjacent stereogenic centers are of increasing interest in the pharmaceutical industry (Figure 1).³

1.1.1 Established Strategies to Access α -Heterocyclic Amine Derivatives

Due to their importance, heterocyclic compounds have been utilized to develop simple functionalizations in organic chemistry research, with a special emphasis on methods that can replace C–H bonds with novel and intriguing functionalities in a single, direct, and selective operation. The methods that have been developed to access these nitrogen-containing bioactive amine molecules include diastereoselective addition of organometallics to enantiopure pyridyl imines produced from Ellman auxiliary

(Scheme 1a),⁴ and enantioselective reduction of a pyridyl ketone, conversion to a leaving group, and azide displacement followed by reduction to amines (Scheme 1b).⁵ With remarkable control over both regioselectivity and enantioselectivity, the Phipps group reported direct addition of α -amino alkyl radicals to the 2-position of basic heteroarenes by a combination of enantioselective Brønsted acid and photoredox catalysis (Scheme 1c).⁶

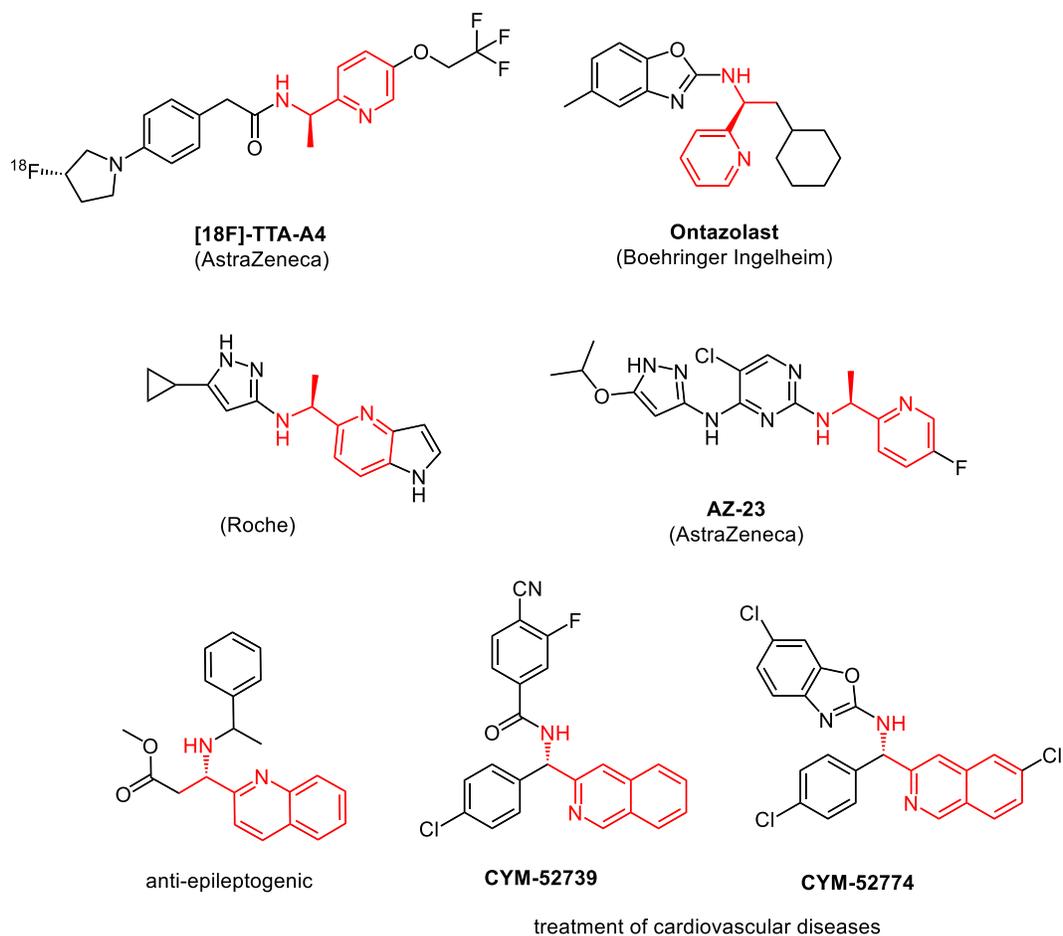
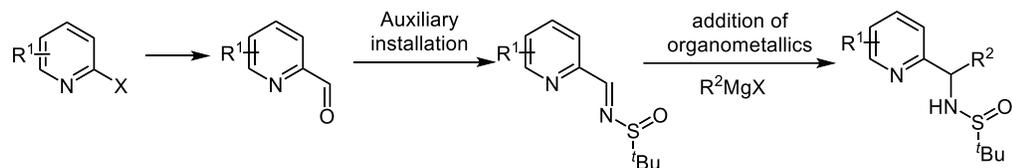


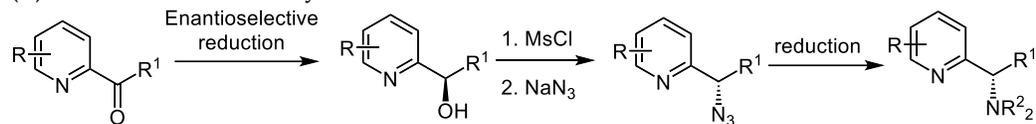
Figure 1: Biologically active compounds containing *N*-heteroarenes

Scheme 1: Typical approaches to α -heterocycle amine derivatives

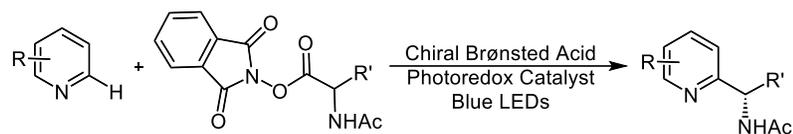
(a) Using Ellman's sulfonamide auxiliary



(b) Enantioselective catalysis



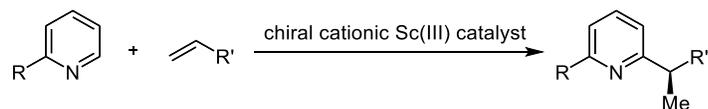
(c) Enantioselective Minisci-type addition to heteroarenes



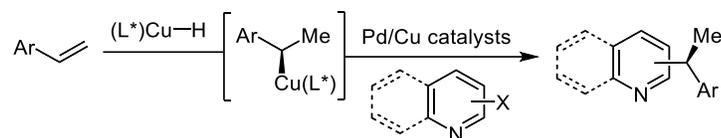
Although numerous other methods have been developed to prepare alkylated *N*-heteroarenes⁷, protocols for enantioselective synthesis of chiral alkylated *N*-heteroarenes are rather limited. Stereospecific cross-coupling reactions of *N*-heteroaryl halides with optically pure organotin,⁸ organoboron,⁹ and organozinc reagents,¹⁰ or lithiated *N*-heteroarenes with chiral alkylboronates¹¹ have been reported. However, these stereospecific transformations require stoichiometric amounts of optically pure reagents and do not create new stereogenic centers.¹²

Scheme 2: Synthesis of chiral alkylated *N*-heteroaromatic compounds

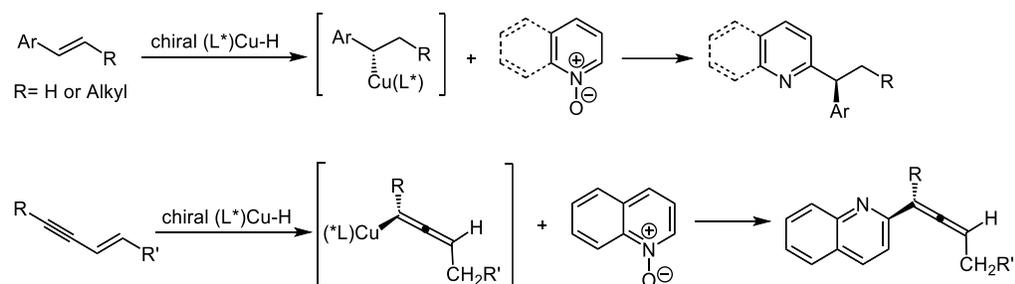
(a) Enantioselective hydroheteroarylation of alkenes with pyridines



(b) Pd/Cu-catalyzed enantioselective couplings of halopyridines with vinylarenes



(c) Enantioselective heteroarylation of vinylarenes/1,3-enynes with heteroaromatic *N*-oxides



As a strategy of enantioselective alkylation of α -heteroarenes, Hou and co-workers reported a scandium-catalyzed enantioselective hydroheteroarylation of aliphatic alkenes with 2-substituted pyridines (Scheme 2a).¹³ However, this reaction requires a highly moisture- and air-sensitive scandium-alkyl catalyst precursor and the highly electrophilic nature of this scandium catalyst limits the reaction scope. Furthermore, quinolines do not undergo this scandium-catalyzed enantioselective hydroarylation because they show stronger coordination to the scandium center than 2-substituted pyridines. In 2016, Buchwald and co-workers reported an enantioselective cross-coupling reaction of heteroaryl halides with vinylarenes (Scheme 2b)¹⁴ and this transformation requires a combination of palladium and copper catalysts.

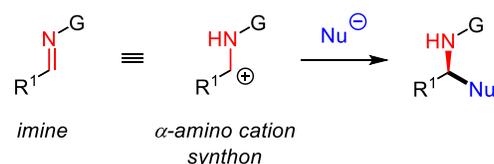
Enantioselective insertion of alkenes into a chiral metal–hydride bond represents a general approach into a chiral metal–alkyl species.¹⁵ In the 2010s, chiral Cu–alkyl

complexes, formed by migratory insertion of alkenes into a chiral Cu–H species,¹⁶ have provided a platform for a wide range of enantioselective organic reactions and can readily react with various electrophiles, including hydroxylamine *O*-benzoyl esters,¹⁷ carbonyl compounds,¹⁸ imines,¹⁹ and allyl halides.²⁰ In 2017, Ge and co-workers suggested that challenges in the development of metal-catalyzed enantioselective alkylation of heteroarenes stem from the low electrophilicity and strong binding affinity of heteroarenes to metal catalysts.²¹ They reasoned that the readily available quinoline *N*-oxides could serve as quinoline surrogates for enantioselective alkylation reactions because the oxidation of quinolines into their *N*-oxides weakens their binding affinity and enhances their electrophilicity. Accordingly, quinoline *N*-oxides have been employed as electrophiles for various nucleophilic addition reactions.²² Ge and co-workers envisioned that a chiral Cu–alkyl species, generated by insertion of alkenes into a chiral Cu–H complex, could react with quinoline *N*-oxides to produce chiral 2-alkylated quinolines (Scheme 2c).²¹

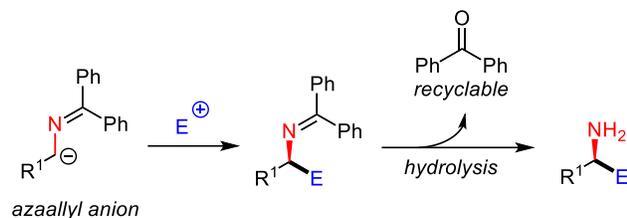
1.1.2 Utilization of 2-Azadienes to Access α -Aminoalkyl Metal Species

Scheme 3: Normal and reverse polarity strategies to prepare chiral amines

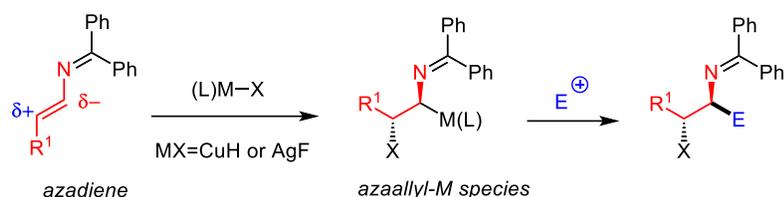
(a) Normal polarity C–C bond-forming approaches



(b) Azaallyl anions as imine umpolung building blocks



(c) Azadienes as novel enamine umpolung building blocks

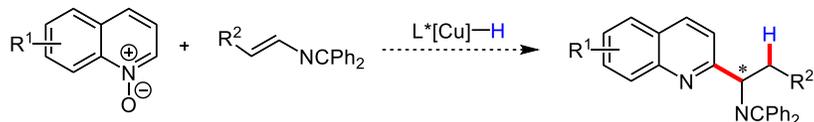


One of the strategies to access functionalized amines is the catalytic production of α -aminoalkyl metal species.²³ Various methods have been developed using protected and unprotected amines, including α -amino cation synthon, azaallyl anion synthon (trapping α -amino anions with transition metal species),²⁴ and azaallyl-metal species (Scheme 3). Herein, I investigated a route by utilizing 2-azadienes as enamine umpolung reagents in which the olefin portion of the azadiene engages in migratory insertion of M-X. In this step, the electrophilic β -position undergoes addition by X and the α -position is trapped with M, which affords a nucleophilic 2-azaallyl metal species. Our group has been studying Cu-H addition to 2-azadienes to furnish this species, which engages in stereoselective couplings with ketones and imines to afford 1,2-amino alcohols and diamines, respectively.^{18d, 19d}

1.2 Enantioselective Alkylation of Heteroarene *N*-oxides

1.2.1 Reaction Design

Scheme 4: Copper-catalyzed enantioselective alkylation of heteroarene *N*-oxides with 2-azadienes



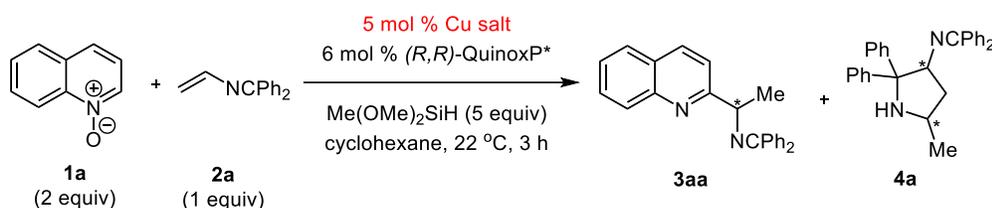
Capitalizing on the Ge group's strategy and our own umpolung strategy for preparing chiral amines,^{18d,19d} I envisioned the enantioselective α -alkylation of quinoline *N*-oxides with 2-azadienes through reductive coupling with a copper-based catalyst. Possible challenges to this enantioselective reaction might include a reductive dimerization of the 2-azadiene, reduction of quinoline *N*-oxides to quinolines by hydrosilanes in the presence of a Cu-H catalyst, and potential catalyst deactivation by the formed quinolines as discussed in Ge's research. If these challenges can be overcome, this umpolung strategy could represent one of the practical protocols to prepare chiral 2-alkylated quinolines from readily available quinoline *N*-oxides and alkenes. Therefore, this method will be able to be used as one of the means for synthesis of pharmaceutical and bioactive molecules.

1.2.2 Reaction Optimization

I chose to begin this study with the reaction of quinoline *N*-oxide (**1a**) and terminal 2-azadiene (**2a**) to identify a chiral copper catalyst and reaction conditions for the enantioselective transformation. The reactions were conducted with 5 mol % Cu salt

and 6 mol % chiral ligands in the presence of 5 equivalents of hydrosilane at room temperature for 3 hours (Table 1). Due to the previous success of (*R,R*)-QuinoxP* ligand in Cu-catalyzed alkylation of quinoline *N*-oxides with vinylarenes,^{15a} I initially probed the same ligand in this reaction. 2-Alkylated quinoline (**3aa**) was identified as the major product.

Table 1: Copper salt optimization

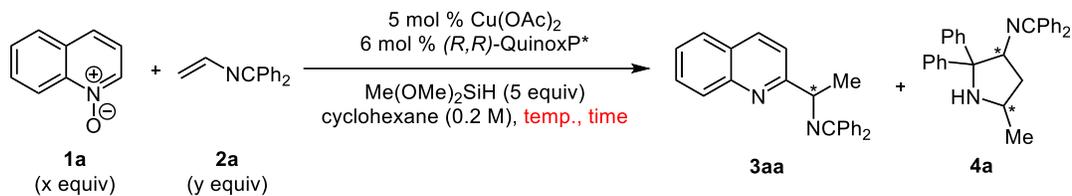


entry ^a	Cu salt	3aa (%) ^b	4a (%) ^b	er of 3aa ^c
1	CuOAc	57 (48)	trace	87:13
2	CuTc	44 (43)	trace	87:13
3	Cu(OAc) ₂	44 (48)	trace	91:9
4	Cu(OTf) ₂	trace	trace	n/a
5	CuCl	54	22	n/a
6	CuCl ₂	34	18	n/a
7	CuF ₂	33	16	n/a

^aReaction under N₂ with 0.1 mmol azadiene **2a** for 3 h. ^bDetermined by 500 MHz ¹H NMR spectroscopy of the unpurified mixture using an internal standard. Isolated yield in parentheses.

^cDetermined by HPLC analysis of purified **3aa**.

Among seven copper salts, Cu(OAc)₂ showed the best result in terms of product (**3aa**) yield and enantioselectivity (entry 3). Quinoline *N*-oxide (**1a**) was also reduced to quinoline in most reactions as I expected as one of the possible issues in this transformation. To mitigate the reduction of quinoline *N*-oxide, I conducted the reactions under modified procedures and conditions, which will be discussed in section 1.2.4.

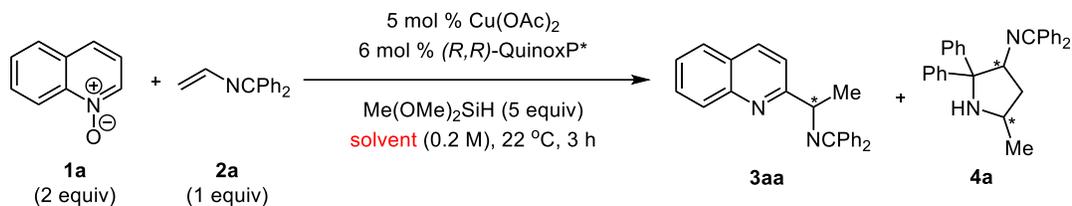
Table 2: Reagent ratio and reaction temperature optimization

entry ^a	temp. (°C) / time (h)	x	y	3aa (%) ^b	4a (%) ^b	er of 3aa ^c
1	22 / 3	1	2	56 (62)	20	90.5:9.5
2	22 / 3	2	1	44 (48)	trace	91:9
3	6 / 20	1	2	46 (49)	34	91:9
4	6 / 20	2	1	51 (49)	trace	90:10

^aReaction under N₂. 1 equiv is 0.1 mmol. ^bDetermined by 500 MHz ¹H NMR spectroscopy of the unpurified mixture using an internal standard. Isolated yield in parentheses. ^cDetermined by HPLC analysis of purified **3aa**.

Lower temperature was also tested but did not improve the enantioselectivity (Table 2). 2-Azadiene (**2a**) was added as the limiting reagent to mitigate dimer (**4a**) formation in the reaction, and no dimer was obtained (entry 2 and 4).

Other reaction conditions, including solvent, were then explored (Table 3). The desired reaction could proceed in both polar and nonpolar solvents. Most solvents showed similar product yield and 1:1 mixture of solvents showed lower er value compared to a single solvent system (entries 6–8). The best er value (91:9) was obtained in cyclohexane solvent (entry 1).

Table 3: Solvent optimization

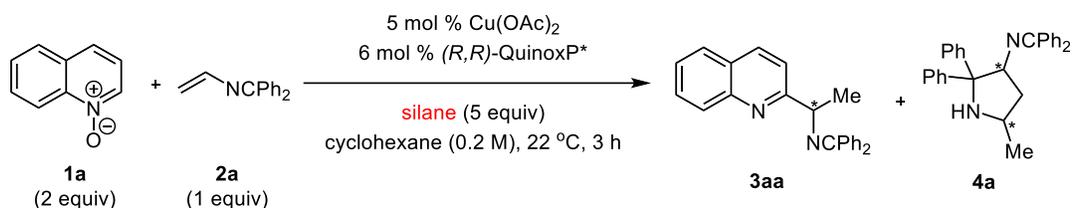
entry ^a	solvent	3aa (%) ^b	4a (%) ^b	er of 3aa ^c
1	cyclohexane	44 (48)	trace	91:9
2	DME	45 (44)	22	86:14
3	dioxane	51 (58)	22	87.5:12.5
4	THF	38 (57)	17	86.5:13.5
5	toluene	46 (32)	trace	86.5:13.5
6	cyclohexane/THF (1:1)	49 (51)	trace	77:23
7	cyclohexane/dioxane (1:1)	53 (46)	trace	85:15
8	cyclohexane/toluene (1:1)	54 (51)	trace	82:17

^aReaction under N_2 with 0.1 mmol azadiene **2a** for 3 h. ^bDetermined by 500 MHz ^1H NMR spectroscopy of the unpurified mixture using an internal standard. Isolated yield in parentheses. ^cDetermined by HPLC analysis of purified **3aa**.

Different silanes were also tested for the reaction (Table 4). PhSiMe_2H , $(i\text{-Pr})_3\text{SiH}$, and Ph_3SiH failed to give the desired product (entries 5–7). Dimethoxymethylsilane (DMMS) gave the best result in terms of both product yield (48%) and e.r. (91:9) (entry 1), and other related silanes showed slightly lower er values and lower product yields compared to DMMS (entries 2–4). With $\text{Cu}(\text{OAc})_2$ as the copper source and DMMS as hydride source, different ligands were also screened (Scheme 5). (R,R) -QuinoxP*, (R) -BINAP, (R) -tol-BINAP showed similar er values with decent yield (20–40%). (R,R) -NORPHOS, (S,S) -BDPP, and (R,S) -Josiphos (SL-J003-1) with cyclohexyl substituents for the phosphines failed to give the desired product. Decent to moderate yield and er

values were obtained with other ligands, including BIPHEP, SEGPHOS, and other Josiphos ligands (SL-J002-1 and SL-J006-1).

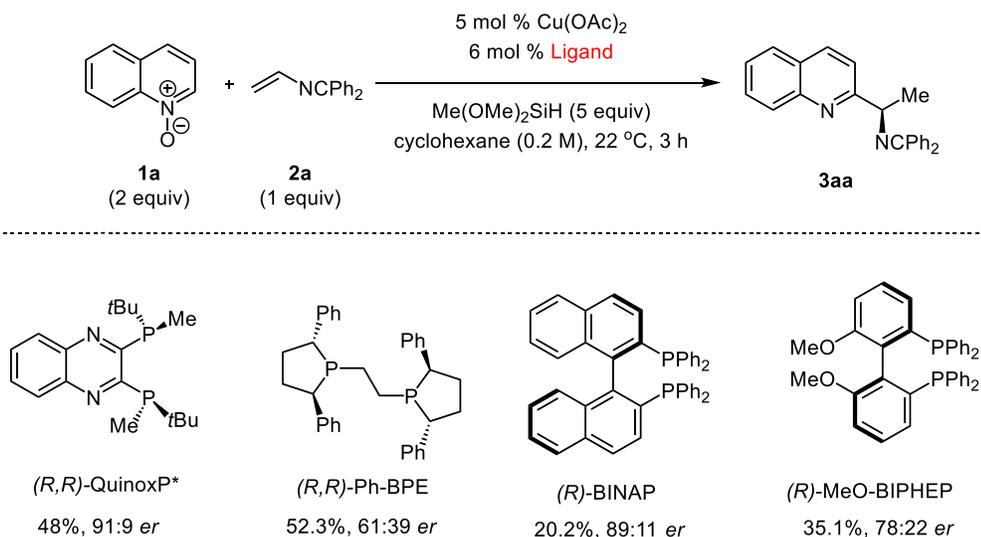
Table 4: Silane screening

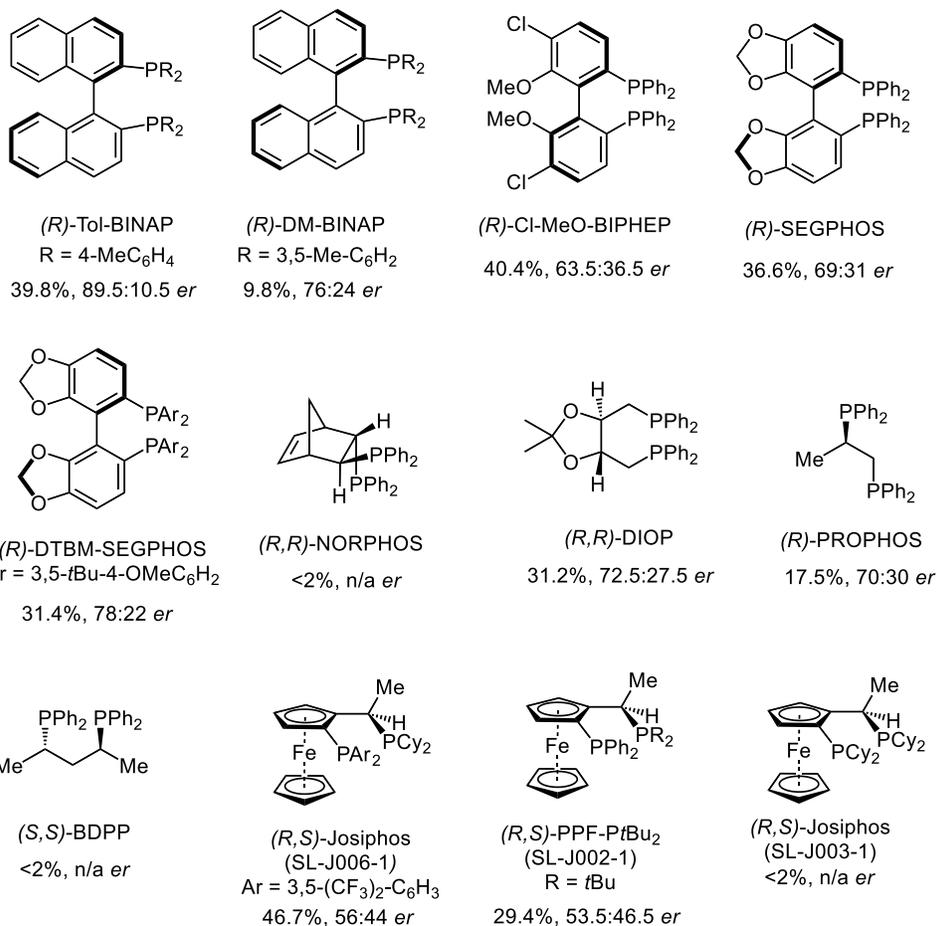


entry ^a	silane	3aa (%) ^b	er of 3aa ^c
1	DMMS	44 (48)	91:9
2	DEMS	29 (32)	83:17
3	TMDS	14 (30)	87.5:12.5
4	(OEt) ₃ SiH	26 (31)	85:15
5	PhSiMe ₂ H	none	n/a
6	(<i>i</i> -Pr) ₃ SiH	none	n/a
7	Ph ₃ SiH	none	n/a

^aReaction under N₂ with 0.2 mmol azadiene **2a** for 3 h. ^bDetermined by 500 MHz ¹H NMR spectroscopy of the unpurified mixture using an internal standard. Isolated yield in parentheses. ^cDetermined by HPLC analysis of purified **3aa**.

Scheme 5: Ligand screening



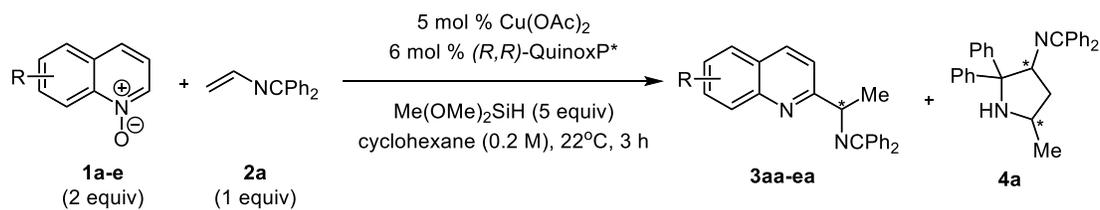


1.2.3 Quinoline *N*-Oxide and 2-Azadiene Scope

With these results described above in hand, I then proceeded to expand quinoline *N*-oxide (Table 5) and 2-azadiene scope (Scheme 6). 6-Methyl and 6-methoxyquinoline *N*-oxide afforded the desired product (**3ca**) with 34% and 32% conversion respectively (entries 2–3), but *er* value was not obtained since the desired products (**3ba** and **3ca**) were not isolable from trace amount of azadiene dimer (**4a**).

Unfortunately, 6-iodo, and 7-methoxyquinoline *N*-oxides failed to afford significant quantities or any desired product (entries 4–5). This might be attributed to the electron-rich quinoline ring by electron-donating substituents, which possibly makes the quinoline *N*-oxides less electrophilic. 6-Iodoquinoline failed the reaction, which might be due to its poor solubility in cyclohexane. In order to investigate the effect of substituents, additional experiments will be necessary. For 2-azadiene scope, desired product (**3ab**) formed with 31.5% conversion, but er value was not obtained due to the purification issue.

Table 5: Quinoline *N*-oxide scope

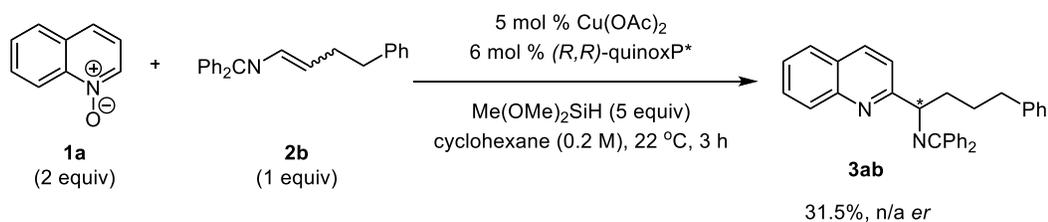


entry ^a	R	3aa-ea (%) ^b	4a (%) ^b	er of 3aa-ea ^c
1	1a , H	44 (48)	trace	91:9
2 ^d	1b , 6-Me	34 (30)	trace	9:91
3	1c , 6-OMe	32	trace	n/a
4	1d , 7-OMe	none	none	n/a
5	1e , 6-I	none	none	n/a

^aReaction under N₂ with 0.1 mmol azadiene **2a** for 3 h. ^bDetermined by 500 MHz ¹H NMR spectroscopy of the unpurified mixture using an internal standard. Isolated yield in parentheses.

^cDetermined by HPLC analysis of purified **3aa-ea**. ^d(*S,S*)-quinoxP* was used.

Scheme 6: 2-Azadiene scope



1.2.4 Procedure Modification to Mitigate Reduction of Quinoline *N*-oxide and Investigation of NHC Ligands

As described in section 1.2.2., the biggest challenge of this reaction is reduction of quinoline *N*-oxide to quinoline, which gives a lower amount of electrophile available to react with the 2-azadiene, thus giving lower product yield. In order to suppress the reduction of quinoline *N*-oxide, I have modified the reaction setup such as adding quinoline *N*-oxide after silane, slow addition of mixture of silane and quinoline *N*-oxide, and slow addition of quinoline *N*-oxide. However, these modifications have not significantly mitigated the reduction of quinoline *N*-oxide, but rather afforded azadiene dimer (**4a**) in higher yield. This might be because slow addition of quinoline *N*-oxide results in low concentration of electrophile in the reaction solution, thus facilitating dimerization of azadiene.

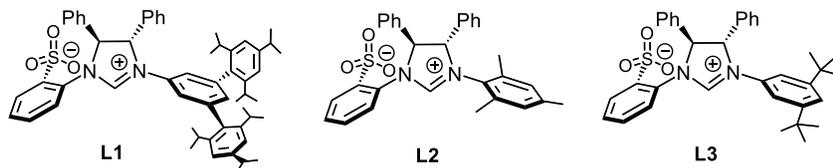


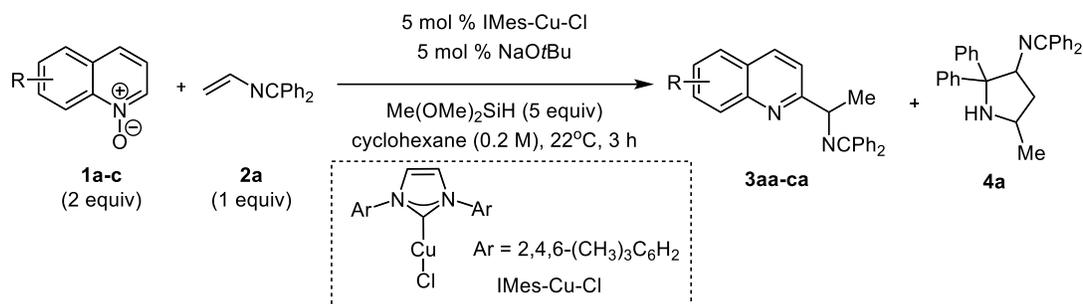
Figure 2: Chiral NHC ligands

I have decided to investigate other types of ligands such as chiral NHC ligands (Figure 2)²⁵ and **L1** was first prepared by reported procedure.²⁶ Prior to investigation of chiral NHC ligands, an achiral NHC was tested (Table 6). Among three electrophiles, 6-methylquinoline *N*-oxide (**1b**) showed decent conversion to the desired product (entry 2).

Table 7 shows the result of chiral NHC ligand **L1**. For 6-methylquinoline *N*-oxide, the desired product was obtained with 14% conversion (entry 2), which is lower compared to (*R,R*)-QuinoxP* ligand with 24% conversion (entry 2, Table 5) and achiral NHC with 46% conversion (entry 2, Table 6). The best conversion was obtained with 6-methoxyquinoline *N*-oxide (entry 3). It was also supposed that 7-methoxyquinoline *N*-oxide is not very electrophilic considering that it gives no reduction and no desired product (entry 4).

Future studies will focus on synthesis of two additional chiral NHC ligands (**L2** and **L3**), their investigation for the copper-catalyzed reductive coupling reaction, and mechanism study.

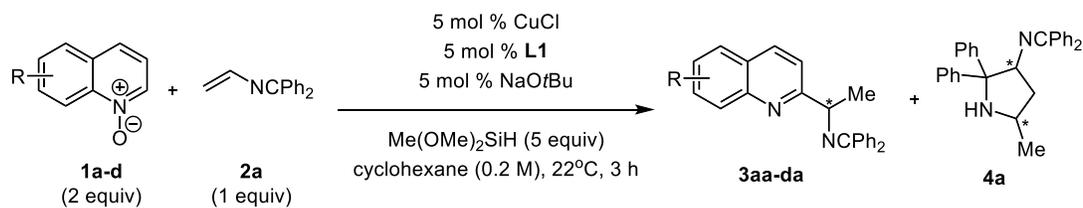
Table 6: Investigation of achiral NHC ligand



entry ^a	R	3aa-ca (%) ^b	4a (%) ^b
1	1a , H	36	trace
2	1b , 6-Me	46 (30)	trace
3	1c , 6-OMe	22	trace

^aReaction under N₂ with 0.1 mmol azadiene **2a** for 3 h. ^bDetermined by 500 MHz ¹H NMR spectroscopy of the unpurified mixture using an internal standard. Isolated yield in parentheses.

Table 7: Investigation of chiral NHC ligand (L1) and substituted quinoline N-oxides



entry ^a	R	3aa-da (%) ^b	4a (%) ^b
1	1a , H	23 (33)	trace
2	1b , 6-Me	14	trace
3	1c , 6-OMe	32 (34)	trace
4	1d , 7-OMe	none	none

^aReaction under N₂ with 0.1 mmol azadiene **2a** for 3 h. ^bDetermined by 500 MHz ¹H NMR spectroscopy of the unpurified mixture using an internal standard. Isolated yield in parentheses.

1.3 Conclusion and Outlook

In summary, I have developed a copper-catalyzed enantioselective α -aminoalkylation of quinoline *N*-oxide to afford enantioenriched α -alkylated quinoline. Based on our previous work, I have showed that 2-azadienes can function as an alkene source for migratory insertion to prepare azaallyl-metal species. It was hypothesized that quinoline *N*-oxide could be utilized as electrophile to prepare various functionalized amines, α -alkylated quinolines in this case.

2-Azadiene and quinoline *N*-oxide react in the presence of copper, chiral ligand, and silane in cyclohexane to afford α -alkylated product. However, we have encountered an issue of reduction of quinoline *N*-oxide, giving lower product yield. Several methods were investigated to mitigate the reduction, such as modified procedure and chiral NHC ligand screening. Unfortunately, they have not improved the results and another issue was observed, inconsistency, irreproducibility of the reactions, and large discrepancy between conversion and isolated yield.

Due to these challenges, there would possibly be additional investigation in this group following this work. They include variations of the reaction design to mitigate reduction of quinoline *N*-oxide, modification of reaction workup such as purification step to have high accuracy and precision.

1.4 Experimental

1.4.1 General Information

General Procedures. All reactions were carried out in oven- (120 °C) or flame-dried glassware under an inert atmosphere of dry N₂ unless otherwise noted. Oven-dried (60 °C or 120 °C) stainless steel cannulas and/or glass syringes (or N₂-flushed plastic syringes) were used for reagent transfer. Organic solutions were concentrated under reduced pressure using a rotary evaporator (Büchi). Flash column chromatography was performed using a Teledyne Isco Combiflash autocolumn or by hand using SiliCycle SiliaFlash® P60 Silica Gel. Room temperature was between 22 °C and 23 °C.

Reagents. The following chemicals were used as received.

(*R,R*)-(-)-2,3-Bis(*tert*-butylmethylphosphino)quinoxaline ((*R,R*)-QuinoxP*)
(Strem), (-)-1,2-bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane ((*R,R*)-Ph-BPE) (Strem), (*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene ((*R*)-BINAP) (Strem), (*R*)-(+)-2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl ((*R*)-MeO-BIPHEP) (Strem), (*R*)-(+)-2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthyl ((*R*)-Tol-BINAP) (Strem), (*R*)-(+)-2,2'-Bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl ((*R*)-DM-BINAP) (Strem), (+)-2,2'-Bis(diphenylphosphino)-5,5'-dichloro-6,6'-dimethoxy-1,1'-biphenyl ((*R*)-(+)-Cl-MeO-BIPHEP), (*R*)-(+)-5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole ((*R*)-(+)-SEGPPOS) (Strem), (*R*)-(-)-5,5'-Bis[di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino]-4,4'-

bi-1,3-benzodioxole ((*R*)-(-)-DTBM-SEGPHOS) (Strem), (*4R,5R*)-(-)-4,5-
 Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane ((*R,R*)-DIOP) (Strem), (*R*)-(+)-
 1,2-Bis(diphenylphosphino)propane ((*R*)-PROPHOS) (Strem), (*2S,4S*)-(-)-2,4-
 Bis(diphenylphosphino)pentane ((*S,S*)-BDPP) (Strem), (*R*)-(-)-1-[(*S*)-2-[Bis(3,5-di-
 trifluoromethylphenyl)phosphino]ferrocenyl]ethyldicyclohexylphosphine (Strem), (*R*)-(-)-
 1-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine (Strem), (*R*)-(-)-1-
 [(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine (Strem),
 dimethoxy(methyl)silane (DMMS) (TCI), diethoxy(methyl)silane (DEMS) (Fisher),
 1,1,3,3-tetramethyldisiloxane (TMDS) (Sigma Aldrich), triethoxysilane (Sigma Aldrich),
 dimethylphenylsilane (TCI), triisopropylsilane (Sigma Aldrich), triphenylsilane (Alfa
 Aesar), quinoline (Alfa Aesar or VWR), 6-methylquinoline (VWR), 6-methoxyquinoline
 (Thermo Fisher), 7-methoxyquinoline (Ambeed), 3-chloroperoxybenzoic acid (Thermo
 Fisher), benzophenone imine (Chem Impex), 2-chloromethylamine hydrochloride
 (Thermo Fisher), triethylamine (TCI), sodium sulfate (VWR), sodium hydride (60% in
 oil) (Sigma Aldrich), hydrogen chloride (2.0 M in diethyl ether) (Sigma Aldrich), 3-
 phenylpropanal (Alfa Aesar), *n*-butyllithium (2.5 M in hexanes) (Sigma Aldrich)

Solvents. Solvents were sparged with dry N₂ and purified under a positive
 pressure of dry N₂ by an Innovative Technologies PureSolve solvent purification system:
 tetrahydrofuran (Sigma-Aldrich), dichloromethane (Sigma-Aldrich), 1,4-dioxane (Sigma-
 Aldrich), diethyl ether (Sigma-Aldrich) and toluene (Sigma-Aldrich) were passed

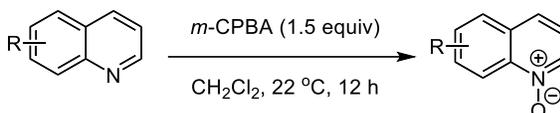
through two consecutive alumina columns. Dimethylformamide and methanol was purchased from Sigma-Aldrich and used as received. Cyclohexane was purchased from Acros and was dried under N₂ atmosphere before use. Hexanes (Fisher or VWR) and EtOAc (Fisher or VWR) were used for flash column chromatography and used as received. HPLC-grade hexanes (Sigma-Aldrich) and isopropanol (Sigma Aldrich) were used as received.

Instrumentation. ¹H NMR spectra were recorded on a Bruker (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration (CDCl₃: δ 7.26) as the internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz), integration. ¹³C NMR spectra were recorded on a Bruker (500 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from chloroform as the internal reference (CDCl₃: δ 77.16). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz), integration. Enantiomer ratios (er values) were determined by HPLC (Phenomenex™ Lux® Amylose I column (4.6 mm x 250 mm) in comparison with authentic racemic materials on a Shimadzu Prominence Modular HPLC.

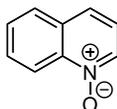
1.4.2 Synthesis of Starting Materials and Ligands

I. Synthesis of Quinoline *N*-oxides

General Method A:²⁶

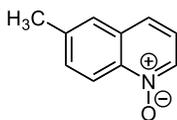


To a flame-dried 250-mL round bottom flask equipped with a magnetic stir bar, quinoline derivatives (1.0 equiv), 3-chloroperbenzoic acid (*m*-CPBA) (1.5 equiv) and CH₂Cl₂ (0.2 M) were added. The mixture was allowed to stir for 12 h at room temperature and then the organic phase was washed with a saturated aqueous NaHCO₃ solution to remove residual *m*-CPBA, and washed with brine. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give crude products, which were further purified by column chromatography on silica gel (EtOAc:MeOH as eluent) or recrystallization in hexane/DCM (1:1).



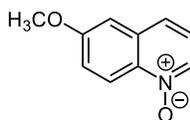
1a

Quinoline *N*-oxide (1a): Prepared according to General Method A on 20.0 mmol scale and the title compound was isolated as a light brown solid (0.99 g, 6.82 mmol, 34.1% yield) with spectral data in agreement with literature values. ¹H NMR (500 MHz, CDCl₃), δ 8.73 (d, *J* = 8.8 Hz, 1H), 8.52 (d, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.74 (td, *J* = 8.2, 5.8 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.22 (m, 1H).



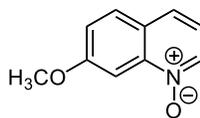
1b

6-methylquinoline N-oxide (1b): Prepared according to General Method A on 10.0 mmol scale (eluent: 10:0 to 8:2 EtOAc:MeOH) and the title compound was isolated as a light brown solid (1.26 g, 0.79 mmol, 79.2% yield) with spectral data in agreement with literature values. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.58 (d, $J = 8.9$ Hz, 1H), 8.42 (d, $J = 5.7$ Hz, 1H), 7.61 (d, $J = 8.2$ Hz, 1H), 7.57 (s, 1H), 7.53 (dd, $J = 8.9, 1.6$ Hz, 1H), 7.20 (dd, $J = 8.3, 5.9$ Hz, 1H), 2.49 (s, 3H).



1c

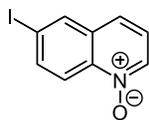
6-methoxyquinoline N-oxide (1c): Prepared according to General Method A on 10.0 mmol scale (recrystallization in hexane/DCM (1:1)) and the title compound was isolated as a white solid (1.55 g, 8.85 mmol, 88.5% yield) with spectral data in agreement with literature values. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.68 (d, $J = 9.6$ Hz, 1H), 8.42 (dd, $J = 6.0, 1.0$ Hz, 1H), 7.65 (d, $J = 8.5$ Hz, 1H), 7.41 (dd, $J = 9.5, 2.7$ Hz, 1H), 7.29 – 7.24 (m, 1H), 7.13 (d, $J = 2.7$ Hz, 1H), 3.96 (s, 3H).



1d

7-methoxyquinoline N-oxide (1d): Prepared according to General Method A on 5.0 mmol scale and the title compound was isolated as a light brown solid (0.76 g, 4.49

mmol, 89.8% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 8.55 (dd, $J = 6.1, 1.1$ Hz, 1H), 8.09 (d, $J = 2.6$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.71 (d, $J = 8.3$ Hz, 1H), 7.28 (dd, $J = 9.0, 2.6$ Hz, 1H), 7.18 (dd, $J = 8.3, 6.1$ Hz, 1H), 4.02 (s, 3H).

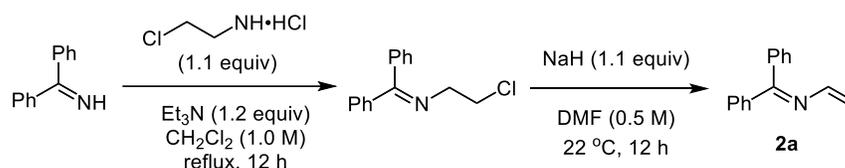


1e

6-iodoquinoline N-oxide (1d): Prepared according to General Method A on 2.0 mmol scale (recrystallization in hexane/DCM (1:1)) and the title compound was isolated as a light orange solid (0.38 g, 1.40 mmol, 70.1% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 8.52 (t, $J = 5.1$ Hz, 1H), 8.46 (dd, $J = 9.5, 3.6$ Hz, 1H), 8.27 (d, $J = 3.7$ Hz, 1H), 8.00 (t, $J = 6.6$ Hz, 1H), 7.62 (dd, $J = 8.7, 3.6$ Hz, 1H), 7.35 – 7.24 (m, 1H).

II. Synthesis of 1,1-diphenyl-*N*-vinylmethanimine (2a)

General Method B:^{20d}



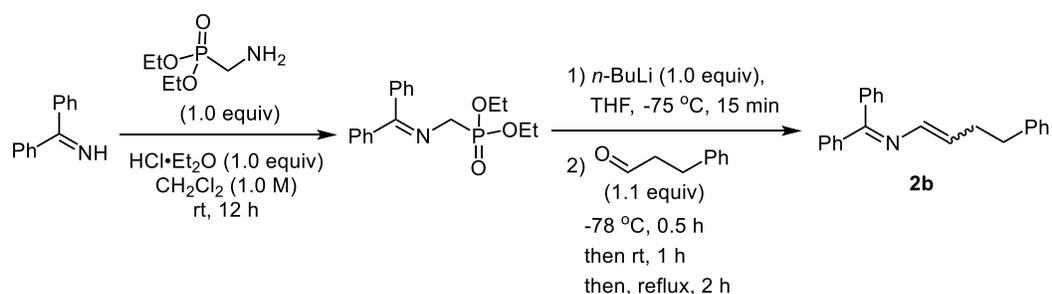
A flame-dried 250-mL round bottom flask, equipped with a stir bar, was charged with benzophenone imine (8.40 mL, 50.0 mmol, 1.00 equiv), CH_2Cl_2 (50.0 mL), 2-chloroethylamine hydrochloride salt (6.38 g, 55.0 mmol, 1.10 equiv), and triethylamine (6.70 mL, 50.0 mmol, 1.0 equiv) and fitted with a reflux condenser. The mixture was allowed to heat under reflux (50 °C) for 12 h. Upon cooling to room temperature, the

solid was filtered off and washed with CH₂Cl₂ (50.0 mL). The filtrate was washed with water and brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude residue was subjected to the next step without any purification.

The product from previous step was dissolved in DMF (50.0 mL) in a 250-mL round bottom flask with a stir bar (open to air). Sodium hydride (60% in mineral oil) (2.2 g, 55.0 mmol, 1.10 equiv) was slowly added, and the reaction was allowed to stir at room temperature for 12 h. The reaction was quenched with water (30.0 mL), ethyl acetate (40.0 mL) was added, and the layers were separated. The organic layer was washed with water (40.0 mL x 3). The combined organic layers were washed with brine (40.0 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to deliver the clean desired product as a light yellow solid (4.23 g, 20.4 mmol, 40.8% yield in two steps) with spectral data in agreement with literature values.^{18d}

III. Synthesis of (*E*)/(*Z*)-1,1-diphenyl-*N*-(4-phenylbut-1-en-1-yl)methanimine (**2b**)

General Method C:



A flame-dried 100-mL round-bottom flask, equipped with a stir bar, was charged with benzophenone imine (3.20 mL, 19.0 mmol, 1.00 equiv), dichloromethane (30.0 mL), diethyl (aminomethyl)phosphonate²⁷ (3.2 g, 19.0 mmol, 1.00 equiv), and HCl•Et₂O (9.5 mL, 19.0 mmol, 1.00 equiv, 2.0 M in diethyl ether) was added. The mixture was allowed to stir at room temperature for 12 h. The solid was filtered off and washed with CH₂Cl₂ (20 mL). The filtrate was washed with brine, dried over anhydrous Na₂SO₄, the solution was concentrated to afford a yellow liquid. The material was purified by silica gel chromatography (hexane:ethyl acetate = 9:1 to 1:1) to obtain a white solid (1.72 g, 5.19 mmol, 27.3% yield) with spectral in agreement with literature values.²⁸

Diethyl (((diphenylmethylene)amino)methyl)phosphonate (1.66 g, 5.00 mmol, 1.00 equiv) obtained from previous step was dissolved with THF (10.0 mL) in a 50-mL flame-dried round bottom flask with a stir bar under nitrogen. The solution was cooled to -78 °C and *n*-BuLi (2.0 mL, 5.00 mmol, 1.00 equiv, 2.5 M in hexanes) was added. The mixture was allowed to stir at -78 °C for 15 minutes. 3-Phenylpropanal (0.66 mL, 5.00 mmol, 1.00 equiv) was added and the mixture was allowed to stir at -78 °C for 0.5 h before allowing to warm to room temperature and stir for another 1 h. The mixture was then refluxed for 2 h. The reaction was allowed to cool to room temperature and was quenched with water (20.0 mL). The organic layer was separated, and the aqueous layer was washed with ethyl acetate (30.0 mL x 3). The organic layers were combined and washed with brine (20.0 mL). The combined organic layers were then dried over

anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to deliver the title compound as a yellow oil (0.77 g, 2.46 mmol, 49.2% yield). ¹H NMR spectra matched with literature values.^{18d}

IV. Synthesis of Imidazolinium NHC salt (L1)

General Method D: L1 was prepared through a procedure from established methods.^{29,30}

1.4.3 Cu-Catalyzed Enantioselective Alkylation of Quinoline *N*-oxides with 2-Azadienes

General Method E: Copper salt optimization (Table 1)

In an N₂-filled glovebox, an oven-dried (160 °C) 2-dram vial, equipped with a magnetic stir bar, was charged with Cu salt (0.005 mmol, 0.05 equiv), (*R,R*)-QuinoxP* (2.0 mg, 0.006 mmol, 0.06 equiv), quinoline *N*-oxide (29.0 mg, 0.2 mmol, 2.0 equiv), azadiene (20.7 mg, 0.1 mmol, 1.0 equiv), and dry cyclohexane (0.5 mL). The vial was capped and removed from glovebox and the mixture was allowed to stir at room temperature for 10 min. Dimethoxymethylsilane (0.5 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at room temperature for 3 h. The mixture was diluted with EtOAc (2 mL), passed through a short silica gel plug, and

concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford the product.

General Method F: Reagent ratio and temperature optimization (Table 2)

In an N₂-filled glovebox, an oven-dried (160 °C) 2-dram vial, equipped with a magnetic stir bar, was charged with Cu(OAc)₂ (0.9 mg, 0.005 mmol, 0.05 equiv), (*R,R*)-QuinoxP* (2.0 mg, 0.006 mmol, 0.06 equiv), quinoline *N*-oxide, azadiene, and dry cyclohexane (0.5 mL). The vial was capped and removed from glovebox and the mixture was allowed to stir at room temperature for 10 min. Dimethoxymethylsilane (0.5 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at room temperature for 3 h or at 60 °C for 20 h. The mixture was diluted with EtOAc (2 mL), passed through a short silica gel plug, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford the product.

General Method G: Solvent optimization (Table 3)

In an N₂-filled glovebox, an oven-dried (160 °C) 2-dram vial, equipped with a magnetic stir bar, was charged with Cu(OAc)₂ (0.9 mg, 0.005 mmol, 0.05 equiv), (*R,R*)-QuinoxP* (2.0 mg, 0.006 mmol, 0.06 equiv), quinoline *N*-oxide (29.0 mg, 0.2 mmol, 2.0 equiv), azadiene (20.7 mg, 0.1 mmol, 1.0 equiv), and dry solvent (0.5 mL). The vial was

capped and removed from glovebox and the mixture was allowed to stir at room temperature for 10 min. Dimethoxymethylsilane (0.5 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at room temperature for 3 h. The mixture was diluted with EtOAc (2 mL), passed through a short silica gel plug, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford the product.

General Method H: Silane screening (Table 4)

In an N₂-filled glovebox, an oven-dried (160 °C) 2-dram vial, equipped with a magnetic stir bar, was charged with Cu(OAc)₂ (0.9 mg, 0.005 mmol, 0.05 equiv), (*R,R*)-QuinoxP* (2.0 mg, 0.006 mmol, 0.06 equiv), quinoline *N*-oxide (29.0 mg, 0.2 mmol, 2.0 equiv), azadiene (20.7 mg, 0.1 mmol, 1.0 equiv), and dry cyclohexane (0.5 mL). The vial was capped and removed from glovebox and the mixture was allowed to stir at room temperature for 10 min. Silane (0.5 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at room temperature for 3 h. The mixture was diluted with EtOAc (2 mL), passed through a short silica gel plug, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford the product.

General Method I: Ligand screening (Scheme 5)

In an N₂-filled glovebox, an oven-dried (160 °C) 2-dram vial, equipped with a magnetic stir bar, was charged with Cu(OAc)₂ (0.9 mg, 0.005 mmol, 0.05 equiv), ligand

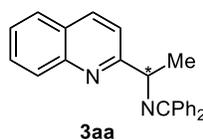
(0.006 mmol, 0.06 equiv), quinoline *N*-oxide (29.0 mg, 0.2 mmol, 2.0 equiv), azadiene (20.7 mg, 0.1 mmol, 1.0 equiv), and dry cyclohexane (0.5 mL). The vial was capped and removed from glovebox and the mixture was allowed to stir at room temperature for 10 min. Dimethoxymethylsilane (0.5 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at room temperature for 3 h. The mixture was diluted with EtOAc (2 mL), passed through a short silica gel plug, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford the product.

General Method J: Quinoline *N*-oxide (Table 5) and 2-azadiene scope (Scheme 6)

In an N₂-filled glovebox, an oven-dried (160 °C) 2-dram vial, equipped with a magnetic stir bar, was charged with Cu(OAc)₂ (0.9 mg, 0.005 mmol, 0.05 equiv), (*R,R*)-QuinoxP* (0.006 mmol, 0.06 equiv), quinoline *N*-oxide (0.2 mmol, 2.0 equiv), azadiene (0.1 mmol, 1.0 equiv), and dry cyclohexane (0.5 mL). The vial was capped and removed from glovebox and the mixture was allowed to stir at room temperature for 10 min. Dimethoxymethylsilane (0.5 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at room temperature for 3 h. The mixture was diluted with EtOAc (2 mL), passed through a short silica gel plug, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford the product.

General Method K: NHC ligands screening (Table 6 and 7)

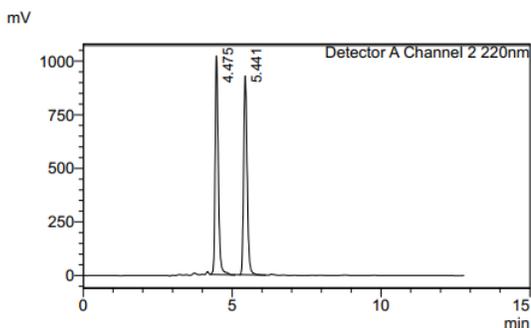
In an N₂-filled glovebox, an oven-dried (160 °C) 2-dram vial, equipped with a magnetic stir bar, was charged with Cu(OAc)₂ (0.9 mg, 0.005 mmol, 0.05 equiv), NHC ligand (0.006 mmol, 0.06 equiv), quinoline *N*-oxide (0.2 mmol, 2.0 equiv), azadiene (0.1 mmol, 1.0 equiv), and dry cyclohexane (0.5 mL). The vial was capped and removed from glovebox and the mixture was allowed to stir at room temperature for 10 min. Dimethoxymethylsilane (0.5 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at room temperature for 3 h. The mixture was diluted with EtOAc (2 mL), passed through a short silica gel plug, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford the product.



1,1-diphenyl-*N*-(1-(quinolin-2-yl)ethyl)methanimine (3aa): Prepared according to General Method E (eluent: 100:0 to 85:15 hexanes:EtOAc) and the title compound was isolated as a colorless oil (16.1 mg, 0.048 mmol, 48.0% yield). ¹H NMR (500 MHz, CDCl₃), δ 8.17 (1H, d, *J* = 8.6 Hz), 8.00 (1H, dd, *J* = 8.2, 1.1 Hz), 7.95 (1H, d, *J* = 8.6 Hz), 7.80 (1H, dd, *J* = 8.0, 1.4 Hz), 7.77 – 7.70 (2H, m), 7.66 (1H, ddd, *J* = 8.5, 6.8, 1.5 Hz), 7.52 – 7.31 (7H, m), 7.16 (2H, m), 4.92 (1H, q, *J* = 6.6 Hz), 1.59 (3H, d, *J* = 6.7 Hz). **HPLC:**

Column: Phenomenex Lux Amylose-I, 90:10 hexanes, *i*-PrOH, 1.0 mL/min, 220 nm in comparison with racemic material, er = 9:91 (HPLC data was re-obtained with (*S,S*)-quinoxP* instead).

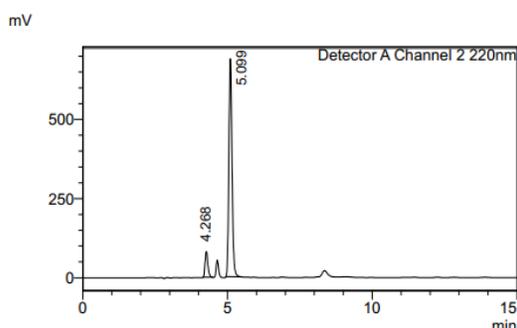
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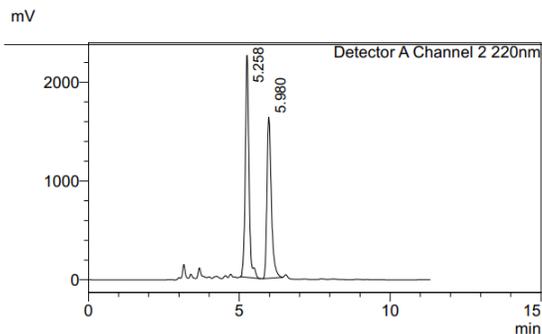
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Peak#	Ret. Time	Conc.
1	4.268	9.441
2	5.099	90.559
Total		100.000



***N*-(1-(6-methylquinolin-2-yl)ethyl)-1,1-diphenylmethanimine (3ba):** Prepared according to General Method E ((*S,S*)-quinoxP* was used). (eluent: 100:0 to 85:15 hexanes:EtOAc) and the title compound was isolated as a colorless oil (10.4 mg, 0.030 mmol, 30.0% yield). ¹H NMR (500 MHz, CDCl₃), δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.73 (dd, *J* = 8.6, 4.0 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.56 (dt, *J* = 6.9, 1.6 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 3H), 7.23 – 7.15 (m, 3H), 7.04 – 6.98 (m, 2H), 4.74 (q, *J* = 6.6 Hz, 1H), 2.35 (s,

3H), 1.42 (d, $J = 6.6$ Hz, 3H). **HPLC:** Column: Phenomenex Lux Amylose-I, 90:10 hexanes, *i*-PrOH, 1.0 mL/min, 220 nm in comparison with racemic material, er = 9:91.

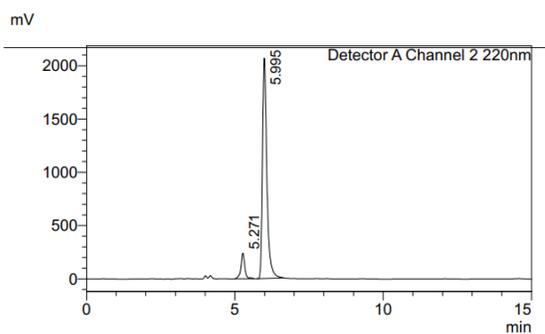
<Chromatogram>



<Peak Table>

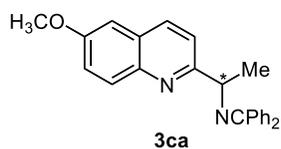
Peak#	Ret. Time	Conc.
1	5.258	54.125
2	5.980	45.875
Total		100.000

<Chromatogram>

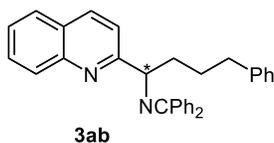


<Peak Table>

Peak#	Ret. Time	Conc.
1	5.271	9.411
2	5.995	90.589
Total		100.000



***N*-(1-(6-methoxyquinolin-2-yl)ethyl)-1,1-diphenylmethanimine (3ca):** Prepared according to General Method K (eluent: 100:0 to 85:15 hexanes:EtOAc) and the title compound was isolated as a colorless oil (12.5 mg, 0.034 mmol, 34.0% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 8.06 (d, $J = 8.5$ Hz, 1H), 7.89 (dd, $J = 8.9, 2.7$ Hz, 2H), 7.76 – 7.70 (m, 2H), 7.43 (tt, $J = 4.3, 2.4$ Hz, 2H), 7.40 – 7.30 (m, 4H), 7.23 – 7.13 (m, 3H), 7.07 (d, $J = 2.9$ Hz, 1H), 4.88 (q, $J = 6.6$ Hz, 1H), 3.92 (s, 3H), 1.58 (d, $J = 6.6$ Hz, 3H).



1,1-diphenyl-*N*-(4-phenyl-1-(quinolin-2-yl)butyl)methanimine (3ab): Prepared according to General Method J (eluent: 100:0 to 85:15 hexanes:EtOAc) and the title compound was isolated as a colorless oil (31.5% conversion with no isolated yield). ¹H NMR (500 MHz, CDCl₃), δ 8.13 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.77 (m, 3H), 7.72 (dt, *J* = 7.0, 1.5 Hz, 2H), 7.44 – 7.30 (m, 7H), 7.22 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.17 – 7.11 (m, 1H), 7.11 – 7.07 (m, 2H), 7.06 – 7.02 (m, 2H), 4.86 – 4.78 (m, 1H), 2.56 (ddd, *J* = 8.6, 6.8, 2.0 Hz, 2H), 2.08 (dt, *J* = 9.9, 5.6 Hz, 2H), 1.78 – 1.51 (m, 2H).

Conclusion

Our previous research showed that 2-azadienes can function as an alkene source for migratory insertion to prepare azaallyl-metal species. Based on the result, I aimed to expand a method of 2-alkylation of quinoline *N*-oxide to prepare functionalized amines, α -aminoalkylated quinolines in this study. I have found that a copper catalyst, $\text{Cu}(\text{OAc})_2$, with (*R,R*)-QuinoxP* ligands and dimethoxymethylsilane (DMMS) promotes α -aminoalkylation of quinoline *N*-oxides with 2-azadienes to afford enantioenriched α -aminoalkylated quinolines.

However, we have encountered an issue of reduction of quinoline *N*-oxide, giving lower product yield. In order to mitigate the reduction, several methods were investigated, including modified procedure and chiral NHC ligand screening. Despite the effort, the results have not been significantly improved and inconsistency, irreproducibility of the reactions, and large discrepancy between conversion and isolated yield were obtained as additional issues.

Due to these challenges, additional investigation would be possibly required following this work. They include variations of the reaction design to mitigate reduction of quinoline *N*-oxide, modification of reaction workup such as purification step to have high accuracy and precision.

References

- (1) Heravi, M. M.; Zadsirjan, V. *RSC Adv.* **2020**, *10*, 44247.
- (2) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; Wiley-VCH Verlag GmbH & Co, Weinheim, 2nd ed. 2003.
- (3) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Yamada, M.; Azuma, K.; Yamano, M. *Org. Lett.* **2021**, *23*, 3364. (c) Weaver, D. F.; Campbell, A. J. Preparation of β -heterocycl- β -amino acids as anti-epileptogenic agents. U.S. Patent US 20030114441, June 19, 2003. (d) Roberts, E.; Rosen, H.; Urbano, M.; Guerrero, M. A. Sphingosine-1-phosphate receptor modulators for treatment of cardiopulmonary disorders. U.S. Patent WO 2016053855, April 7, 2016.
- (4) Maury, J.; Zawodny, W.; Clayden, J. *Org. Lett.* **2017**, *19*, 472.
- (5) Shin, C.; Okabe, A.; Ito, A.; Ito, A.; Yonezawa, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1583.
- (6) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. *Science*, **2018**, *360*, 419.
- (7) (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. (b) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666. (c) Guan, B.-T.; Hou, Z. *J. Am. Chem. Soc.* **2011**, *133*, 18086. (d) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2012**, *14*, 5400. (e) Andou, T.; Saga, Y.; Komai, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 3213. (f) Chen, Q.; du Jourdin, M.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 4958. (g) Gui, J.; Zhou, Q.; Pan, C.-M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4853.
- (8) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607.
- (9) (a) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (b) Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856. (c) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307. (d) Molander, G. A.; Wisniewski, S. R.; Hosseini-Sarvari, M. *Adv. Synth. Catal.* **2013**, *355*, 3037. (e) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027. (f) Zhou, Q.; Cobb, K. M.; Tan, T.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 12057.
- (10) (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (b) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083.

- (11) Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 10958.
- (12) (a) Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330. (b) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480. (c) Wang, D.; Wu, L.; Wang, F.; Wan, X.; Chen, P.; Z.; Liu, G. *J. Am. Chem. Soc.* **2017**, *139*, 6811. (d) Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153.
- (13) Song, G.; Wylie, W. N. O.; Hou, Z. *J. Am. Chem. Soc.* **2014**, *136*, 12209.
- (14) (a) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 8372. (b) Friis, S. D.; Pirnot, M. T.; Dupuis, L. N.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 7242. For a nonenantioselective version of this reaction, see: Semba, K.; Ariyama, K.; Zheng, H.; Kameyama, R.; Sakaki, S.; Nakao, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 6275.
- (15) (a) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330. (b) Yang, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 16748. (c) Jordan, A. J.; Lalic, G.; Sadighi, J. P. *Chem. Rev.* **2016**, *116*, 8318. (d) Yu, S.; Wu, C.; Ge, S. *J. Am. Chem. Soc.* **2017**, *139*, 6526.
- (16) (a) Rendler, S.; Oestreich, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 498. (b) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916. (c) Sorádová, Z.; Šebesta, R. *ChemCatChem* **2016**, *8*, 2581. (d) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48.
- (17) (a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1498. (c) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62. (d) Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9716. (e) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620. (f) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1638. (g) Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 776. (h) Wang, H.; Yang, J. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8428.
- (18) (a) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5821. (b) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144. (c) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8126. (d) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 598.
- (19) (a) Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 4666. (b) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 9787. (c) Liu, R. Y.; Yang, Y.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 14077. (d) Shao, X.; Li, K.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 7083.

- (20) (a) Han, J. T.; Jang, W. J.; Yun, N. J. *J. Am. Chem. Soc.* **2016**, *138*, 15146. (b) Wang, Y.-M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5024.
- (21) (a) Yu, S.; Sang, H. L.; Ge, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 15896. (b) Yu, S.; Sang, H. L.; Zhang, S.-Q.; Hong, X.; Ge, S. *Commun. Chem.* **2018**, *1*, 64.
- (22) (a) Bering, L.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 3134. (b) Wang, H.; Pei, Y.; Bai, J.; Zhang, J.; Wu, Y.; Cui, X. *RSC Adv.* **2014**, *4*, 26244. (c) Lian, Y.; Coffey, S. B.; Li, Q.; Londregan, A. T. *Org. Lett.* **2016**, *18*, 1362. (d) Yu, H.; Dannenberg, C. A.; Li, Z.; Bolm, C. *Chem. Asian J.* **2016**, *11*, 54. (e) Bi, W.-Z.; Sun, K.; Qu, C.; Chen, X.-L.; Qu, L.-B.; Zhu, S.-H.; Li, X.; Wu, H.-T.; Duan, L.-K.; Zhao, Y.-F. *Org. Chem. Front.* **2017**, *4*, 1595.
- (23) (a) Murai, T.; Aso, H.; Kato, S. *Org. Lett.* **2002**, *4*, 1407. (b) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946. (c) DiPucchio, R. C.; Roşca, S. C.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 3469. (d) McGrew, G. I.; Stanciu, C.; Zhang, J.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 11510. (e) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. *Chem. Rev.* **2020**, *120*, 2613.
- (24) Tang, S.; Zhang, X.; Sun, J.; Niu, D.; Chruma, J. J. *Chem. Rev.* **2018**, *118*, 10393.
- (25) (a) Iwamoto, H.; Endo, K.; Ozawa, Y.; Watanabe, Y.; Kubota, K.; Imamoto, T.; Ito, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 11112. (b) Lee, J.; S. Torker.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 821. (c) Sun, Y.; Zhou, Y.; Shi, Y.; Pozo, J.-d.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 12087.
- (26) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. *Org. Lett.* **2014**, *16*, 1840.
- (27) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengeler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8177.
- (28) Goulioukina, N. S.; Mitrofanov, A. Y.; Beletskaya, I. P. *J. Fluorine Chem.* **2012**, *136*, 26.
- (29) Jung B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490.
- (30) Sun, Y.; Zhou, Y.; Shi, Y.; Pozo, J.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 12087.