# The Development of Palladium and Cobalt-Catalyzed Methods for the Syntheses of α-Trifluoromethyl and Alkyl Amines

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
Chemistry in the Graduate School
of Duke University

2022

ABSTRACT

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# Abstract

The prevalence of nitrogen-containing compounds in medicinal chemistry has driven the need for the development of methodologies for the construction of chiral amines in organic synthesis. Amongst these chiral amines, α-trifluoromethyl and alkyl amines are an important subclass that have been sought after because of their relevance in drug discovery. With respect to α-trifluoromethyl amines, the role of fluorine in altering lipophilicity, influencing $pK_a$, and affecting conformational bias of bioactive compounds has caused a surge in the development of new synthetic strategies for the construction of this functionality. Umpolung methods are robust technologies that enable streamlined synthesis of different types of chiral amines that are more challenging to obtain with a normal polarity approach. For example, the addition of nucleophiles to electrophilic imines, which is one commonly used strategy, limits the chemical space that may be generated for the preparation of chiral amines. Thus, other enabling strategies are desired.

In this work, we describe three methods for the preparation of different chiral amine motifs, detailing 1) the synthesis of α-trifluoromethyl benzylic amines through a vicinal fluoroarylation of difluoroazadienes, 2) the diastereo- and enantioselective synthesis of α-trifluoromethyl homoallylic amines *via* a catalytic hydroalkylation of dienes as well as 3) the enantioselective synthesis of alkyl amines enabled by a 5,6-hydroalkynylation of substituted 2-azatrienes.

# Dedication

This one's for me and my parents.

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# List of Abbreviations

[O] = oxidation

$[\alpha]_D$ = specific rotation relative to the D line of sodium lamp

Ac = acetyl

AcOH = acetic acid

aq = aqueous

Ar = aryl

$BAr^{F_4}$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

BDPP = 2,4-Bis(diphenylphosphino)pentane

BINAP = (1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)

BINOL = (1,1′-Bi-2-naphthol)

Bn = benzyl

Boc = tert-butyloxycarbonyl

BPE = 1,2-bis(2,5-diphenylphospholano)ethane

BQ = 1,4-benzoquinone

Bu = butyl

Bz = benzoyl

calc'd = calculated

Cl-OMe-BIPHEP = 5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl

COD = 1,5-cyclooctadiene

Cy = cyclohexyl

dba = dibenzylideneacetone

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE = 1,2-dichloroethane

DEMS: diethoxymethylsilane

DIBAL-H = diisobutylaluminum hydride

DMAP = 4-(dimethylamino)pyridine

DMF = *N*,*N*′-dimethylformamide

DMSO = dimethyl sulfoxide

DPEphos = (oxydi-2,1-phenylene)bis(diphenylphosphine)

dppb = bis(diphenylphosphino)butane

dppe = bis(diphenylphosphino)ethane

dr = diastereomeric ratio

DTBM = di(3,5-di-tert-butyl-4-methoxyphenyl)

E+ = electrophile

equiv = equivalents

er = enantiomeric ratio

Et = ethyl

EWG = electron-withdrawing group

$HBF_4$ = tetrafluoroboric acid

HMDS = hexamethyldisilazide

HPLC = high-performance liquid chromatography

HRMS = high resolution mass spectrometry

i-Pr = isopropyl

IPA/*i*Pr-OH = isopropyl alcohol

IR = infrared spectroscopy

Josiphos = 2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine

LC-MS = liquid chromatography mass spectrometry

LDA = lithium diisopropylamide

M = metal

Me = methyl

Ms = mesityl

MS = molecular sieves

MTBE = methyl *tert*-butyl ether

*n*-BuLi = n-butyllithium

$NaBAr^{F}_4$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

ND = not determined

NMR = nuclear magnetic resonance

NPhth = phthalimido

Nu = nucleophile

OTf = trifluoromethanesulfonate

PCC = pyridinium chlorochromate

Ph = phenyl

PHOX = phosphinooxazoline

PLP = pyridoxal phosphate

PMHS = polymethylhydrosilane

PMP = *para* methoxyphenyl

PNB = *para* nitrobenzene

Pr = propyl

PTC = phase transfer catalyst

pyr = pyridine

QuinoxP* = 2,3-bis(tert-butylmethylphosphino)quinoxaline

rr = regiomeric ratio

RuPhos = 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

sat = saturated

SEGPHOS = 5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole

SYNPHOS = [(5,6),(5',6')-bis(ethylenedioxy)biphenyl-2,2'-diyl]bis(diphenylphosphine)

*t*-Bu = *tert*-butyl

TBAF = tetrabutylammonium fluoride

TBDPS = *tert*-butyldiphenylsilyl

TBS = *tert*-butyldimethylsilyl

TDAE = tetrakis(dimethylamino)ethylene

Tf = trifluoromethanesulfonyl

TFA = trifluoroacetic acid or trifluoroacetate

TFE = 2,2,2-trifluoroethanol

THF = tetrahydrofuran

TMEDA = N,N,N′,N′-tetramethylethylenediamine

TMS = trimethylsilyl

TMSCN = trimethylsilyl cyanide

$TMSCF_3$ = trimethylsilyl trifluoromethyl

TOF = time of flight

Ts = tosyl

Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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# 1. Introduction

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Onyeagusi, C. I.; Malcolmson, S. J. Strategies for the Catalytic Enantioselective Synthesis of α-Trifluoromethyl Amines. *ACS Catal.* **2020**, *10*, 12507–12536.

## *1.1 The Importance of α-Trifluoromethyl Amines in Biologically Active Small Molecules*

The introduction of fluorine into organic molecules has become significantly important as the impact of fluorine in changing conformational bias[1], influencing $pK_a$, and lipophilicity[2-3] of drug molecules has become widely known and explored. Unlike atoms such as nitrogen and oxygen that are found abundantly in nature/natural compounds, atoms like fluorine are not used in nature's synthetic pathways. This lack of natural incorporation of fluorine in compounds has led to many synthetic efforts for introducing fluorine into molecules and has resulted in diverse fluorinated compounds in pharmaceutical research and applications. For example, the use of fluorine/fluorinated compounds as a proliferation marker in positron emission tomography (PET) has also been on the rise as the longer half-life for the $^{18}F$ isotope (109.8 mins) compared to $^{11}C$ (20.4 mins) increases its utility for medicinal purposes.[4-5]

Among these fluorinated drug compounds, one medicinally important functionality is the α-trifluoromethylamino group. The prevalence of α-trifluoromethyl (α-$CF_3$) amines in biologically active molecules remains a driving force for the development of methods to access this amine scaffold.

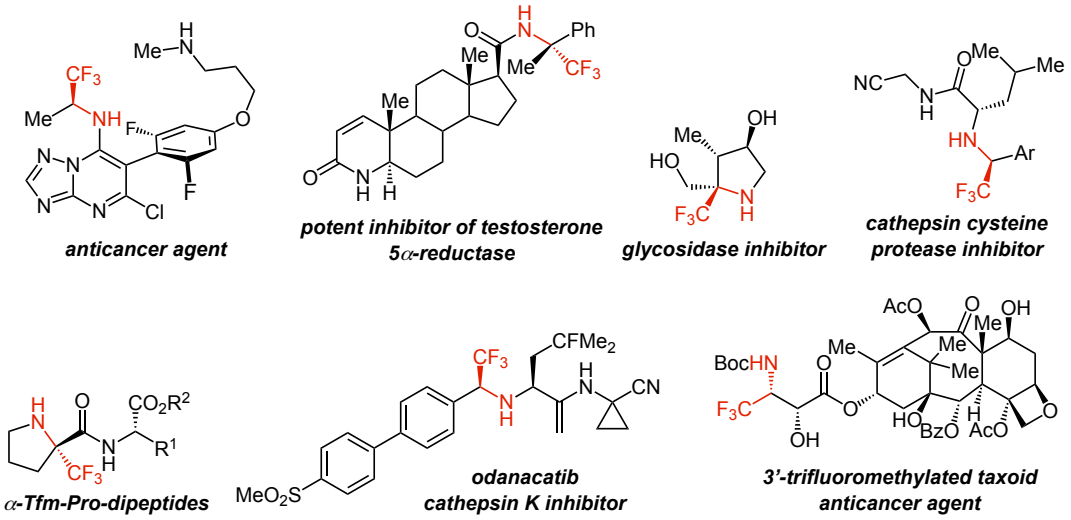



**Figure 1: α-Trifluoromethyl Amine Motif in Biologically Active Molecules**

For example, Merck advanced odanacatib,[6-7] a cathepsin K inhibitor, which contains this α-trifluoromethyl amine motif, has been used in the treatment of osteoporosis (Figure 1). Additionally, a 3′-trifluoromethylated taxoid compound has been developed as a second-generation anticancer agent, having fewer side effects and much improved activity against drug-resistant tumors.[8] Non-naturally occurring microtubule-stabilizing triazolopyrimidines have been revealed to be both brain penetrant and orally bioavailable, indicating that these compounds are potential candidates in the development of microtubule-stabilizing therapies for the central nervous system.[9] Structure-Activity Relationship (SAR) studies have also shown that a trifluoromethyl amine group at the 5-position is required to achieve high potency as an anticancer agent.[10]

Additionally, the replacement of hydrogen for fluorine atoms in molecules has also been explored extensively in drug design, especially the substitution of a $CH_3$ moiety for a $CF_3$ group, in efforts to modulate potency or interfere with metabolic modification.[3] Modulation in $pK_a$ can manifest changes in potency, selectivity, toxicity, and pharmacokinetic (PK) properties including absorption, distribution, metabolism, and excretion (ADME).[11] Because of its strong electronegativity and inductive effect, fluorine is an important handle for tuning the $pK_a$ of proximal functional groups and electron density of aromatic and heteroaromatic rings. The position of fluorine (whether proximal or distal) to some functional groups (such as amines, esters, alcohols, etc.) in molecules has a marked effect on $pK_a$. For example, in linear aliphatic systems, the influence on $pK_a$ following the substitution of H for F atoms is additive (Figure 2A). Trifluoroethylamine $CF_3CH_2NH_2$ ($pK_a$ = 5.7) is so weakly basic that this moiety has been exploited as an amide isostere in both peptidometics and small molecules, especially in the mechanism-based inhibitors of the cathepsin family of cysteine protease inhibitors from which the cathepsin K inhibitor, odanacatib, was derived. Comparatively, hydrocarbon-based ethylamine $CH_3CH_2NH_2$ is much more basic ($pK_a$ = 10.7), while those with fewer fluorine atoms have $pK_a$ values in between (Figure 2A).

Meanwell and coworkers have elaborated on the use of fluorine and its application in bioisosteres for drug design and development.[3] Incorporating fluorine into molecules alters their pharmacological characteristics. For instance, the $CF_3$ group

can act as a proteolysis-resistant amide surrogate. One key feature of trifluoroethylamine derivatives is the mimicry between the $CF_3CH_2NHR$ moiety and an amide analogue (Figure 2B).[12] This can be looked at in terms of geometric and electronic parameters. The key C–C–N bond angle of the $CF_3CH_2NHR$ functionality is comparable to that of an amide,[13] while the electron withdrawing effects of the $CF_3$ moiety decrease the basicity of the amine such that the H-bond donating properties of the N–H group are more like that of a N-H amide. Electronically, C–F dipoles emulate the amide oxygen lone pairs. Furthermore, not only is the length of a C–F bond (1.35 Å) close to that of a C=O bond (1.23 Å), their size/volume is almost about the same. (2.82 $Å^3$ vs 2.72 $Å^3$ respectively).[14]

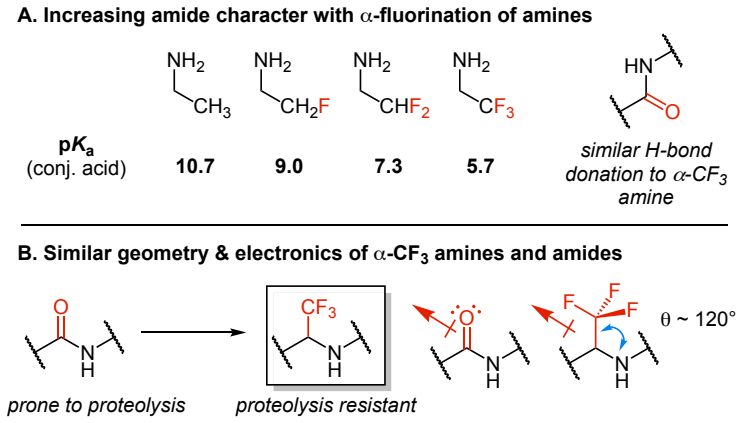



**Figure 2: Properties of Fluorinated/α-Trifluoromethyl Amines**

The substitution of amides by $CF_3$ amines may enhance complementarity with a specific target due to the structural differences and the rotational freedom of an $sp^3$ center compared to the constraints of the $sp^2$ carbonyl in an amide bond. Also, the use of $CF_3CH_2NH$ moieties eliminates metabolic sensitivity of these compounds to amidases,

esterases and proteases while also introducing an added element of stereochemistry in the form of an α-$CF_3$ stereogenic center. Therefore, the development of methods that furnish α-$CF_3$ amines is an important synthesis goal.

Several methods have been used to access α-trifluoromethyl amines;[15-19] however, the next sections will focus on three main strategies: i) ketimine reduction of trifluoromethyl-substituted imines, ii) addition of carbon-based nucleophiles to trifluoromethyl imines, and iii) imine umpolung reactions.

### 1.1.1 Ketimine Reduction Strategies

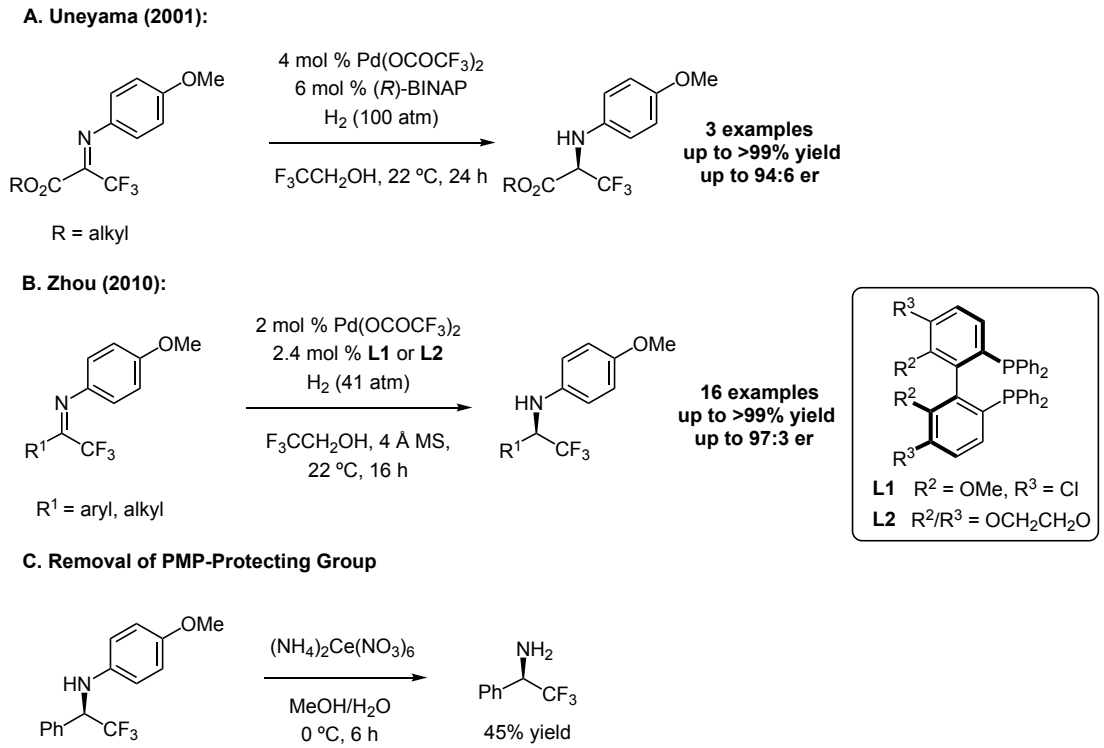
Catalytic enantioselective hydrogenation of α-trifluoromethyl imines is a common approach for accessing enantioenriched trisubstituted α-trifluoromethyl amines. Catalytic hydrogenation (involving the use of hydrogen gas) of ketimines has been useful for synthesizing chiral amines in industrial processes; however, there has been less development in enantioselective methodologies involving ketimines compared to olefins. A major concern in the transition-metal catalyzed hydrogenation of imines is the possibility of having E/Z stereoisomers of the substrate imines,[20] which may give rise to opposite enantiomers of the amine products, thereby lowering enantioselectivity. Additionally, imines bearing a fluoroalkyl group pose an even greater challenge for stereoselective transformations: even though the presence of electron withdrawing fluoroalkyl groups in imines enhance reactivity with nucleophiles, they weaken coordination with the transition metal center. Additionally, the inductive effect and

electronegativity of fluorine in these groups increases the acidity of the α-proton of the product amines, leading to a higher rate of enantiomerization under reaction conditions. Fortunately, several groups have reported great contributions to the enantioselective metal- (Pd, Ru, Rh) and organocatalyzed reductions of imines/imine equivalents with hydrogenation or transfer hydrogenation protocols as elaborated in the next subsection. Enantioselective reductions of enamines,[21] enamides,[22] and hydrazones[23] have also been investigated for accessing α-trifluoromethyl amines.

#### 1.1.1.1 Enantioselective Hydrogenation

In 2001, Uneyama and coworkers developed a Pd-catalyzed hydrogenation of α-fluorinated imino esters to afford the corresponding highly enantioenriched α-amino esters in up to 94:6 er, albeit with a very limited scope (Scheme 1A).[24] Following this work, Zhou and coworkers were able to extend the transformation to other classes of fluoroalkyl ketimines several years later (Scheme 1B).[25-26] As elucidated in Uneyama's work, the choice of solvent was integral to the success of this reaction as polar solvents like methanol and ethanol undergo addition to the electrophilic imines; thus, both a high pressure of hydrogen gas and trifluoroethanol as a non-nucleophilic alcohol solvent were crucial. They also propose that this may be due to increased solvent stabilization of the active catalyst or hydrogen bonding. It has been established that dihydrogen bonding can occur between fluorinated alcohols and metal hydride complexes. TFE coordinates weakly to palladium and hence is easily replaced with the fluorinated imine

and then reaction can occur readily. In addition to imino esters that Uneyama had used as electrophiles in this hydrogenation, aryl-substituted imines and enamines are also tolerated using Zhou's improved method.




**Scheme 1: Enantioselective Hydrogenation for the Synthesis of α-Trifluoromethyl Amines**

It should be noted that the imines used for these reductions mostly require an activating/protecting group on the nitrogen. This renders the electrons on the imine nitrogen less nucleophilic for participation in any deleterious side reactions. This group is usually a *para*-methoxyphenyl (PMP) group that can be cleaved in a subsequent step (Scheme 1C). In addition to providing a non-atom economic approach, this adds another synthetic hurdle for accessing the free amines. A chiral rhodium-based catalyst has also

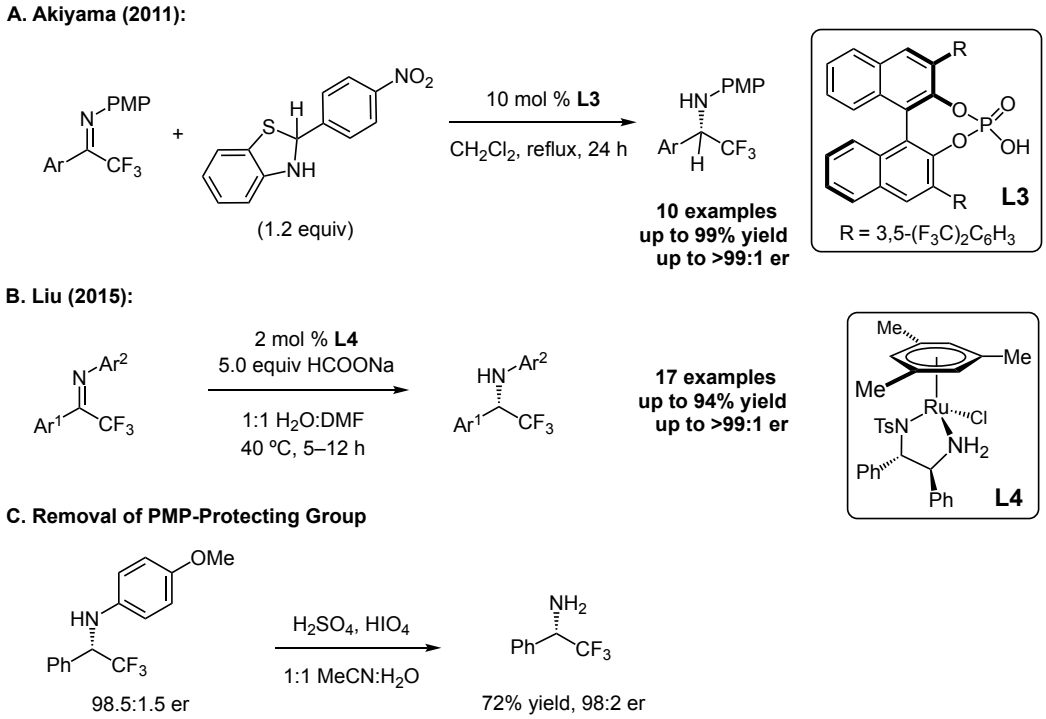
been used for enantioselective hydrogenation by Zhang and co-workers to provide access to a new class of *N*-aryl α-amino acid derivatives from α-enamino esters in high yield and stereoselectivity.[26]

#### 1.1.1.2 Enantioselective Transfer Hydrogenation

Enantioselective Transfer Hydrogenation (ETH) has provided an attractive route for the reduction of imines due to its less hazardous operation as it avoids the use of hydrogen gas and metallic hydrides. In addition, byproducts are often molecules such as acetone or carbon dioxide, which are easily separated from the amine products.

In 2011, Akiyama and coworkers reported an unprecedented enantioselective phosphoric acid-catalyzed synthesis of aromatic and heteroaromatic trifluoromethylated amines (Scheme 2A).[27] An electron-deficient benzothiazoline was used as a hydride source in this transformation, allowing for excellent levels of er compared to a commonly used Hantzsch ester. In this study, experiments using a deuterated benzothiazoline provide evidence of the origin of the hydrogen atom incorporated in the amine. This method also allowed the construction of the *N*-PMP-protected ketimines *in situ* to provide a direct reductive amination approach to the products. More recently, a related reaction using chiral phosphoric acids has been described by Peng and co-workers in the reduction of fluorinated alkynyl ketimines.[28] This method allowed access to chiral fluorinated propargylamines in spite of chemoselectivity challenges such as

partial or complete reduction of the alkyne triple bond.[29-30] Another enantioselective reduction of alkynylimines has been reported.[31]




**Scheme 2: Transfer Hydrogenation for the Synthesis of α-Trifluoromethyl Amines**

Transfer hydrogenations with the same class of imines utilizing Noyori's catalyst have also recently been disclosed by Liu and coworkers (Scheme 2B).[32] The use of sodium formate as the reducing agent is important to achieving both high yield and enantioselectivity, as other reducing agents lead to poor yield (*i*-PrOH) or poor yield and modest enantioselectivity (formic acid or formic acid/$Et_3N$). Though use of sodium formate is more atom economical than that of benzothiazoline in Akiyama's aforementioned work, employing chiral phosphoric acid **L3** might have cost advantages

over Ru-based complexes. Liu's reaction scope is limited to aryl imines, but yields and enantioselectivities are high for substrates with a range of steric and electronic characteristics and for a number of *N*-aryl groups as well. Strongly acidic and oxidizing conditions again have to be employed for unveiling the primary amine (Scheme 2C).

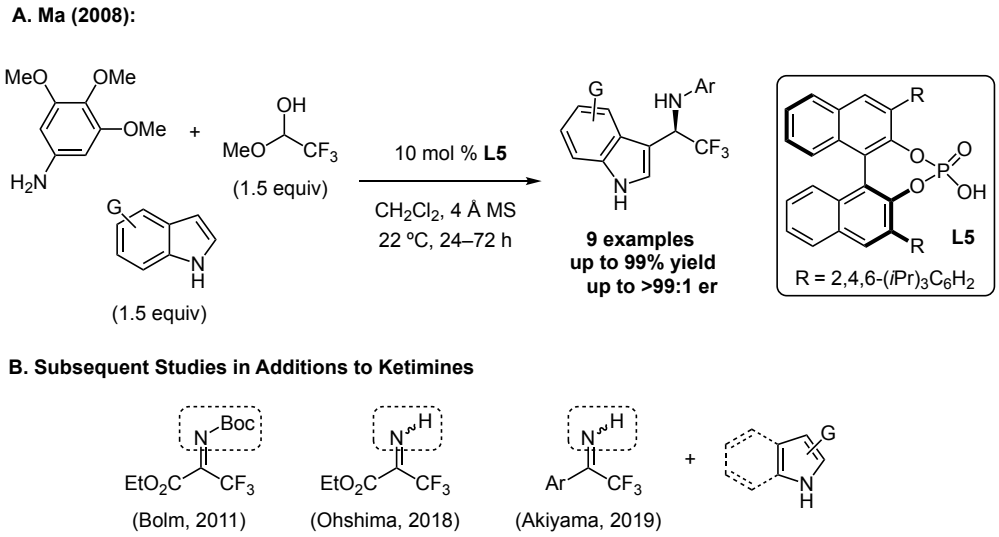
The Cahard laboratory have also disclosed a related transfer hydrogenation using a Ru–amino alcohol catalyst and *i*-PrOH as the reducing agent to enable an enantioselective reduction of *N*-PMP trifluoroketimines.[33] Under these conditions, aryl ketimines again lead to high enantioselectivity but alkyl ketimines are ineffective, resulting in low reactivity and/or poor enantioselectivity. The poorer behavior of alkyl ketimines might be attributed to imine–enamine tautomerism and/or to a mixture of imine stereoisomers.

### 1.1.2 Addition of Carbon-Based Nucleophiles to Imines

Enantioselective additions of carbon-nucleophiles to trifluoromethyl imines have been explored extensively for the synthesis of α-trifluoromethyl amines. Many of these nucleophiles have been used in conjunction with chiral auxiliary strategies in addition to catalytic enantioselective strategies, including a number of organometallic reagents, alkynes, aryl nucleophiles, and cyanide.[15, 17, 19, 34-36] Both aldimine and ketimine electrophile substrates have been employed, giving rise to α-secondary and α-tertiary amines.

#### 1.1.2.1 Arylation Strategies

The addition of aryl nucleophiles to trifluoromethyl imines is a powerful strategy for the construction of benzylic amines. Therefore, a handful of research groups have invested efforts into this strategy (some other methods are discussed in section 2.1.1). The Xu group has disclosed an enantioselective arylboronic acid addition to cyclic sulfonyl imines using a chiral sulfur−olefin ligand.[37] Although the conditions are similar to those for other Rh−diene-catalyzed imine arylation reactions,[38-40] excellent reactivity and enantioselectivity with their ligand is seen with several cyclic sulfonyl imine classes, including the cyclic trifluoromethyl imine. Several research groups have investigated the addition of indoles and pyrroles to trifluoromethyl aldimines and ketimines catalyzed by BINOL-derived chiral phosphoric acids. Ma and coworkers have disclosed an organocatalytic enantioselective three-component Friedel-Crafts aminoalkylation of indoles with aldehyde surrogates and aniline (Scheme 3A).[41] A bulky 3,4,5-trimethoxyaniline protecting group is important, as the commonly used PMP-substituted aniline leads to racemic product. The use of unprotected indoles is also critical: *N*-benzyl and *N*-acetylindoles are unreactive, which the authors attribute to a required weak hydrogen-bonding interaction of the indole N−H and phosphoric acid. Byproducts arising from bis-indole arylation as well as attack of the nucleophilic indole onto electrophilic trifluoroacetaldehyde are not observed in any example.

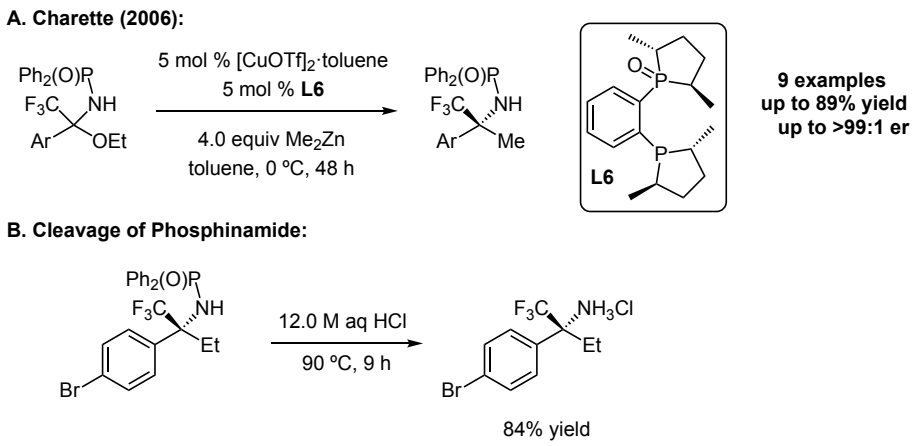



**Scheme 3: Chiral Phosphoric Acid-Catalyzed Indole/Pyrrole Additions**

Although the lengthy reaction times are not ideal, a general scope of indoles can be tolerated in this reaction, providing >95:5 er in great yields. Other indole/pyrrole addition methods using chiral phosphoric acids have been reported as well (Scheme 3B): Bolm and coworkers showed indole additions to an *N*-Boc trifluoromethylpyruvate-derived imine with phosphoric acid **L5**.[42] Subsequently, the Ohshima group disclosed a direct enantioselective Friedel-Crafts alkylation of unprotected α-ketimino esters using an unsymmetrical chiral phosphoric acid for indole and pyrrole additions.[43] Akiyama has also reported a Friedel-Crafts alkylation with pyrroles and indoles with N–H $CF_3$ ketimines using the same chiral phosphoric acid catalyst.[44] The Lin group has reported several examples of indole couplings with $CF_3$ imines.[45-48]

### 1.1.2.2 Alkylation Strategies, Strecker, and Mannich Reactions

The construction of α-trifluoromethyl amines bearing an aliphatic group at the stereogenic center is an important goal in organic synthesis, as they are a valuable subset of compounds. Regardless, methods to access these motifs through catalytic enantioselective strategies remain limited. An explored avenue for their synthesis is the use of organometallic reagents. For instance, organozinc additions to imines have provided an alkylation route to the generation of α-trifluoromethyl tetrasubstituted amines.



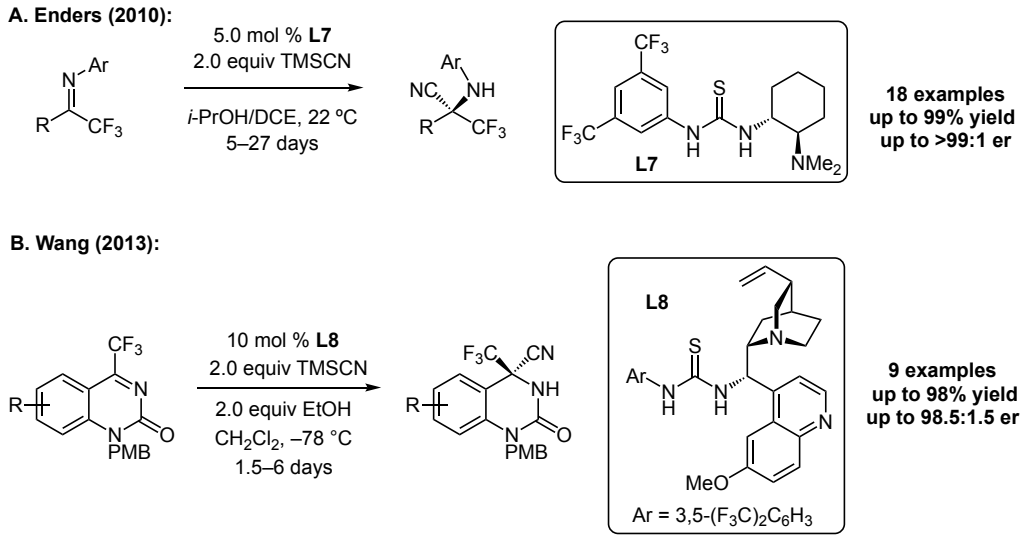

**Scheme 4: Addition of Diorganozincs to Aryl $CF_3$ Ketimines**

In 2006, Charette and coworkers disclosed a Cu-catalyzed enantioselective addition of dialkylzinc reagents to *N*-phosphinoyl imines generated *in situ* from hemiaminals (Scheme 4A).[49] These hemiaminals serve as a surrogate for the corresponding imines and were chosen as they are more air-stable and easy to manipulate solids. The presence of the phosphinoyl moiety as an activating group on the nitrogen renders a more active electrophile for this coupling but requires cleavage by

heating the direct phosphinamide product in concentrated HCl at 90 °C for 9 h, affording the free amines (Scheme 4B). Similarly, the Hoveyda and Snapper groups has also reported a methylation of aryl-substituted trifluoroketimines using dimethylzinc mediated by a zirconium catalyst bearing a phenylalanine–valine derived dipeptide ligand.[50]

#### 1.1.2.3 Strecker and Mannich Reactions

Strecker reactions have provided a reliable route for accessing α-amino acids, and thus, enantioselective versions have garnered considerable attention.[51] Cyanide additions to ketimines provide an avenue to α,α-disubstituted amino acids, which are important motifs for introducing secondary structure to peptides among other applications. The addition of cyanide to $CF_3$-substituted ketimines has also been explored. Stereoselective synthesis of this motif had initially proceeded using chiral auxiliaries bound to the imine nitrogen[52-53] but in 2010, Enders disclosed the first enantioselective Strecker synthesis of α-quaternary α-trifluoromethylated amino acids using Takemoto's thiourea catalyst **L7** to afford α-amino nitriles in excellent yields and enantioselectivities (Scheme 5A).[54] This was particularly important as the addition of cyanide to ketimines had been reported but were usually limited to methyl ketimines. TMSCN was chosen as the cyanide source and a bifunctional urea catalyst provided reactivity. A significant drawback to this method is the long reaction times needed, the shortest of which is 5 days and some that require up to 27 days.



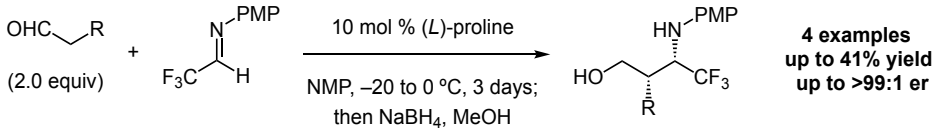

**Scheme 5: Thiourea and Urea-Catalyzed Strecker Reactions with $CF_3$ Ketimines**

Another Strecker reaction for the construction of enantioenriched trifluoromethyl dihydroquinazolinones has been developed. The Wang group have used a quinine-derived chiral catalyst **L8** for the addition of cyanide to trifluoromethyl 2(1*H*)-quinazolinones (Scheme 5B).[55] This reaction is still considerably slow, requiring up to 6 days for complete conversion of some substrates. Another carbon-nucleophile addition effort has been made by the same group involving coupling of nitroalkanes to this same imine scaffold.[56] More recently, the Kürti group also disclosed the first direct catalytic enantioselective allylation of acyclic α-amino ketoesters to afford α-allyl- α-trifluoromethyl aminoesters.[57] However, the scope of this reaction is limited to addition of allylboronic acid pinacol ester, limiting the utility of this method. Another use of allylation for the construction of enantioenriched α-trifluoromethyl amines was by

Waser[58], in which a Pd-catalyzed allylation of trifluoropyruvate-derived imines with a scope of allylic acetates was explored.

Mannich reactions have also been used for the catalytic enantioselective synthesis of α-trifluoromethyl amines.[56, 59-63] These reactions are typically promoted either by H-bond donor or chiral amine catalysts. In 2005, Simón-Fuentes and coworkers described a diastereo- and enantioselective Mannich reaction as a route to fluorinated *syn* 1,3–amino alcohols using (*L*)-proline as a catalyst (Scheme 6).[64] (*L*)-proline has also been used as a catalyst in other Mannich additions and this method only allows for introduction of diversity into the α-fluoroalkyl chain and the α-alkyl group.

**Simon-Fuentes (2005):**




**Scheme 6: Proline-Catalyzed Mannich Addition to $CF_3$ Aldimines**

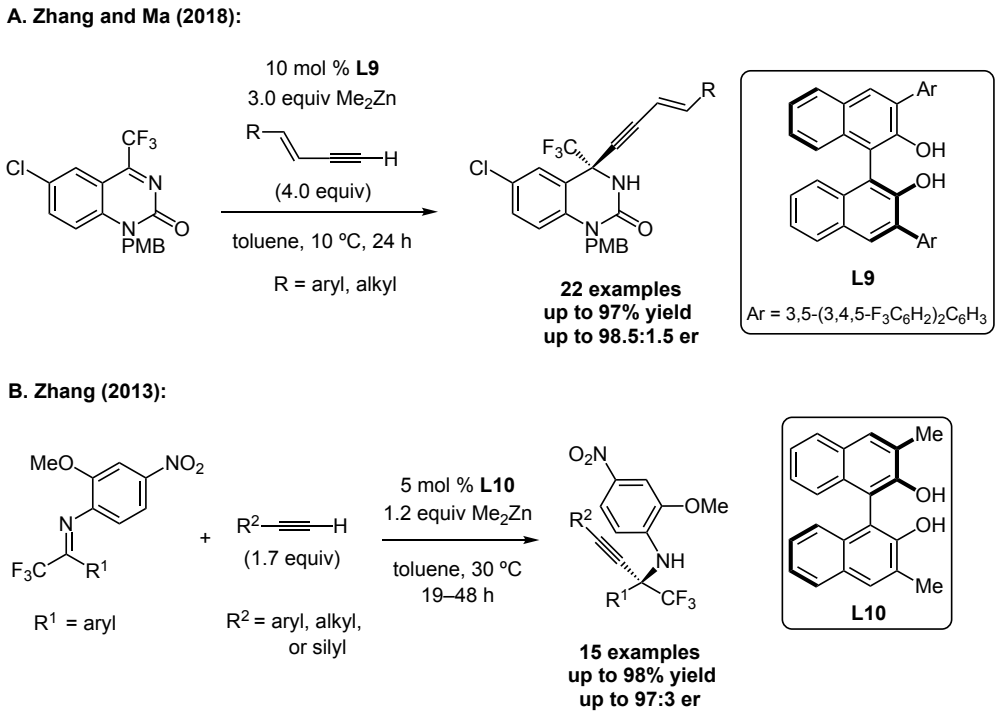
Although this reaction improves on previous work, yields for this method are not optimal, and only a small substrate scope is explored. More so, long reaction times and temperature-sensitive conditions are required. More recently, Trost has developed an enantioselective vinylogous Mannich addition of butenolides to trifluoromethyl alkynyl ketimines to furnish trifluoromethyl amines with two contiguous stereogenic centers using a Zn-ProPhenol catalyst.[65]

#### 1.1.2.4 Alkynylation Strategies

Enantioenriched propargylamines have emerged as synthetic intermediates for natural products and compounds of pharmaceutical relevance. Consequently, enantioselective addition of terminal alkynes to imines have gained attention from organic chemists. A significant number of strategies employing transition metal catalysts have been established including those geared towards the synthesis of α-$CF_3$ propargylic amines. One important alkynylation reaction involves the addition to $CF_3$-substituted quinazolinones for the construction of Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) analogues which have been explored as HIV therapeutics.[66] Previous efforts geared towards the construction of these compounds comprised diastereoselective 1,4-addition of a magnesium acetylide to quinazolinones containing a chiral auxiliary substituent[67-68] or 1,2-enantioselective addition of a lithium acetylide, coordinated by cinchona alkaloids, to cyclic *N*-acyl ketimines.[69] These methods required the use of 3–5 equivalents of organometallic acetylides at low temperature (–60 °C to –75 °C) and under strongly basic conditions, decomposition of the product was observed. Also, another challenge in preparing these NNRTIs is forming the tertiary carbinamine in an enantioselective fashion. However in 2004, Jiang and a coworker reported a direct alkynylation reaction at room temperature utilizing a stoichiometric chiral zinc–amino alcohol complex, generating dihydroquinazolinones efficiently in high yield and enantioselectivity.[70] Terminal 1,3-enyne additions to these cyclic trifluoromethyl

ketimines have also been reported recently by Zhang, Ma, and coworkers (Scheme 7A).[71] Although, a stoichiometric amount of dimethylzinc is required, a substoichiometric quantity of the chiral BINOL catalyst **L9** can promote the reaction efficiently. The substrate scope is tolerant to aryl and alkyl substituted ketimines, and notably, the products can be crystallized to higher levels of enantiopurity.

Zhang and coworkers have also made important contributions to alkynylation reactions. Building on their efforts with trifluoropyruvate-derived ketimines,[72] they developed a BINOL-catalyzed alkynylation of acyclic trifluoromethyl ketimines by employing stoichiometric dimethylzinc and a substoichiometric quantity of a different BINOL derivative **L10** (Scheme 7B).[73] The tunability of both the chiral catalyst and protecting group of the ketimine provide synergistic effects on reactivity for this method development. Modification of the *N*-protecting group by introducing a *p*-nitro group to increase electrophilicity and altering the steric and electronic effects at the 3,3′ positions of BINOL was crucial to reaction efficiency. *N*-aryl ketimines were added to the scope of this reaction to provide the corresponding alkynylated amine products in good yields and enantioselectivities. Catalytic enantioselective additions of terminal alkynes to *N*-protected imines of trifluoropyruvates using Rh and Zn catalysts have been reported by Oshima and Ma, respectively.[74-75]




**Scheme 7: Enantioselective Alkyne Additions to Trifluoromethyl Imines**

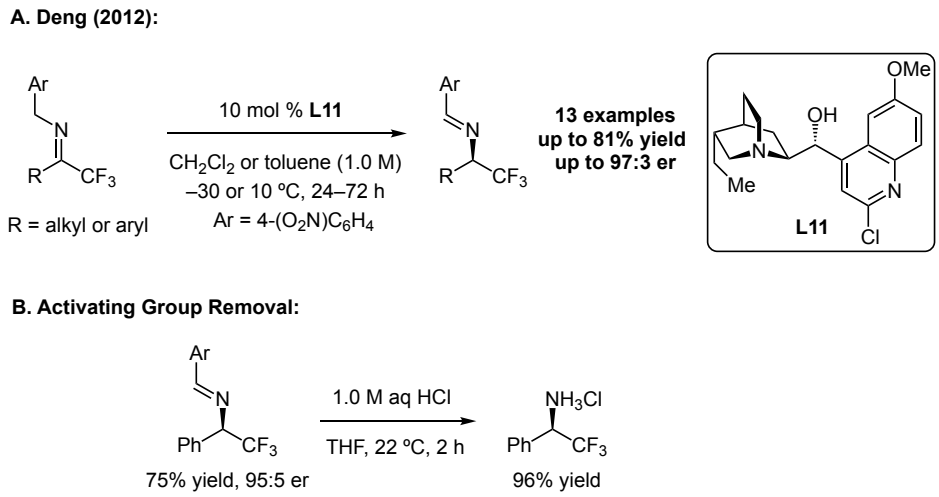
## 1.1.3 Imine Umpolung Strategies

Umpolung methods are robust technologies that enable direct synthesis of different types of chiral amines that are more challenging with a normal polarity approach. For example, the addition of traditional nucleophiles to electrophilic imines limits the chemical space that may be generated for the preparation of chiral amines. The development of umpolung chemistry in C–C bond forming reactions allows a different but practical approach to the synthesis of nitrogen containing molecules. Rendering the carbon atom of imines electron-rich creates a new class of nucleophiles, thereby facilitating the development of new chemical transformations and opportunities. The reverse-polarity reactivity of imines has been used in different methods and provides a

prominent portal to diverse class of amines in general, but specifically also explored for enantioselective construction of α-trifluoromethyl amines.

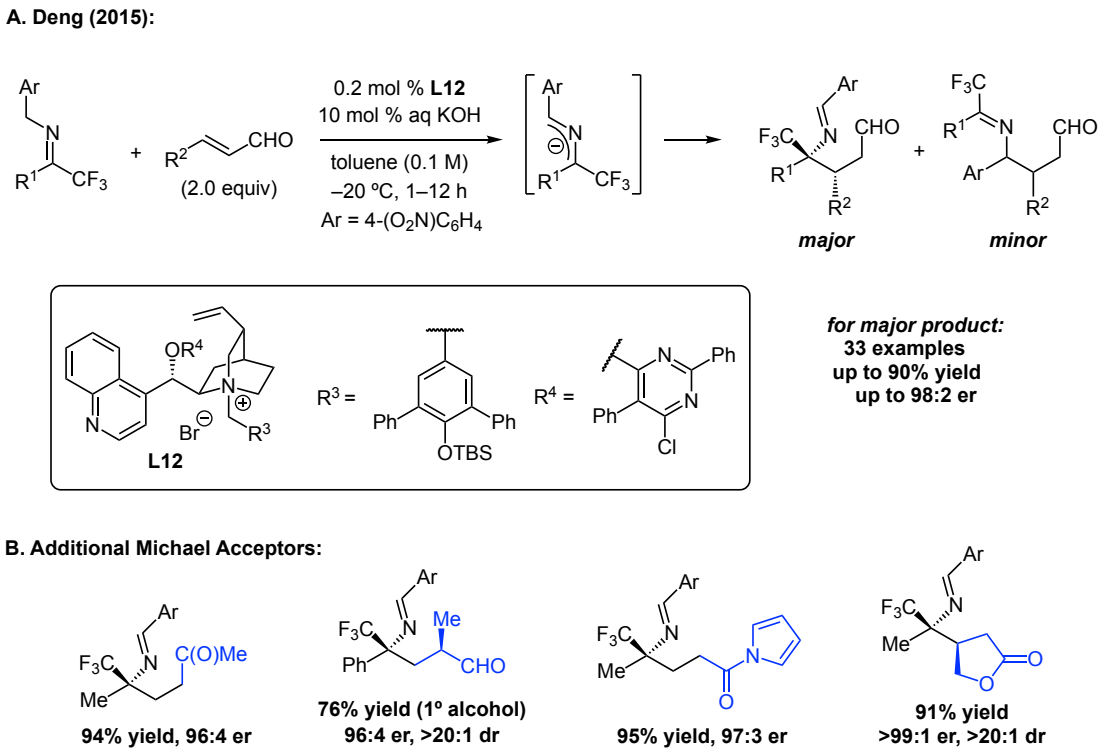
Another viable route to α-trifluoromethyl amines is the isomerization of *N*-benzyl $CF_3$ ketimines; a pathway that is utilized by PLP-dependent transaminases.[76] Early attempts at a [1,3]-prototropic shift were met with limitations as described by Soloshonok,[77] where a room temperature isomerization of *N*-benzyl trifluoromethylphenyl imines catalyzed by a cinchonidine-derived organic catalyst was performed in up to 67.5:32.5 er and long reaction times. To broaden the scope, Plaquevent and coworkers[78] attempted to employ aliphatic imines which fared even worse than the aryl counterparts, requiring a significantly elevated temperature (50–100 °C). However in 2012, Li Deng and coworkers addressed those issues *via* an enantioselective organocatalytic isomerization of aromatic and aliphatic imines at room temperature to furnish trisubstituted α-trifluoromethyl amines in good yields and enantioselectivity (Scheme 8A).[79] Crucial to the success of this reaction is the identity of the phase transfer catalyst (PTC) which contains a free 9-hydroxy group and an electron-withdrawing chloride on the quinoline ring that enable higher conversions. The aforementioned studies by Soloshonok and Plaquevent had shown the importance of the activating group on nitrogen for isomerization of imines and this work provided more evidence as the introduction of an electron-withdrawing *para*-nitro benzyl group allowed an increase in conversion. Aryl-substituted imines are able to be converted to

the desired isomer at low temperature (–30 °C) with electron-withdrawing substituents offering more reactivity than electron-donating counterparts. Alkyl-substituted imines can also be tolerated, albeit with a relatively higher reaction temperature (10 °C). The activating group on the aldimine products can be hydrolyzed under mild acidic conditions to deliver the ammonium chloride salts in high yield, without erosion of enantiopurity (Scheme 8B).




**Scheme 8: Isomerization of Imines and Activating Group Removal**

Shortly after this work, Shi and coworkers reported the enantioselective prototropic shift using a different cinchona alkaloid catalyst as well.[80] The use of cinchona-derived alkaloids in the construction of α-trifluoromethyl amines using umpolung reactivity has been widely explored by Deng. Following their aforementioned 2012 work, in 2015, Deng and coworkers elucidated an unprecedented development of new tunable chiral phase transfer catalysts that promote a highly enantioselective umpolung reaction of imines with the electrophilic enals.[81]




**Scheme 9: Li Deng's Umpolung Strategy in Conjugate Addition**

These modified PTCs, in conjunction with a base, can mediate the deprotonation of imines, leading to the formation of a 2-azaallyl anion, which is poised for conjugate addition to enals in a highly chemo-, regio-, diastereo-, and enantioselective fashion. It is proposed that the electronic and steric nature of the *N*-benzyl group ($R^3$) on the PTC is crucial to chemoselectivity (conjugate addition versus prototropic shift) and $\pi$–$\pi$ interactions between the ketimine and the catalyst are necessary for desired reactivity. The reaction proceeds efficiently affording the desired imines in up to 90% yield and 98:2 er. Reaction arising from attack of the α-$CF_3$ carbon likely takes place due to inductive effect of the $CF_3$ group. A minor byproduct arising from nucleophilic attack of

the other α-carbon on the enal can also be observed, but in very small quantities (Scheme 9A).

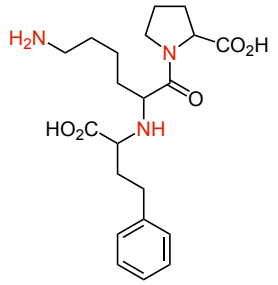
It should be noted that the major product could also be formed *via* a [3+2] cycloaddition between starting imine and enal followed by a retro-Mannich reaction but $^{1}H$ and $^{19}F$ NMR analyses did not show any formation of the [3+2] adduct upon monitoring the reaction. After exploration of enals as acceptors for this addition, Deng has since expanded the scope of this reaction. This conjugate addition can be applied to α,β-unsaturated enones,[82] *N*-acyl pyrroles,[83] α-substituted enals,[84] and esters[85] with each coupling partner delivering products in excellent yields and er (Scheme 9B). Substituted enals and unsaturated lactones afford products with nonadjacent or vicinal stereogenic centers, respectively, with high diastereoselectivities. In each case, optimization of the catalyst with respect to the *N*-benzyl group and the quinoline ring was required. Furthermore, in their more recent couplings with esters, α-substituted enals, and *N*-acyl pyrroles, a catalytic to substoichiometric amount phenol additive is employed to suppress the formation of undesired byproducts. This introduction of phenols as an acid additive or cocatalyst in chiral PTC conjugate additions and aldol additions serves to increase yield by prompting protonation of the enol intermediates that would otherwise undergo reverse conjugate/aldol additions. Optimization of the electronics and sterics of the phenol group was necessary.

## *1.2 The Importance of Chiral Alkyl Amines in Biologically Active Small Molecules*

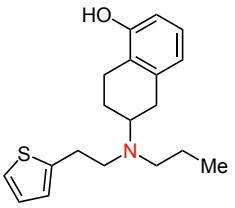
Alkyl amines are another subset of amine motifs that are heavily sought after in organic synthesis due to their utility in medicinal applications.[86] Though the hydrogen bonding-ability of the lone pairs on the nitrogen atom in the amine predispose it to being hydrophilic and soluble in polar media, lipophilicity of the amine is enhanced by the presence of non-polar aliphatic groups on the alkyl chain. The interplay of these two contrasting characteristics is a key feature in governing the physical properties of the amine and also in regulating biological activities *in vivo.* This can present itself in the modulation of the compound's ability to cross cell membranes and the blood-brain barrier, which can be vital for drug delivery. Studies have shown that compounds which contain a higher degrees of saturation are more likely to transition from the drug discovery stage to clinical trials.[87] As a result, aliphatic amine scaffolds are prevalent in bioactive compounds. For example, duloxetine (Figure 3) serves as a serotonin–norepinephrine reuptake inhibitor used as an anti-depressant.[88] Therefore, it is important that synthetic strategies that lead to the generation of complex aliphatic amines to drive medicinal chemistry be established.

In organic synthesis, developing methods for constructing enantioenriched aliphatic amines from readily available starting materials has been an important area of research. A number of traditional approaches including enantioselective hydrogenation of imines/enamines,[89-92] nucleophilic addition to imines,[35, 93-94] and chiral auxiliary-

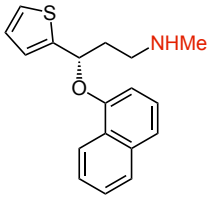
mediated additions[95] have been extensively used and discussed. In this section, however, we will focus on two main strategies: i) hydroamination of alkenes, ii) use of α-amino fragments and imine umpolung reactions.



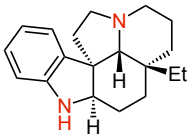

***lisinopril***
*(ACE Inhibitor)*



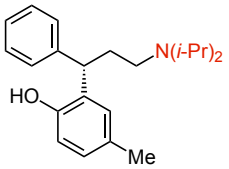

***neupro***
*(muscular skeletal disorder)*



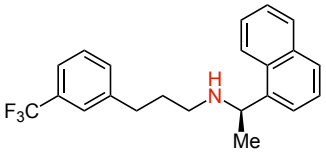

***duloxetine***
*(antidepressant)*




***aspidospermidine***
*(common motif in natural products)*




***tolterodine***
*(urinary disorders)*




***cinacalcet***
*(hormonal disorders)*

**Figure 3: Alkyl Amines in Biologically Active Compounds**

## 1.2.1 Hydroamination

Transition metal-catalyzed hydroamination presents itself as an attractive strategy for the synthesis of chiral alkyl amines, as an amine group can be directly introduced into cheap unfunctionalized hydrocarbon feedstock.[96-97] This has served as a simple, atom-economical route for the synthesis of secondary and tertiary amines. However, there are some challenges that could be faced with hydroamination such as electrostatic repulsion between the nitrogen lone pair and the alkene $\pi$–system, which prevents bond formation, and the difficulty in controlling regioselectivity as

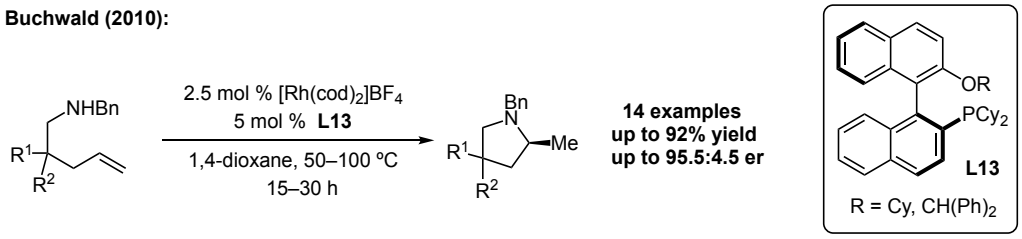
Markovnikov and *anti*-Markovnikov products can be formed.[98] Regardless of these challenges, intermolecular and intramolecular hydroamination strategies have been established and have remained a modern approach for accessing aliphatic chiral amines.

#### 1.2.1.1 Intramolecular Hydroamination

Intramolecular hydroamination is an attractive route for accessing nitrogen-containing heterocycles, a common structural motif in biologically active molecules, from readily available amino-alkenes. Furthermore, intramolecular hydroamination obviates a key challenge in hydroamination, which is the competitive ligation between the strongly coordinating amine and poorly coordinating alkene. Hence, considerable efforts have been spent on the development of catalysts and reactions for this approach in industrial and academic settings.

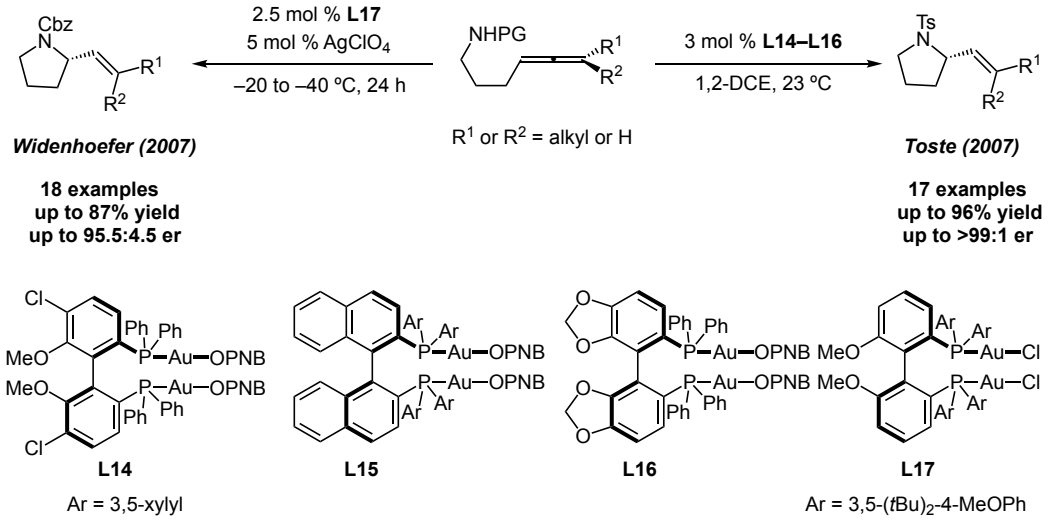
It is known that rare-earth,[99-100] alkaline-earth,[101-102] and group IV metals[103] are catalysts for the intramolecular hydroamination of aminoalkanes, but these catalysts are often air and moisture sensitive with low functional-group tolerance. However, the use of late-transition metal catalysts such as Rh, Ir, Pt, and Au have generally led to more robust methods, arising from the strong metal $\pi$–alkene complexes which activate the alkene for nucleophilic attack.[104] Early work in the 1970s by Zambonelli showed the use of Pt salts for intramolecular hydroamination after forceful conditions[105] but the first general catalytic strategy was disclosed by Widenhoefer and coworkers. In 2005, they showed the Pt-catalyzed conversion of γ- and δ-amino alcohols to the corresponding 2-

methyl pyrrolidines and piperidines respectively in good yields.[106] Following that work, another non-enantioselective hydroamination using a Rh catalyst was pursued by Hartwig.[107] In 2010, Buchwald then reported the first Rh-catalyzed enantioselective intramolecular hydroamination of unactivated alkenes (Scheme 10).[108]




**Scheme 10: Rh-Catalyzed Enantioselective Intramolecular Hydroamination**

This reaction still remains state-of-the-art in enantioselective hydroamination even though later efforts by Michon[109] and Mikami[110] have used Au catalysts supported by phosphoramidite ligands and chiral phosphoric acids, respectively. In addition to the enantioselective intramolecular hydroamination of aminoalkenes, aminoallenes and alkynes have also been used for the generation of aliphatic amines. Aminoallenes offer an advantage compared to their alkene counterparts as the weaker C–C double bond present in allenes allow for less harsh reaction conditions.[111] This is observed in both Widenhoefer[112] and Toste's[113] findings where they show that Au–phosphine complexes are efficient catalysts to promote the hydroamination of γ-aminoallenes to form the corresponding vinylpyrrolidines in high yields and enantioselectivities at lower temperatures relative to Buchwald's work. Yamamoto has reported a Pd-catalyzed hydroamination of alkynes to generate enantioenriched enamines.[114]

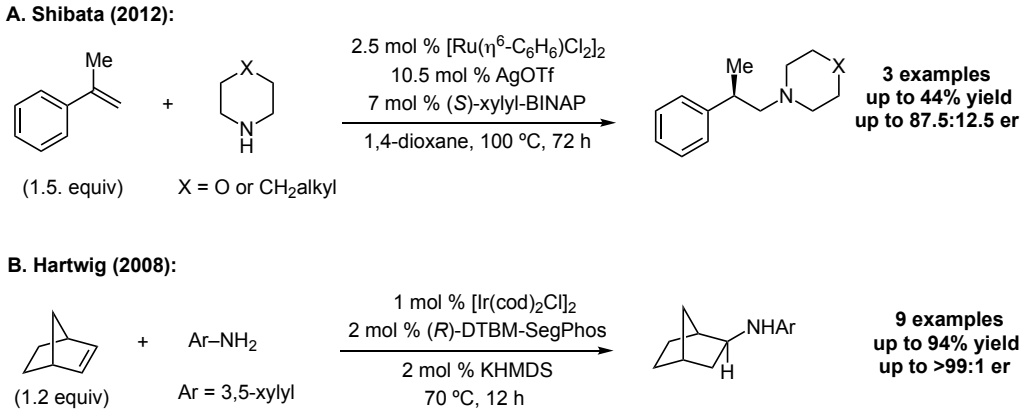



**Scheme 11: Use of Aminoallenes in Enantioselective Hydroamination**

### 1.2.1.2 Intermolecular Hydroamination

Catalytic intermolecular hydroamination reactions remain one of the most sustainable C–N bond-forming strategies due to the atom economy of the process as well as the availability of the substrates. General catalytic strategies for intermolecular hydroamination emerged in the late 1990s by Beller and coworkers using Rh catalysts;[115] however, the reaction was fairly inefficient leading to byproducts from oxidative amination. In 2003, Hartwig was able to deliver a more efficient approach for the Rh-catalyzed *anti*-Markovnikov hydroamination of styrenes and vinylpyridines, albeit with racemic product.[116] The first enantioselective *anti*-Markovnikov hydroamination was reported about a decade later by Shibata, employing a Ru-based catalyst to furnish the desired product in up to 87.5:12.5 er (Scheme 12A).[117] In 2008, Hartwig disclosed an Ir-catalyzed enantioselective addition of anilines to aliphatic alkenes (Scheme 12B).[118] It is

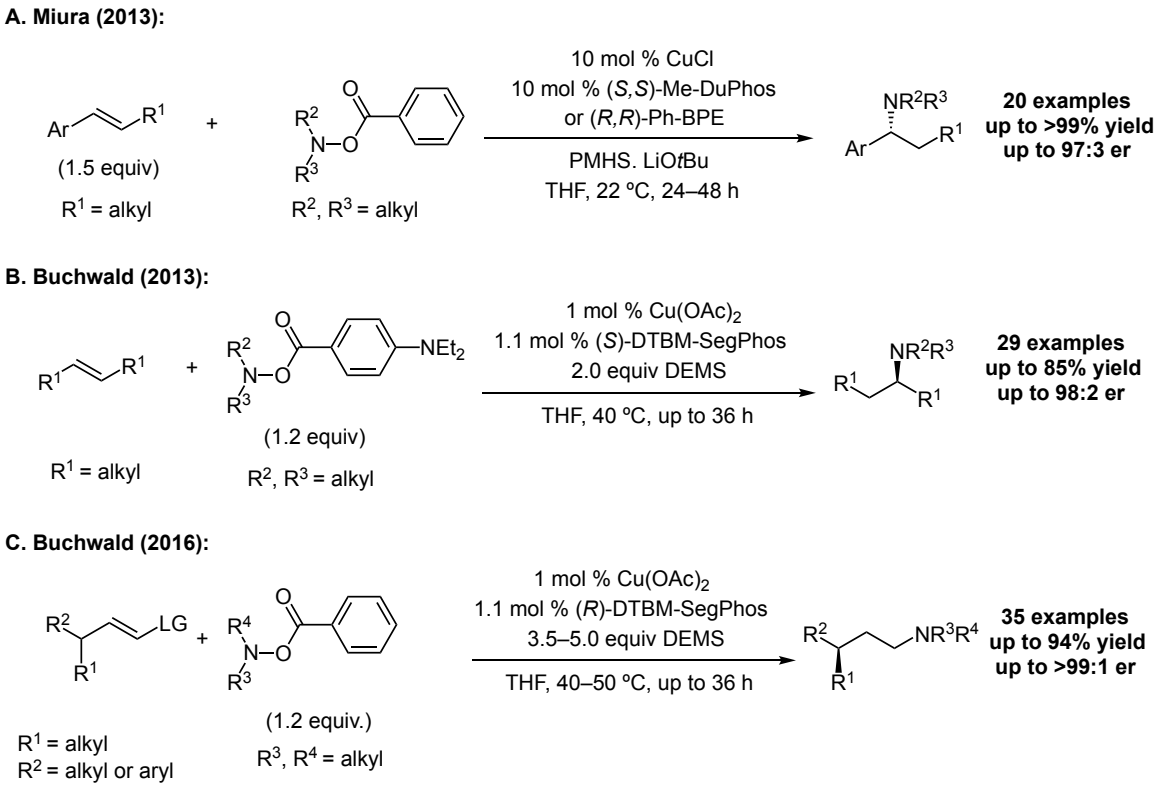
worthy to note that aliphatic alkenes are more challenging substrates as they do not benefit from pre-coordination to the metal catalyst.[119] This method proceeds fairly smoothly, affording the bicyclic aliphatic amine in high yields and enantioselectivity. Hartwig has also recently disclosed another enantioselective hydroamination of an internal aliphatic alkene.[120] Other reports by Hartwig and Grubbs have shown the intermolecular addition of anilines to styrenes non-enantioselectively.[121-122]




**Scheme 12: Enantioselective Intermolecular Hydroamination**

The addition of alkyl amines to styrenes poses a greater challenge due to the increased basicity of alkyl amines, which lead to off-cycle byproducts. However, there has been one report by Hartwig which constitutes the only example of transition metal-catalyzed enantioselective intermolecular hydroamination of alkenes with alkyl N–H amines.[123] Although hydroaminations of dienes have been explored extensively, they lead to the formation of allylic amines and will not be included in this section. Miura[124] and Buchwald[125] have also performed enantioselective hydroaminations of alkenes using copper catalysts and *O*-benzoylhydroxylamines as the amine source (Scheme 13A and

13B). Crucial to these highly-stereoselective reactions is the formation of a chiral Cu–H species. Buchwald has since reported other hydroamination reactions to furnish tertiary and secondary amine products in excellent er.[126] Interesting among these findings is the hydroamination of remote alkenes through a reductive relay process that leads to the formation of amines with a remote stereogenic center (Scheme 13C), a motif that is not easily accessed through other strategies (see section 4.1).[127]




**Scheme 13: Enantioselective Hydroamination using *O*-Benzoylhydroxylamines**

## 1.2.2 Alpha-amino methods

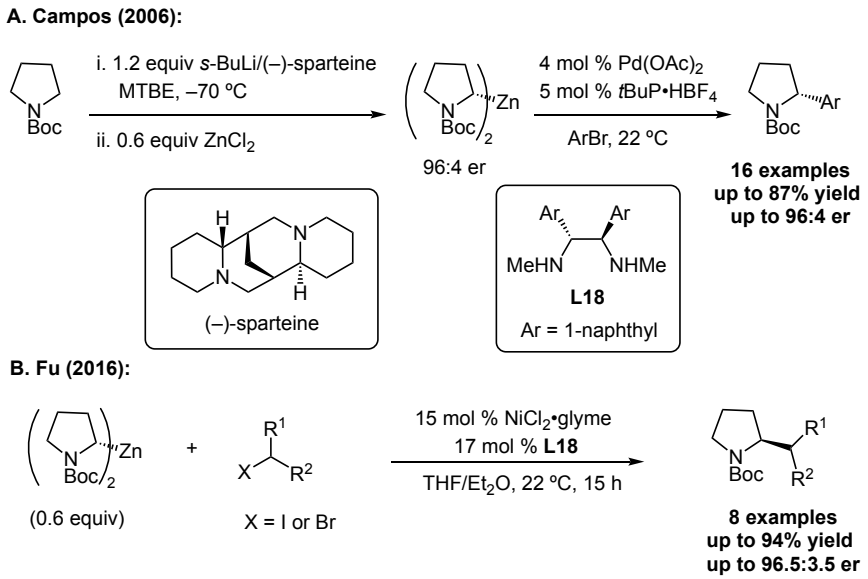
In recent years, the utilization of C–C bond forming strategies for accessing enantioenriched chiral alkyl amines has gained significant attention through other

protocols such as C–H functionalization, alkyl–alkyl cross-coupling, and photoredox catalysis. While each of these methods allow for the construction of different alkyl motifs, the majority of these strategies deliver chiral aliphatic amines with alpha-stereogenic centers. Hence, the coupling of α-amino alkyl fragments represents a major and attractive strategy for the synthesis of chiral amines with an alkyl group at the stereogenic center. In this section, we will direct our attention to some methods that describe some of the recent technologies geared towards the enantioselective synthesis of chiral alkyl amines through key α-aminoalkyl intermediates in i) coupling of α-aminoalkyl metal species, ii) coupling of α-aminoalkyl radicals and iii) coupling of imines with carbon electrophiles (imine umpolung strategies).

#### 1.2.2.1 Alpha-aminoalkyl Metal Species in Chiral Amine Synthesis

The use of secondary alkyl organometallic reagents for chiral amine synthesis is often challenging due to issues arising from slow transmetalation or rapid β-hydride elimination. Therefore, the use of α-aminoalkyl-metal species as an alternative approach has gained significant attention. These species are typically obtained through either base-mediated deprotonation, transmetalation of an α-amino organometallic reagent to Zn, Pd, Ir, or metal-catalyzed direct C–H activation at the N-α-position. In 2006, Campos and coworkers leveraged the α-lithiation of *N*-Boc-pyrrolidines in the presence of stoichiometric (–)-sparteine, followed by transmetalation leading to the formation of a stereodefined α-aminoalkyl zinc species (Scheme 14A).[128] The isolated organometallic

zinc species could then participate in a stereospecific Negishi coupling to form the α-arylation product with high enantioselectivity.

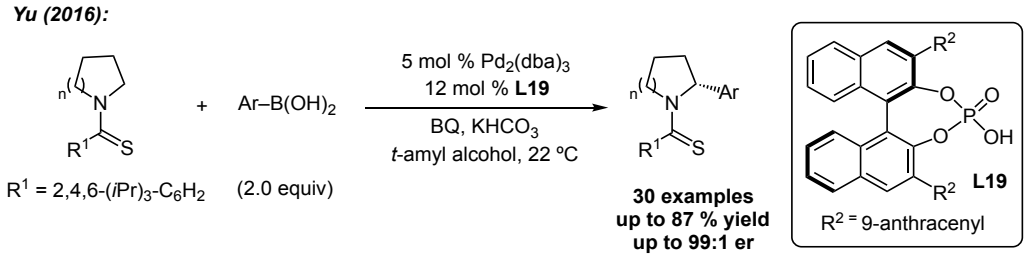



**Scheme 14: Functionalization of Pyrrolidines using Organometallic Zinc Reagents**

Following that work, Gawley and coworkers showed a related highly enantioselective preparation of 2-substituted piperidines through a catalytic dynamic resolution of α-lithiated *N*-Boc piperidine.[129-130] Fu and coworkers have also disclosed a Ni-catalyzed enantioconvergent alkyl–alkyl cross coupling with secondary alkyl halides and *N*-Boc-pyrrolidines.[131] This method is particularly important as the coupling of two secondary alkyl fragments have proven to be difficult, with only a few examples reported. Enantioselective methods requiring stoichiometric metalation at the α-position of the amine are not ideal as they have been limited to cyclic pyrrolidine and piperidine nucleophiles as described above.[132] In addition, the pre-formation of the organometallic

zinc species, which are highly reactive, air- and moisture-sensitive, is necessary and may require multiple steps.

To address these issues, other strategies that led to the *in situ* generation of α-aminoalkyl metal species *via* C–H activation have been investigated. In 2017, Yu and coworkers described a Pd(II)-catalyzed enantioselective α-C–H arylation of thioamides with arylboronic acids (Scheme 15).[132] The supporting chiral phosphoric acid **L19** not only affords high enantioselectivities, but also provides exclusive regioselectivity with a single alkylation of the C–H bond. Other Pd-catalyzed efforts using thioamides have been reported.[133]




**Scheme 15: Yu's Enantioselective C–H Arylation of Thioamides**

Iridium-catalyzed reactions have also been used for C–H functionalization mediated by α-amino metal species.[134-135] Shibata has described an Ir(I)/Ir(III) enantioselective alkylation of C–H bonds in 2-(alkylamino) pyridines to furnish the corresponding functionalized chiral amines in high yields and enantioselectivities.[136]

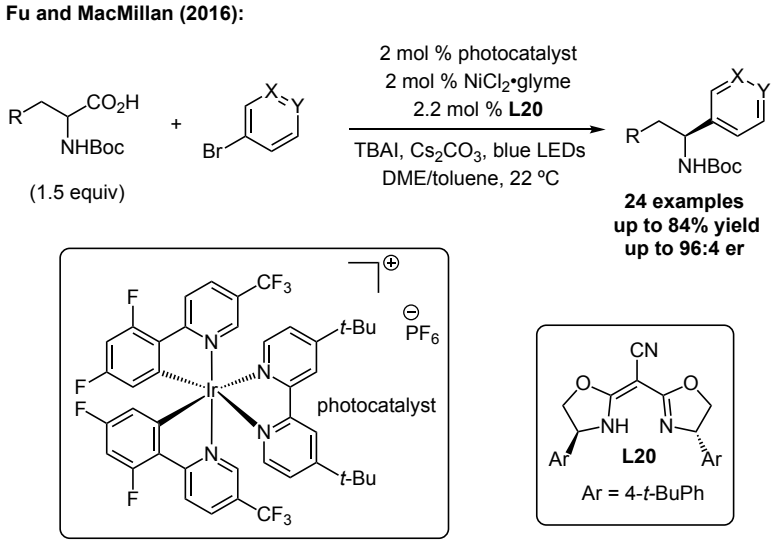
### 1.2.2.2 Alpha-aminoalkyl Radical Species in Chiral Amine Synthesis

The development of reactions utilizing α-amino radicals as synthetically useful intermediates for accessing chiral alkyl amines has also gained significant attention.

Some representative methods for accessing α-amino radicals include single-electron oxidation, decarboxylation, and desilylation of α-silylamines.

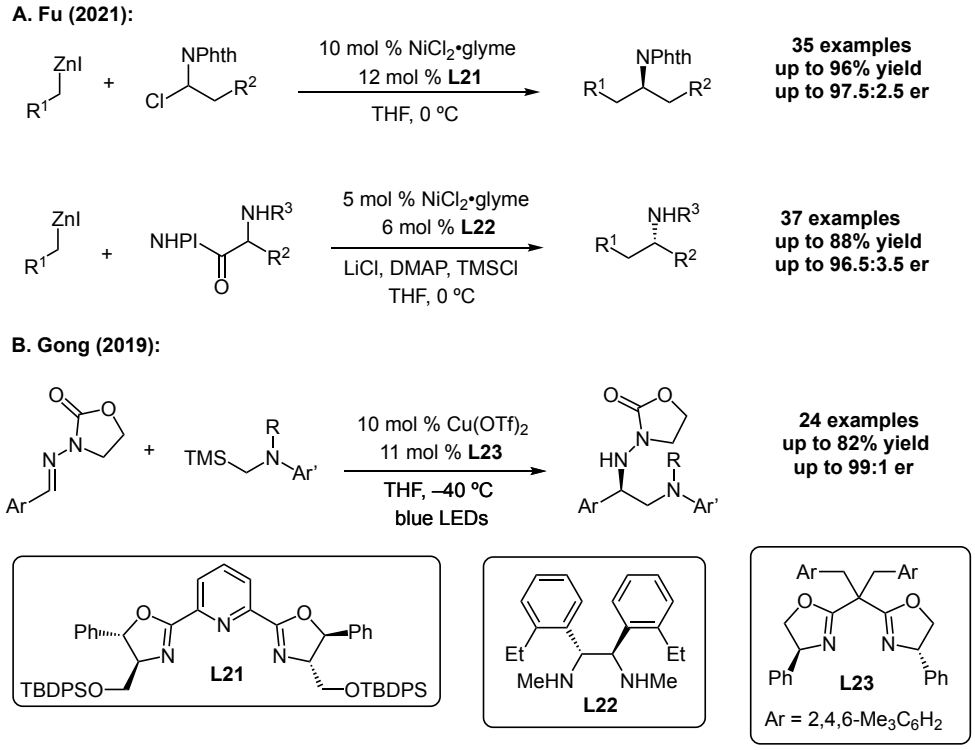
In 2016, Fu and MacMillan reported the first enantioconvergent C($sp^3$)–C($sp^2$) cross-coupling reaction using photoredox and nickel catalysis (Scheme 16).[137] Through this method, chiral benzylic amines, which are valuable pharmacophores, are obtained through coupling of abundant α-amino acids and commercially available aryl halides. The reaction employs a photocatalyst which mediates oxidation and decarboxylation of an α-amino acid to generate a prochiral α-amino radical. Activation of the aryl halide *via* oxidative insertion would lead to a Ni(II)–aryl complex which could undergo coupling with the aforementioned radical to generate the desired product upon reductive elimination. The reaction is robust, delivering the enantioenriched amines in high yields and enantioselectivities. Martin and Montgomery have also made joint contributions in this area by developing dual photoredox and nickel-catalyzed enantioselective C($sp^3$)–H arylation reactions.[138] The generation of radical intermediates for alkyl–alkyl cross coupling using alkyl halides or *N*-hydroxyphthalimide (NHPI) esters has also been explored. These substrates either undergo halide abstraction[139] or decarboxylation[140] to form active radicals that can propagate these reactions. Very recently, Fu and coworkers reported two methods for the Ni-catalyzed enantioconvergent synthesis of protected amines using an alkylzinc reagent and an α-phthalimido alkyl chloride or an NHPI ester of a protected α-amino acid (Scheme 17A).[141] The reactions are general and versatile,

allowing for a broad scope and good functional-group tolerance. The NHPI esters can be generated *in situ* from commercially available α-amino acid derivatives and then coupled directly, resulting in a one-pot catalytic enantioselective synthesis of a variety of compounds.




**Scheme 16: Dual Photoredox/Nickel Catalysis by Fu and MacMillan**

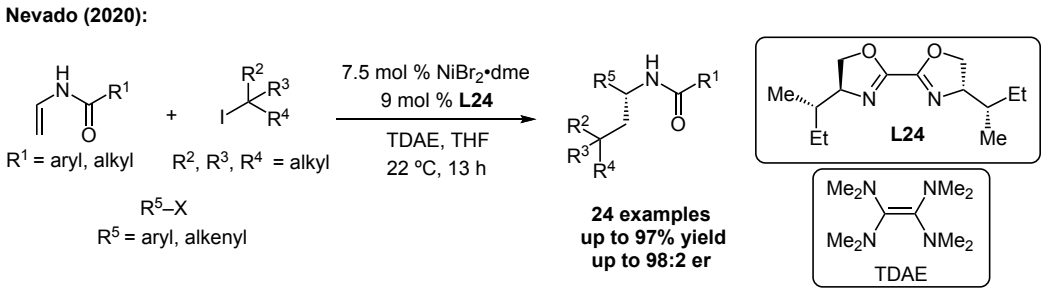
Enantioselective dual photoredox/copper catalysis has been used for the generation of chiral vicinal diamines from the α-aminoalkylation of oxazolidine-2-one-derived imines with α-silylarylamines by Gong and coworkers (Scheme 17B).[142] In this work, they elucidate the importance of the versatile copper(II) catalyst as it serves to perform single electron oxidation of the α-silylarylamine substrate to generate the α-aminoalkyl radical, lewis-acid activation of the imine, and subsequent control of the newly generated stereogenic center.




**Scheme 17: Strategies using α-Amino Radical Species**

The use of α-amino radicals in three-component coupling for the generation of enantioenriched amines have been disclosed by Nevado and coworkers (Scheme 18).[143] In this work, *N*-acyl enamines are used in the enantioselective radical relay reductive coupling with a tertiary alkyl iodide and an alkenyl/aryl halide. These electrophiles are activated through oxidative insertion by the Ni catalyst, then subsequent trapping of the C(sp$^2$)–Ni intermediate by the *N*-acyl enamine forms a new alkyl–Ni(III) species, thus enabling a second C–C bond formation. In this intermolecular reductive dicarbofunctionalization of a pendant activated alkene, a variety of readily available C(sp$^2$) and C(sp$^3$)-halides are added consecutively across the olefin in a highly regio- and enantioselective manner. Additionally, this method avoids the use of sensitive

organometallic reagents, relying on an organic reductant. Three-component Cu-catalyzed reactions enabled by α-amino radicals involving the cyanation or etherification of enamides has also been reported.[144]

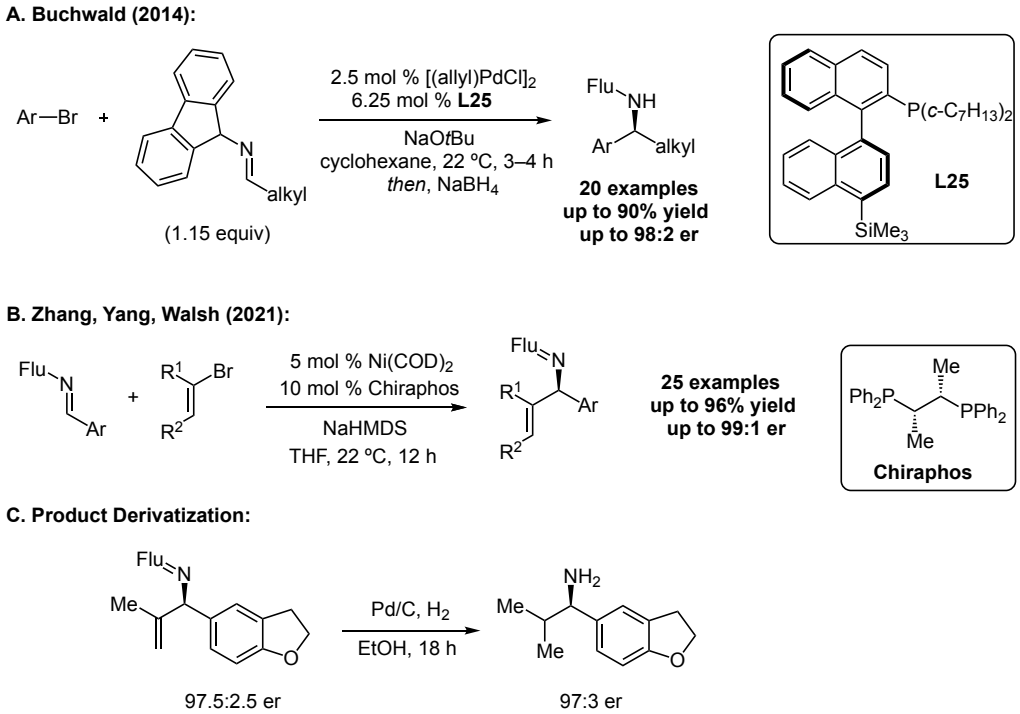



**Scheme 18: Ni-Catalyzed Enantioselective Dicarbofunctionalization of *N*-Acyl Enamines**

### 1.2.2.3 Imine Umpolung Reactions in Chiral Amine Synthesis

The use of umpolung reactivity of imines for the synthesis of alkyl amines has also been explored. Pioneering work was performed by the Buchwald group in 2014 where they demonstrated Pd-catalyzed enantioselective arylation of *N*-fluorenyl imines for the generation of benzylic amines.[145] Owing to the acidity of the C–H bond of the fluorenyl group, base-mediated deprotonation using sodium *tert*-butoxide is facile leading to the formation of an azaallyl anion (or α-amino anion equivalent). The reaction is general, tolerating a wide scope of aryl halides and alkyl amines in high yield and enantioselectivity. Zhang, Yang, and Walsh have also very recently disclosed a vinylation reaction involving 2-azaallyl anions.[146] A chiral bisphosphine allows the stereoselective coupling of alkenyl bromides to *N*-fluorenyl imines allowing the direct preparation of the enantioenriched allylic amine. Subsequent reduction of the allylic C–

C bond by Pd/C under $H_2$ could furnish the desired α-alkyl amine in 70% yield and 97:3 er.

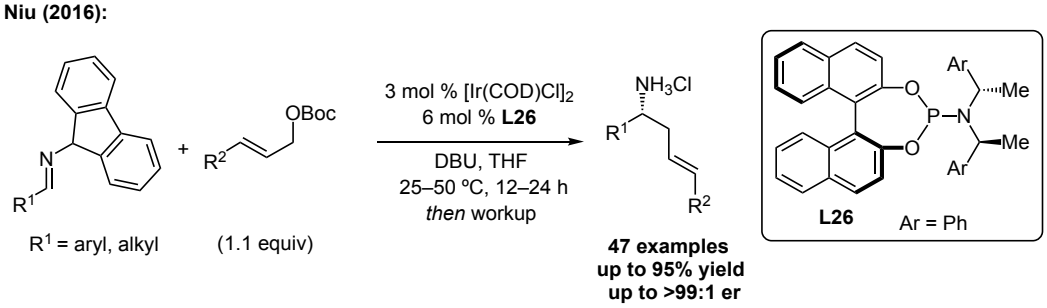



**Scheme 19: Ni and Pd-Catalyzed Imine Umpolung Approaches**

Iridium-catalyzed umpolung allylic alkylations have also been developed using *N*-fluorenyl imines.[147] A mild base (DBU), which facilitates the deprotonation of the starting imine while also avoiding racemization of the generated homoallylic amine product, is crucial to the success of the reaction. Other similar efforts using Ir have also been reported (see section 3.2).

Chruma and coworkers have also disclosed an enantioselective Pd-catalyzed decarboxylative allylation of imines.[148] *N*-metalated azomethine ylides have provided chemists with alternative reagents for designing syntheses of nitrogen-containing

heterocycles through [3+2]-dipolar cycloaddition and conjugate addition reactions.[149-152] But recent studies have expanded on the utility of *N*-metalated azomethine ylides to alkylation methods. Zhang and Wang have made considerable contributions to the alkylation of aldimine esters with allylic acetates leading to the formation of nonproteinogenic α-amino acids.[153-159] Zi and coworkers have also demonstrated a Pd/Cu dual catalysis strategy for the stereodivergent coupling of aldimine esters to terminal and internal 1,3-dienes.[160] Couplings of enamines/2-azadienes mediated by metal hydride insertion have also been used for the generation of α-amino transition-metal species for the enantioselective synthesis of chiral alkyl amines (see section 4.2).[161-164]




**Scheme 20: Ir-Catalyzed Enantioselective Umpolung Allylation of Imines**

# 2. Palladium-Catalyzed Synthesis of α-Trifluoromethyl Benzylic Amines *via* Fluoroarylation of *gem*-Difluoro-2-azadienes

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Daniel, P. E.; Onyeagusi, C. I.; Ribeiro, A. A.; Li, K.; Malcolmson, S. J. Palladium-Catalyzed Synthesis of α-Trifluoromethyl Benzylic Amines *via* Fluoroarylation of *gem*-Difluoro-2-azadienes Enabled by Phosphine-Catalyzed Formation of an Azaallyl–Silver Intermediate. *ACS Catal.* **2019**, *9*, 205–210.

This work was done in collaboration with Paige Daniel.

## *2.1 Introduction*

The role of fluorine in influencing the $pK_a$ of organic compounds, altering lipophilicity of drug molecules,[2] as well as changing conformational bias[1] of drug scaffolds are some compelling reasons why it remains an important atom in bioactive and medicinal compounds.[3, 165] One of such fluorinated moieties is the α-trifluoromethyl (α-$CF_3$) amine motif. The significance and prevalence of α-trifluoromethyl amines in biologically active molecules, including Odanacatib[6] (a cathepsin K inhibitor in osteoporosis treatment), remain a driving force for the development of new and efficient methods to access this amine scaffold (Figure 4).[2] To this end, we sought to develop new methods for preparing $CF_3$-containing amine building blocks. In particular, α-trifluoromethyl benzylic amines are a heavily sought-after class of amines in organic synthesis as they are an important pharmacophore. Consequently, a number of research labs have made great efforts to develop routes for their synthesis.

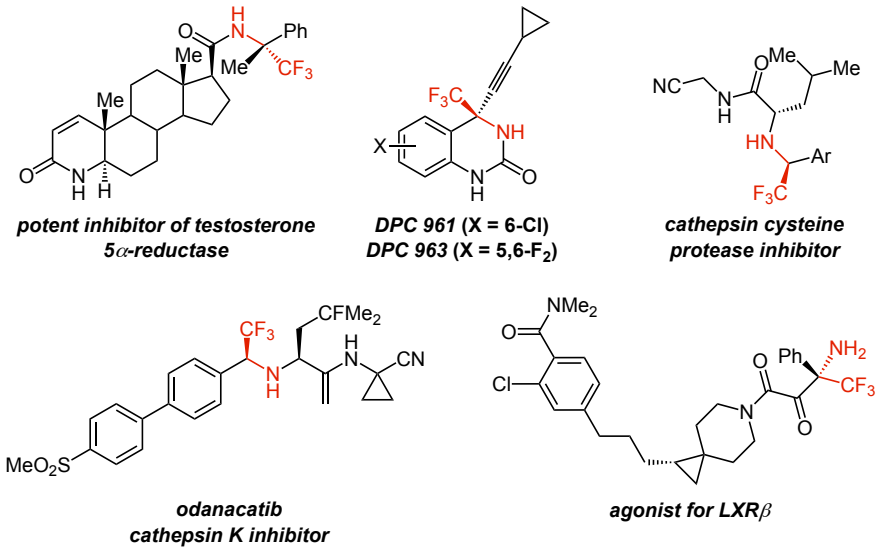


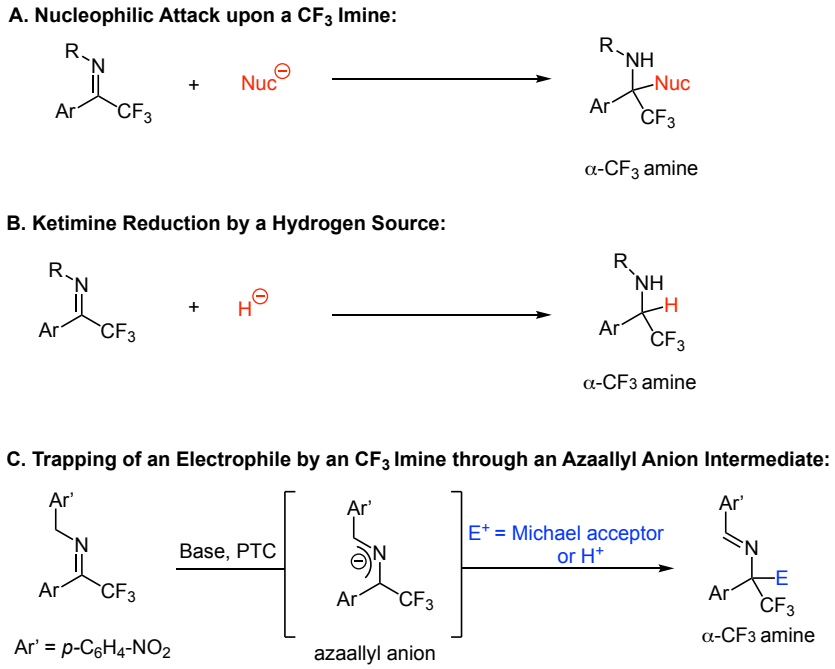

**Figure 4: α-Trifluoromethyl Benzylic Amines in Biologically Active Molecules**

## 2.1.1 Methods for Preparing α-Trifluoromethyl Benzylic Amines

Most of these syntheses have relied on one of three main strategies: i) nucleophilic attack upon a $CF_3$-substituted imine, ii) ketimine reduction of a $CF_3$-imine, or iii) trapping an electrophile by a $CF_3$ imine through an azaallyl intermediate (Scheme 21) as discussed in Chapter 1.

The addition of aryl nucleophiles to $CF_3$-substituted imines is a common way for accessing this class of α-trifluoromethyl benzylic amines (see section 1.1.2.1). In 2013, the Lautens group developed a method for accessing enantioenriched benzylic amines *via* an enantioselective addition of boroxines to aniline-derived *N,O*-acetals of trifluoroacetaldehyde using a neutral Pd(II) catalyst bearing a PyOx ligand (Scheme 22A).[166] The reaction works efficiently for electron-rich aryl boroxines; however, electron-poor nucleophiles do not participate well. It is proposed that the slower

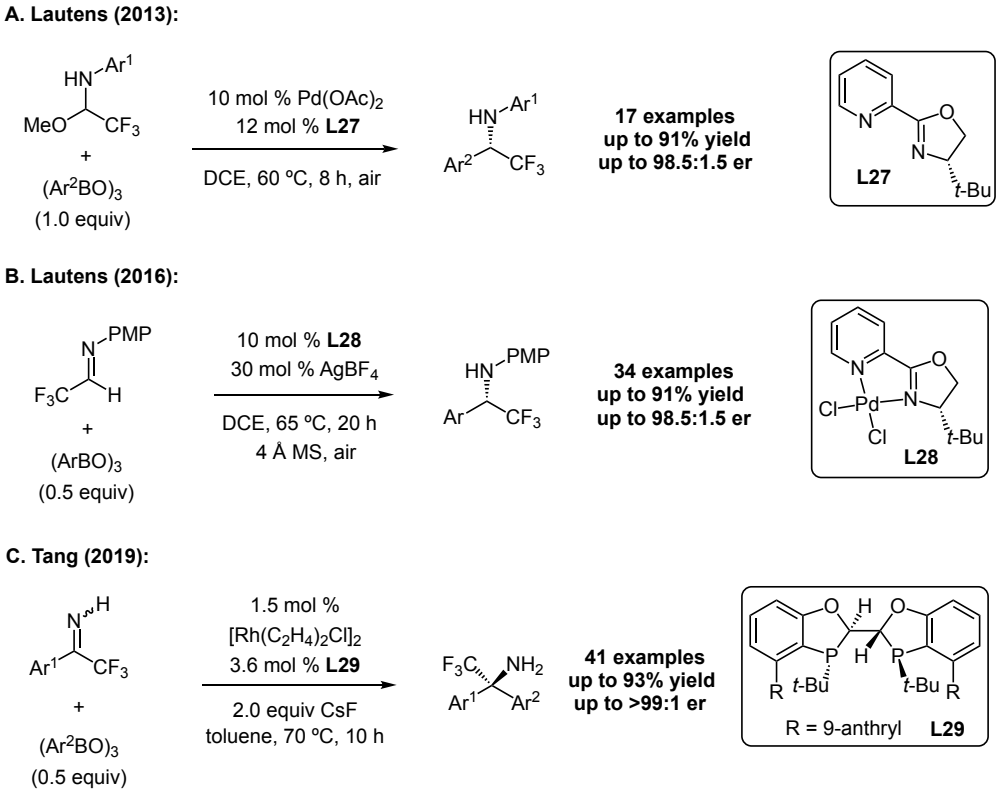
transmetalation rates with electron-deficient nucleophiles and the reduction of the Pd catalyst from Pd(II) to Pd(0) under the reaction conditions are the reasons for low reactivity.




**Scheme 21: Different Strategies for Synthesis of α-Trifluoromethyl Amines**

In their later work in 2016, modification of the catalyst system and the introduction of a silver additive allowed for a wider substrate scope involving electron-deficient arylboroxines (Scheme 22B).[167] The newly-introduced $Cl_2Pd(PyOx)$ complex, in conjunction with a $AgBF_4$ additive, renders the Pd(II) species cationic and facilitates transmetalation of the arylboroxine. Following that work, Tang and coworkers have developed a Rh-catalyzed addition of arylboroxines to N–H trifluoromethyl ketimines for easy access to tetrasubstituted α-$CF_3$-α,α-diaryl amines in high yields and enantioselectivity (Scheme 22C).[168] The use of the unprotected N–H imine allows the

primary amine to be delivered directly without any deprotection workup and also facilitates the formation of the sterically-congested stereogenic center.

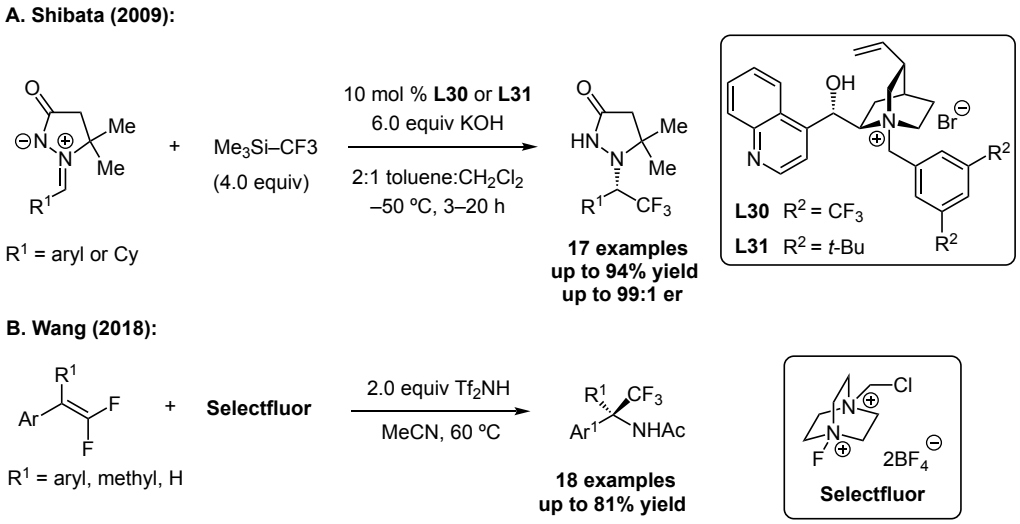



**Scheme 22: Addition of Aryl groups to Trifluoromethyl Imines using Rh and Pd Catalysis**

Besides the addition of aryl-groups to imines to generate α-$CF_3$ benzylic amines, the addition of the trifluoromethyl group to aryl-substituted imines has been used in one instance. Although a less common avenue, nucleophilic trifluoromethylation can serve as a powerful strategy. This allows the generation of the same products but obviates the challenges associated with preparing $CF_3$ imines. However, this route faces some challenges, predominantly the low nucleophilicity of the trifluoromethyl anion. In 2009,

the Shibata group reported the first and thus far only addition of $CF_3$ nucleophiles to prepare α-$CF_3$ amines through $TMSCF_3$ addition to azomethine imines under phase transfer catalysis (Scheme 23A).[169] Azomethine imines, which are commonly used in enantioselective 1,3-cycloaddtion reactions, were crucial for such a challenging approach due to some of its unique properties. First, the increased electrophilicity of the azomethine imine in comparison with an *N*-tosyl imine, promotes efficient coupling with the trifluoromethyl anion (which has low nucleophilicity). In addition, the constrained conformation of the cyclic activating group allows greater levels of reactivity and enantioselectivity. It is also proposed that the carbonyl oxygen of the azomethine imine activating group aids in reaction turnover. In 2012, Shibata also reported another example of a nucleophilic trifluoromethylation but with an environmentally benign SOLKANE® 365 mfc solvent rather than a mixture of toluene and dichloromethane used in their aforementioned work.[170] Modification of the phase transfer catalyst was needed for this transformation. Nucleophilic trifluoromethylation remains an area for development as only a few examples of methods taking advantage of this strategy exist. Electrophilic fluorination has also been used for synthesizing α-$CF_3$ benzylic amines. Recently, the Li and Wang labs have elaborated a novel strategy for the construction of α-$CF_3$ benzylic amines *via* an aminofluorination of *gem*-difluoroalkenes (Scheme 23B).[171] Single-electron oxidation and a subsequent F-atom abstraction aided by

SelectFluor® allows the formation of a benzylic cation that is trapped by acetonitrile in a Ritter-type amination pathway.




**Scheme 23: Nucleophilic Trifluoromethylation and Electrophilic Fluorination Strategies**

## *2.2 Background*

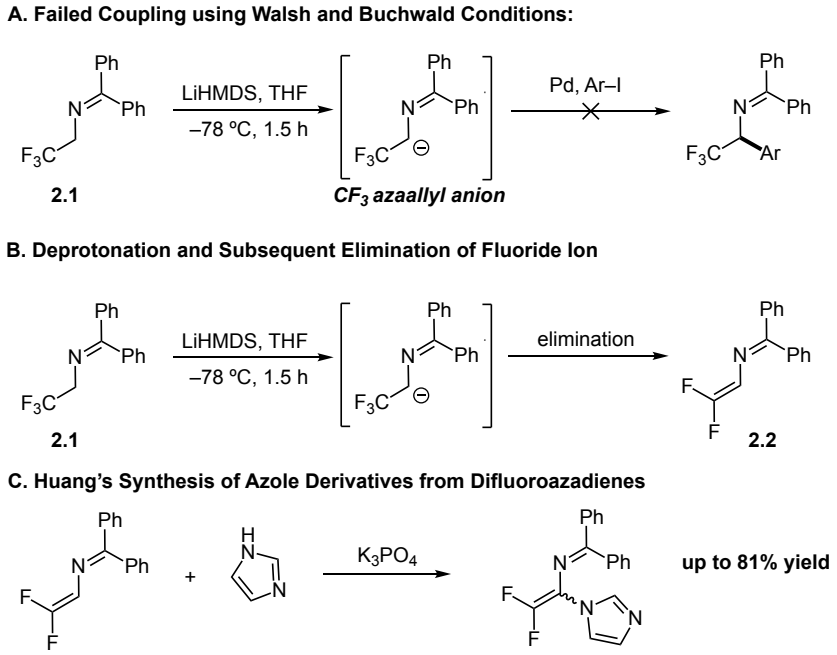
While aryl cross-couplings with azaallyl anions that do not bear the $CF_3$ substituent has been performed by several groups[172-174], including an enantioselective variant by the Buchwald group[145], umpolung strategies for the development of α-$CF_3$ benzylic amines had been an unexplored area. These methods used by Walsh[172] and Buchwald[145] had typically been accomplished through the initial deprotonation of the imine at the α-position, allowing the generation of an azaallyl anion which undergoes cross-coupling with aryl halides. In addition, beyond the early strides in synthesis of α-$CF_3$ amines using [1,3]-prototropic shifts[77, 175], only Michael acceptors had been identified

as carbon-based electrophiles for the azaallyl strategy.[81-84] The concept of utilizing a $CF_3$-substituted azaallyl anion to prepare α-$CF_3$ amines, however, has great appeal.

Therefore, a new strategy to access α-$CF_3$ benzylic amines and provide reactivity beyond conjugate addition would be important and broadly useful. Hence, we first decided to develop a method to enable aryl cross-coupling using a $CF_3$-substituted azaallyl anion to afford α-$CF_3$ benzylic amines.

## 2.3 Results and Discussion

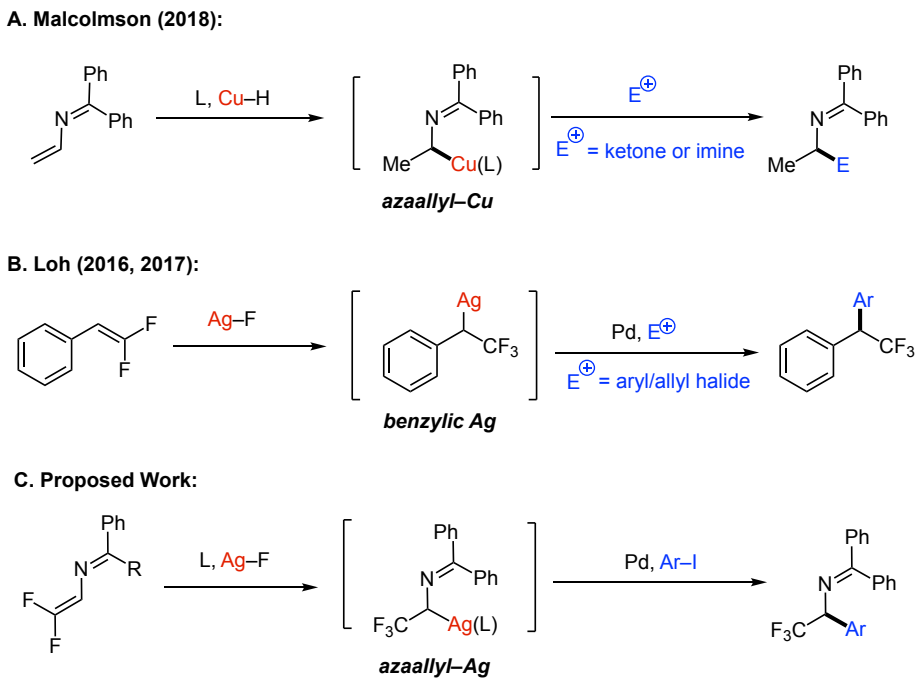
To begin our umpolung studies, we examined the addition of trifluoromethyl imine **2.1** and iodobenzene in the presence of a Pd catalyst and an appropriate ligand (Scheme 25A). These conditions were chosen initially to be modeled after Buchwald and Walsh's reports for the arylation of aldimines using azaallyl anions as intermediates.[145, 172] However, unlike their findings, when this $CF_3$-substituted imine was subjected to strongly basic conditions (i.e. LiHMDS), it rapidly underwent elimination of a fluoride ion to form the corresponding difluoroazadiene (Scheme 24B). These difluoroazadienes had only been described once before in the literature by Huang and coworkers for the synthesis of fluorovinyl azole derivatives that were furnished through the intermediacy of an azaallyl anion (Scheme 24C).[176] Nevertheless, the formation of this difluoroazadiene under basic reaction conditions indicated that the deprotonation strategy would not be feasible for this particular substrate, and that the formation of the azaallyl anion might need to proceed through another strategy.




**Scheme 24: Access to Difluoroazadienes as Substrates for Reaction Development**

We hoped that the results from some of our previous work[162-163] would be beneficial for finding an enabling strategy for accessing the benzylic amine product. In these studies, we had explored the generation of α-aminoalkyl Cu nucleophiles from a Cu–H migratory insertion into 2-azadienes catalytically, allowing for the formation of an azaallyl–Cu intermediate that could undergo addition to electrophilic ketones or imines to furnish vicinal amino alcohols and diamines (Scheme 25A). We envisioned that a related insertion process into a difluoroazadiene might be a route for obtaining reaction. Furthermore, Loh and coworkers reported a Pd-catalyzed fluoroarylation of *gem*-difluorostyrenes with aryl/allylic electrophiles (Scheme 25B).[177-178] In their study, it is proposed that an α-$CF_3$ benzylic silver intermediate, which is derived from the addition

of a nucleophilic fluoride ion, undergoes coupling with aryl iodides/bromides or allylic carbonates. This allowed the delivery of the fluoroarylation product and provided a mild and general strategy for access to chiral trifluoroethane derivatives. Hu and coworkers have also used these *gem*-difluoroalkenes and difluorostyrenes for other transformations.[179-180] More recently, fluoroarylation efforts have also been made by Kobayashi[181] and the team of Yang and Zhang laboratories.[182]



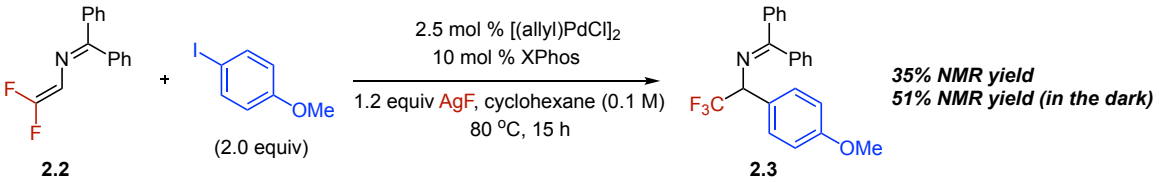

**Scheme 25: Strategies for the Catalytic Generation of Alkyl Nucleophiles for Coupling Reactions**

To generate these α-$CF_3$ benzylic amines, we decided to explore the possibility that difluoroazadienes might be used as precursors for $CF_3$-substituted azaallyl anions. We hypothesized that similarly to Loh's work, a reaction might proceed through the generation of an azaallyl–Ag intermediate, formed from addition of AgF to the

difluoroazadiene, which could further undergo transmetalation with palladium followed by reductive elimination to furnish the fluoroarylation product (Scheme 25C).

### 2.3.1 Reaction Optimization

We began by synthesizing a *gem*-difluoroazadiene that would undergo fluoroarylation to attain the desired benzylic α-$CF_3$ amines. Benzophenone-derived difluoroazadiene **2.2** was chosen as the substrate to establish optimal reaction conditions because of its relative ease of preparation. We examined the coupling of difluoroazadiene **2.2** and 4-iodoanisole using a stoichiometric quantity of AgF, 2.5 mol% $[(allyl)PdCl]_2$, and 10 mol% XPhos in cyclohexane (0.1 M) which mirror Loh's established conditions (Scheme 26). Under the aforementioned reaction conditions, we were able to obtain a 35% yield of the desired fluoroarylation product **2.3** as measured by $^{19}F$ NMR. Owing to the light-sensitive nature of AgF, we decided to exclude light by covering our reaction vessel with aluminum foil and this led to the formation of our desired product in a higher 51% yield. Upon obtaining these promising results, we sought to further optimize the reaction conditions.

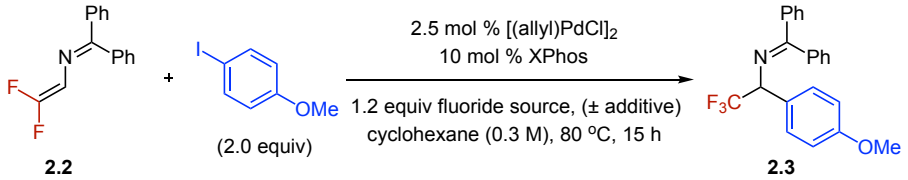



**Scheme 26: Preliminary Findings for Fluoroarylation of Azadienes**

We first determined that we obtained a higher yield of the product at 0.3 M (entry 1) and then decided to determine the importance of the fluoride source in this

reaction: switching to other inorganic sources such as CsF, KF, or $CuF_2$ led to no observable product and elucidated that AgF was crucial for fluoride addition to the azadiene (Table 1, entries 2–4). Furthermore, using a combination of CsF or KF and a silver salt (i.e. $AgNO_3$ or $Ag_2CO_3$) also failed to form product **2.3** (entries 9 and 10). Temperature had a marked effect on reactivity: room temperature and slightly elevated temperatures of 40 °C and 60 °C were detrimental, providing a maximum yield of 9% (entries 7 and 8). Therefore, performing the fluoroarylation reaction at 80 °C was essential. We also screened different aryl halides for this reaction, with the aryl iodides (4-iodoanisole) providing the best yields over the chloro and bromo compounds. Bromides could afford the desired products, albeit in lower yields, while chlorides failed to furnish the benzylic amines (entries 5 and 6).

**Table 1: Optimization of Fluoride Source, Temperature, and Aryl Halide**[a]

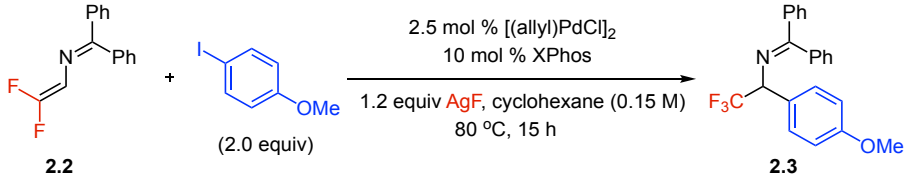



| entry | fluoride source | additive | yield of **2.3** (%) |
|---|---|---|---|
| 1[b] | AgF | - | 78 |
| 2 | KF | - | <2 |
| 3 | CsF | - | <2 |
| 4[c] | $CuF_2$ | - | <2 |
| 5[b,d] | AgF | - | 39 |
| 6[b,e] | AgF | - | <2 |
| 7[f] | AgF | - | <2 |
| 8[g] | AgF | - | 9 |
| 9 | CsF | $Ag_2CO_3$ | <2 |
| 10 | CsF | $AgNO_3$ | <2 |

[a]Reaction concentration of 0.15 M under $N_2$ atmosphere. [b]Reaction run at 0.3 M. [c]Reaction was performed using $[(cinnamyl)PdCl]_2$ at 100 °C. [d]4-bromoanisole used. [e]4-chloroanisole used. [f]Reaction run at 22 °C or 40 °C. [g]Reaction run at 60 °C

We also discovered that this reaction proceeds well in nonpolar organic solvents, with cyclohexane providing optimal results (Table 2, entries 1–4). However, even with our optimal solvent, attempts to shorten the reaction time from 15 h to 1 h or 6 h led to lower levels of conversion (entries 5–6). Switching the Pd source in the reaction from $[(allyl)PdCl]_2$ to $[(cinnamyl)PdCl]_2$ led to a slight increase of yield (78% to 80%) under the same reaction conditions (entries 7 and 8). Further increasing the temperature from 80 °C to 100 °C also increased yield to 84% (entry 9).

**Table 2: Optimization of Solvent and Time**[a]

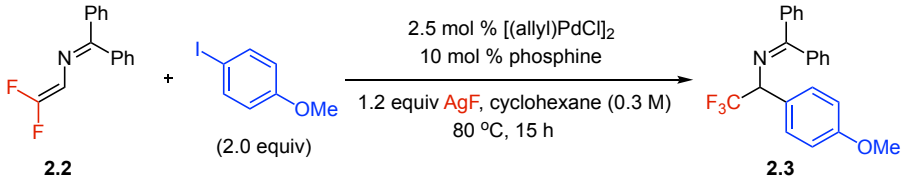



| entry | solvent | time (h) | yield of **2.3** (%) |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 15 | 15 |
| 2 | THF | 15 | 37 |
| 3 | 1,4-dioxane | 15 | 40 |
| 4 | toluene | 15 | 43 |
| 5 | cyclohexane | 1 | 17 |
| 6 | cyclohexane | 6 | 68 |
| 7 | cyclohexane | 15 | 78 |
| 8[b] | cyclohexane | 15 | 80 |
| 9[b,c] | cyclohexane | 15 | 84 |

[a]Reaction concentration of 0.15 M. under $N_2$ atmosphere. [b]Reaction was performed using [(cinnamyl)PdCl]$_2$. [c]Reaction was performed at 100 ºC.

We were also able to perform exclusion experiments to ascertain that Pd, Ag, and phosphine ligand are crucial for the reaction. Excluding either [(allyl)PdCl]$_2$, AgF, or XPhos in this reaction completely led to no observable product. In addition, XPhos was also unique in this reaction as most monophosphine or bisphosphine ligands were largely unsuccessful in this reaction (Table 3).

**Table 3: Evaluation of Ligands**[a]



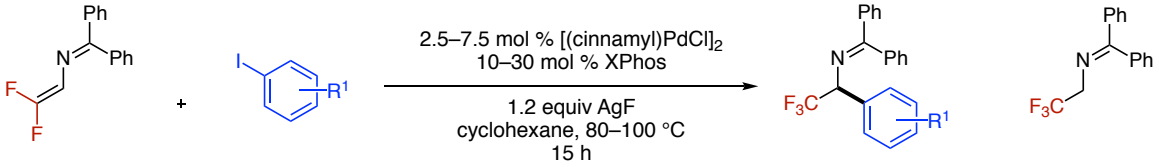

| entry | phosphine | yield of **2.3** (%) |
|---|---|---|
| 1 | RuPhos | 4 |
| 2 | TrixiePhos | <2 |
| 3 | BrettPhos | <2 |
| 4 | XantPhos | <2 |
| 5 | XPhos | 80 |
| 6 | SPhos | 7 |
| 7 | $PCy_3$ | <2 |
| 8 | $PPh_3$ | <2 |
| 9[b] | $PCy_2Ph$ | 17 |
| 10[c] | (*R*)-BINAP | <2 |
| 11 | (*R*)-SEGPHOS | <2 |
| 12 | (*R*)-(+)-MeO-BiPHEP | <2 |
| 13 | (*R,R*)-QuinoxP | <2 |
| 14 | (*R,R*)-Me-DuPhos | <2 |
| 15 | (*R*)-DTBM-SEGPHOS | <2 |
| 16 | (*R*)-SYNPHOS | <2 |
| 17[d] | PEPPSI-*i*Pr | <2 |

[a]Reaction performed at 0.3 M. [b]Reaction performed using $[(cinnamyl)PdCl]_2$ at 100 ºC. [c]Reaction performed at 0.15 M. [d]Reaction performed without $[(allyl)PdCl]_2$; PEPPSI-*i*Pr is an isolated Pd catalyst, and not a phosphine.

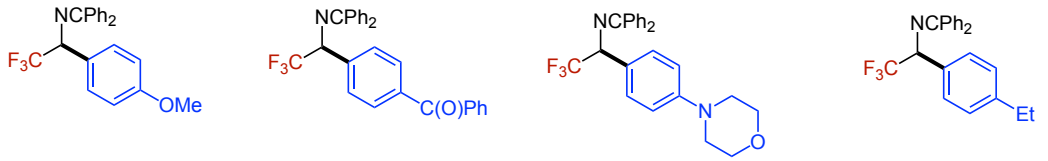
## 2.3.2 Substrate Scope

Upon establishment of our optimal reaction conditions, we decided to investigate the substrate scope of aryl iodides for preparing a variety of benzylic α-$CF_3$ amines.

**Table 4: Substrate Scope for Benzophenone-Derived Substrates**




**2.2** **2.4–2.15** **2.16–2.27** **2.28**



**2.16**[a]: 80% yield **2.17**[b]: 75% yield **2.18**[c]: 45% yield **2.19**[b]: 65% yield

**2.20**[a]: 87% yield **2.21**: 78% yield **2.22**[b]: 72% yield **2.23**[b]: 67% yield

**2.24**[a]: 88% yield **2.25**[d]: 68% yield **2.26**[c]: 82% yield **2.27**[d]: 68% yield

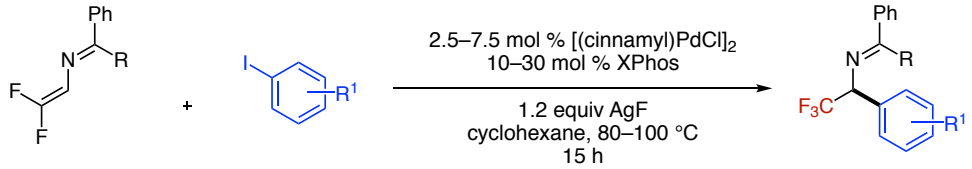
[a]2.5 mol% Pd salt, 10 mol% XPhos, 100 ºC. [b]2.5 mol% Pd salt, 10 mol% XPhos, 80 ºC.
[c]5.0 mol% Pd salt, 20 mol% XPhos, 100 ºC. [d]5.0 mol% Pd salt, 20 mol% XPhos, 80 ºC

Certain trends were observed in the screening of the substrates. In general, sterically accessible *para*- and *meta*-substituted electron-donating aryl-halides provide better coupling efficiency as observed in **2.16** and **2.24** (ca. 80% yield). Electron-neutral substrates are tolerated well: naphthyl- **2.20**, phenyl- **2.21**, and biphenyl-containing **2.26** products are delivered efficiently under the fluoroarylation conditions, affording the desired benzylic amine in ca. 80%, yield for each substrate. Substrates bearing moderately electron-withdrawing groups such as *para*-$CF_3$ **2.25** or *para*-chloro **2.27** were amenable to the reaction conditions, albeit in a slightly lower yield (68% yield for both

substrates). It is worthy to note that aryl iodides bearing an acidic proton such as anilines, carboxylic acids, and enolizable ketones fail to deliver any desired product as these enable protonation of the azaallyl–Ag species formed in the reaction, leading exclusively to the undesired hydrofluorination product **2.28**. Conversely, non-enolizable ketones were amenable, with phenyl ketone product **2.17** delivered in 72% yield.

Interestingly, we observed a trend between the yield obtained and the electronic nature of the aryl iodides. Aryl iodides with electron-donating substituents on the aryl iodide produced favorable reactivity (ca. 80% yield) while aryl iodides with strongly electron-withdrawing groups, such as nitro groups, gave low yields (ca. 40% yield). In addition to low conversion obtained with these electron-withdrawing substrates, we also observed the formation of hydrofluorination product **2.28** in appreciable amounts. As an attempt to rectify this problem, we increased the Pd catalyst loading on low-yielding substrates from 5 to 10 mol% but that still did not provide acceptable yields. We then hypothesized that switching the sterically encumbered benzophenone-derived "diphenyl" difluoroazadiene to a more accessible substrate might address these issues. Ultimately, using a less-hindered benzaldehyde-derived "monophenyl" difluoroazadiene remedied most of the issues we had with challenging substrates.

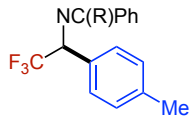
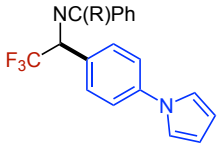
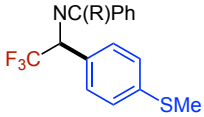
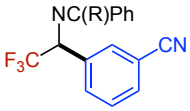
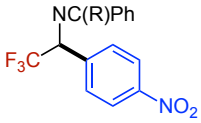
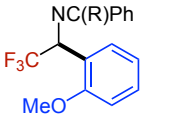
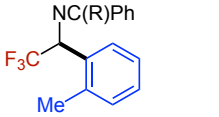
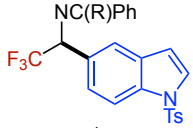
**Table 5: Substrate Scope for Benzophenone- and Benzaldehyde-Derived Substrates**




R = Ph **2.2**
R = H **2.29**

**2.30–2.37**

**2.38–2.53**

| |  |  |  |  |
|---|---|---|---|---|
| R = Ph | **2.38**[a]**:** 81% yield | **2.40**[b]**:** 63% yield | **2.42**[c]**:** 85% yield | **2.44**[b]: 54% yield |
| R= H | **2.39**[a]**:** 77% yield | **2.41**[a]**:** 87% yield | **2.43**[c]**:** 87% yield | **2.45**[a]**:** 87% yield |
| |  |  |  |  |
| R = Ph | **2.46**[d]**:** 37% yield | **2.48**[c]: 40% yield | **2.50**[c]**:** 56% yield | **2.52**[b]**:** 17% yield |
| R= H | **2.47**[a]**:** 82% yield | **2.49**[a]: 90% yield | **2.51**[a]**:** 81% yield | **2.53**[b]: 45% yield |

[a]2.5 mol% Pd salt, 10 mol% XPhos, 100 ºC. [b]7.5 mol% Pd salt, 30 mol% XPhos, 100 ºC.
[c]5.0 mol% Pd salt, 20 mol% XPhos, 100 ºC. [d]5.0 mol% Pd salt, 20 mol% XPhos, 80 ºC

This more reactive monophenyl difluoroazadiene allowed us to obtain good yields with challenging couplings of sterically hindered and electron-deficient aryl iodides, as well as suppress the formation of the hydrofluorination byproduct. For example, product **2.46** obtained from electron-poor *para*-nitro phenyl iodide and benzophenone derived difluoroazadiene **2.2** was isolated in only 37% yield. However, we were pleased to discover that on switching to the less-sterically hindered azadiene, we were able to attain an isolated yield of **2.47** in 82% with essentially no side product. For sterically hindered aryl iodides such as *ortho*-methoxy substrate, we saw an increase

in yield from 40% to 90% upon switching to the monophenyl difluoroazadiene substrate (compare **2.48** and **2.49**).

This modification of our azadiene activating group also allowed better tolerance of some heterocycles. For example, *N*-tosyl indole substrate increased from 17% yield in **2.52** to 45% yield in **2.53**. In addition to obtaining improved yields with this modified substrate, the imine products could be isolated much more cleanly due to low amounts of the hydrofluorination product derived from **2.29**. We attempted to broaden the difluoroazadiene scope of the reaction further; however, several azadiene coupling partners were not amenable with the method (Figure 5). Benzaldehyde-derived azadiene **2.54** resulted in the arylation at the 1-position rather than the desired fluoroarylation product (arylation at the 3-position). To discriminate attack at the imine carbonyl, we switched to the benzophenone-derived substrate **2.55**; however, the substrate proved completely unreactive under the standard reaction conditions. Similarly, monofluoroazadiene **2.56** did not undergo any reaction likely due to decreased electrophilicity.

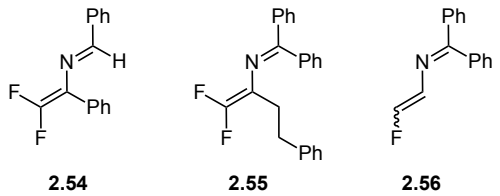
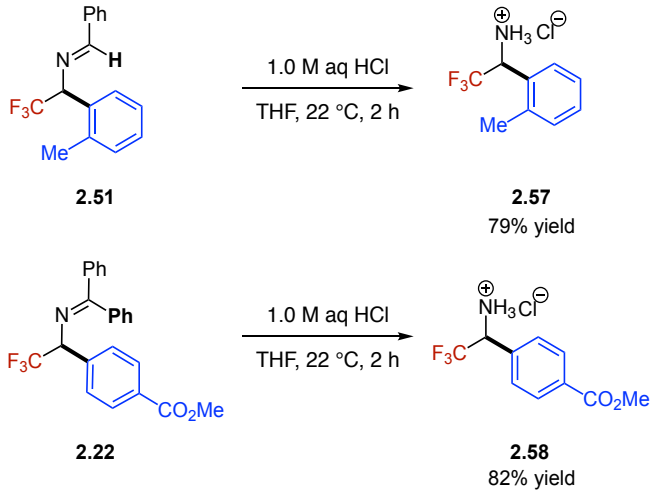



**Figure 5: Incompatible Azadiene Substrates for Fluoroarylation**

### 2.3.3 Hydrolysis of Product Imines to Deliver Primary Ammonium Salts

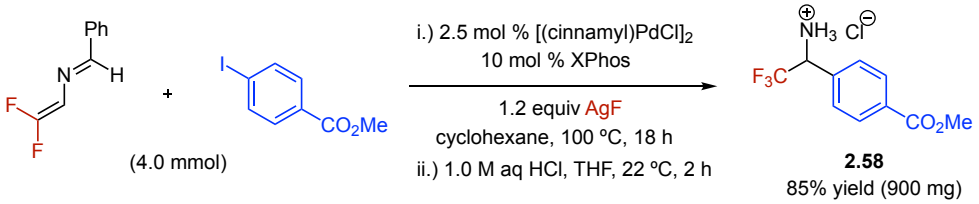
The direct products derived from the fluoroarylation reaction are present as protected amines in the form of imines bearing either a benzaldehyde or benzophenone group. While the benzophenone-derived imines are more robust and can be maintained during further transformations, they are readily hydrolyzed under mildly acidic conditions in a similar fashion as the more labile benzaldehyde-protected imines. Ammonium salts **2.57** and **2.58** were obtained from **2.51** and **2.22**, respectively, with 1.0 M aq HCl at room temperature in 2 hours (Scheme 27).




**Scheme 27: Imine Hydrolysis in Products**

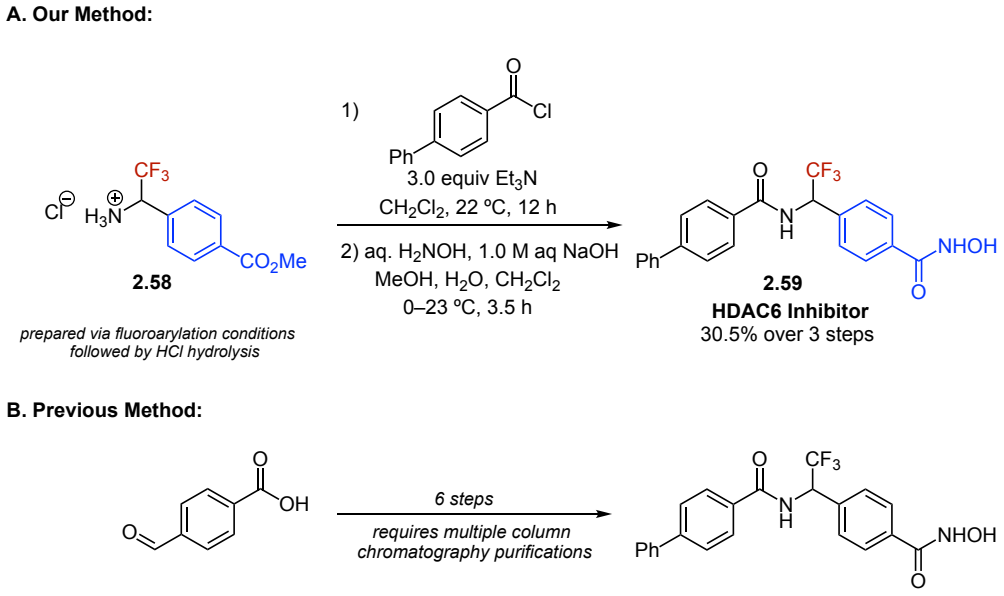
### 2.3.4 Reaction Scale Up and Synthesis of Reported HDAC6 Inhibitor

We explored the scalability of this method using a one-pot protocol. Fluoroarylation and subsequent deprotection of the imine product on a 4.0 mmol scale delivered the primary ammonium salt **2.58** without diminished yield (Scheme 28).




**Scheme 28: Reaction Scale Up/One-Pot Fluoroarylation and Hydrolysis Coupling**

We then sought to functionalize the amine further for its utility in accessing bioactive small molecules. This process allowed us to prepare a reported HDAC6 inhibitor **2.59** in three simple steps: ammonium salt **2.58** generated upon one-pot fluoroarylation and hydrolysis can be acylated in the presence of $Et_3N$ and *para*-phenyl benzoyl chloride, and then a subsequent conversion of the methyl ester to the hydroxamic acid led to the desired bioactive compound of interest (Scheme 29).

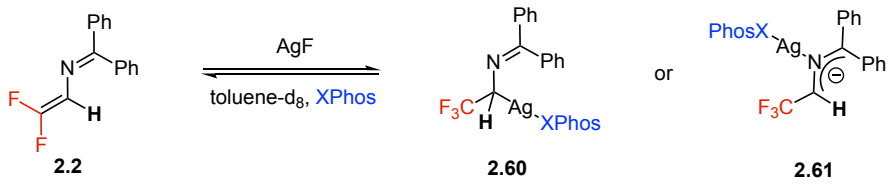



**Scheme 29: Novel Route to the Synthesis of a Reported HDAC6 Inhibitor**

It is worthy to note that this three-step synthesis improves upon a previous method used in the assembly of this compound, which required six steps. Furthermore, this route can be completed without column purification as each step affords clean product after a simple workup.

## *2.4 Characterization of Azaallyl–Ag Intermediate by NMR Spectroscopy Studies*

We proposed that an azaallyl–Ag compound is the nucleophilic species generated during the course of the fluoroarylation reaction and we sought to determine the nature of this intermediate. We then hypothesized that the azaallyl nucleophile could exist as a C–bound azaallyl–silver **2.60** or as an *N*–bound azomethine ylide[183-185] **2.61** (Scheme 30) and conducted a series of NMR spectroscopic experiments to determine the structure of this species.




**Scheme 30: Potential Azaallyl Nucleophiles in Fluoroarylation Reaction**

First, we were able to ascertain that the formation of this complex does not take place in the absence of XPhos likely due to the insolubility of AgF in nonpolar solvents such as cyclohexane and toluene. Hence, the complexation of AgF with the nonpolar XPhos is essential for its addition to the azadiene. We next carried out a combination of a stoichiometric amount of XPhos and AgF in toluene-$d_8$. It is worthy to note that the

cross-coupling reaction works fairly well in toluene as well (see Table 4). We observed a new soluble complex **2.62** by $^{31}P\{^{1}H\}$ NMR, as indicated by two new phosphorus peaks. The coupling constants between the phosphorus nucleus and $^{107}Ag$ (666 Hz) and $^{109}Ag$ (760 Hz) are consistent with the neutral F–Ag–Phosphine complex (Figure 6).[186]

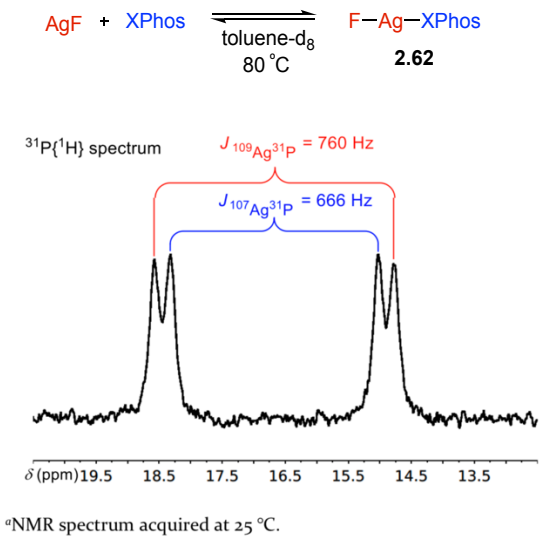



**Figure 6: NMR Spectrum for F–Ag–XPhos Complex 2.62**

Furthermore, the addition of difluoroazadiene **2.2** generated a new species with a different set of doublets upfield of III in the $^{31}P$ NMR spectrum (Figure 7). We determined the Ag–P coupling constant of these new doublets in the $^{31}P$ NMR spectrum to be 402 and 461 Hz, respectively, for $^{107}Ag$ and $^{109}Ag$. Additionally, we observed a new multiplet at 4.18 ppm in the $^{1}H$ NMR spectrum, which corresponded to an azaallylic proton (Figure 7). Decoupling of this proton from both $^{19}F$ and $^{31}P$ nuclei led to the simplification of this multiplet and enabled the determination of its two- and three-bond coupling constants to silver (18.0 Hz) and phosphorus (5.0 Hz), respectively. In the $^{19}F$

NMR spectrum, a new peak at –51.3 ppm was also observed that correlated to the azallylic $CF_3$ group (Figure 7).

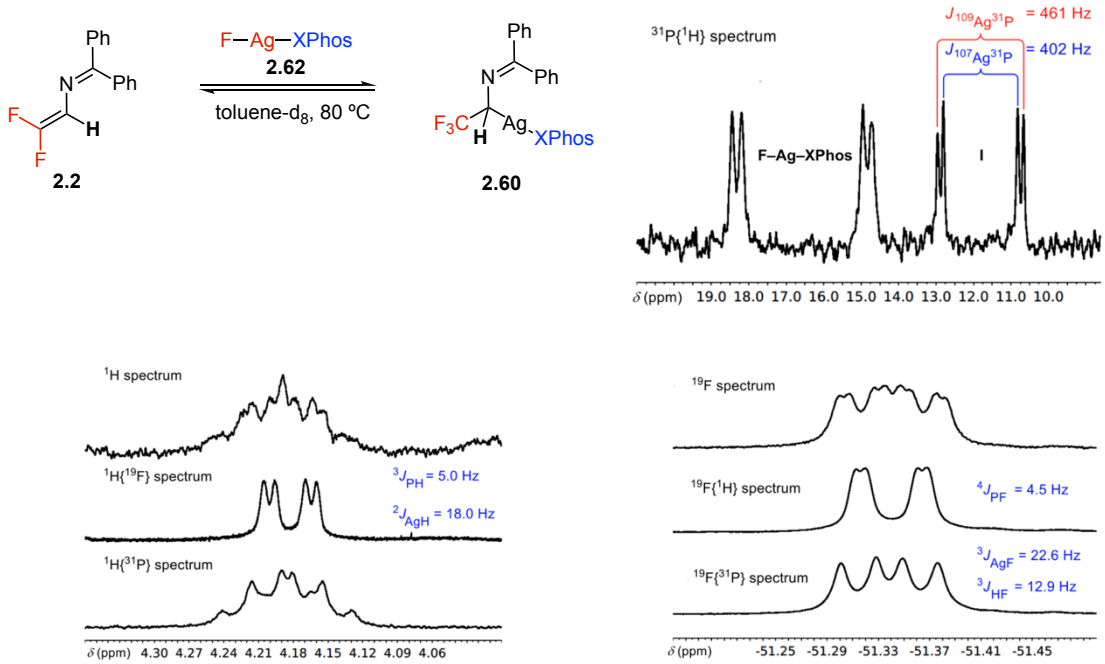


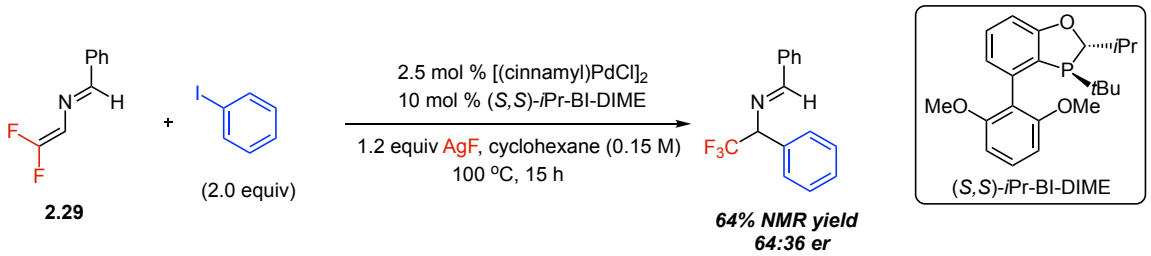

**Figure 7: NMR Characterization of Azaallyl-Ag Complex 2.60**

Similarly, decoupling the fluorine from $^{1}H$ and $^{31}P$ simplified peak multiplicities, allowing calculation of coupling constants of fluorine to silver, hydrogen, and phosphorus nuclei. Crucial to the determination of the identity of this complex was the coupling observed between phosphorus and fluorine. C–bound azaallyl–silver **2.60** (four-bond coupling), rather than Ag-stabilized azomethine ylide **2.61** is more likely the active nucleophile as the latter would require a five-bond $^{19}F$–$^{31}P$ coupling. We also speculated that the calculated Ag–P coupling constants, which are smaller within this generated complex, is an indication of how the larger trans-influence of the carbon within the azaallyl–Ag species weakens the Ag–P bond compared to the fluoride with

(XPhos)AgF. This provided evidence that the C–bound azaallyl silver species **2.60** is most likely the species formed in the stoichiometric reaction. However, in the catalytic reaction, **2.60** was not observed in a detectable quantity, likely due to reversibility of its formation and conversion to the azadiene **2.2** or its rapid transmetalation to Pd to deliver the desired product.

During the time of this work, developing an enantioselective variant was not realized successfully as the desired product was formed in only 64% yield and 64:36 er using a chiral P-stereogenic monodentate ligand (Scheme 31). This is most likely due to the reversibility of the insertion of fluoride, as well as the possibility of homolytic cleavage of the C–Ag or C–Pd bonds prior to reductive elimination. Only recently has an enantioselective fluoroarylation of *gem*-difluoroalkenes been performed using a novel sulfinamide catalyst.[187]

**Preliminary Results for Enantioselective Fluoroarylation:**




**Scheme 31: Development of an Enantioselective Fluoroarylation Reaction**

## 2.5 Conclusions and Outlook

In conclusion, we have developed a method for the construction of α-$CF_3$ benzylic amines enabled by vicinal fluoroarylation of *gem*-difluoro-2-azadienes. Prior to our work, $CF_3$ azaallyl anionic species had only been invoked in conjugate additions giving rise to a narrow range of products. We were able to demonstrate the cross-coupling of $CF_3$ azaallyl–Ag species with aryl iodides using a Pd(XPhos) catalyst. This reaction constitutes the first umpolung method of the construction of chiral α-$CF_3$ benzylic amines using difluoroazadienes as building blocks. A wide scope of sterically and electronically diverse aryl iodides were tolerated, providing the benzylic amines in good yields. Critical to the success of several challenging cross- couplings, such as sterically hindered and electron-poor aryl iodides, was the modification of the azadiene's activating group from a benzophenone imine to a benzylidene. Direct hydrolysis of the cross-coupled imines delivers the desired benzylic amines as their HCl salts under mild conditions. In addition, this method allows us to access a useful HDAC6 inhibitor in a concise manner.

Mechanistic studies indicate that the azaallyl species formed *in situ* in the reaction is the active participant in the coupling however, the exact nature of the Pd catalyst is not elucidated. Nevertheless, we were able to identify and characterize the α-trifluoromethyl azaallyl–Ag species by NMR spectroscopy. This was the first time such a species had been characterized spectroscopically.

## *2.6 Experimental Details*

Additional supporting information, including NMR spectra for new compounds can be found in the supporting information published online for:

Daniel, P. E.; Onyeagusi, C. I.; Ribeiro, A. A.; Li, K.; Malcolmson, S. J. Palladium-Catalyzed Synthesis of α-Trifluoromethyl Benzylic Amines *via* Fluoroarylation of *gem*-Difluoro-2-azadienes Enabled by Phosphine-Catalyzed Formation of an Azaallyl–Silver Intermediate. *ACS Catal.* **2019**, *9*, 205–210.

### 2.6.1 General Information

General Procedures. All reactions were carried out in oven- (120 °C) or flame-dried glassware under an inert atmosphere of dry $N_2$ unless otherwise noted. 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. Silica gel was deactivated in some cases by washing with two column volumes of 5:1:1 ethanol:methanol:$NEt_3$ followed by 5 column volumes of diethyl ether and drying under vacuum.

Reagents. The following chemicals were used as received: acetic acid (Alfa Aesar); $[(allyl)PdCl]_2$ (Sigma Aldrich); benzophenone imine (Chem-Impex); [1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene](3-chloropyridyl)palladium(II) dichloride (Sigma Aldrich); (*R*)-(–)-5,5′-Bis[di(3,5-di--butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (Strem); (*R*)-(+)-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-

biphenyl (Strem); 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos) (Strem); (R)-(+)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole (Strem); (R)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (Alfa Aesar); (R)-(+)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole (Strem); (R,R)-(–)-2,3-bis(tertbutylmethylphosphino)quinoxaline (Strem); 4-bromoanisole (Alfa Aesar); bromobenzene (Alfa Aesar); cesium fluoride (Sigma Aldrich); 4-chloroanisole (Sigma Aldrich); chlorodifluoroacetic acid (TCI); $[(cinnamyl)PdCl]_2$ (Sigma); copper(II)fluoride (Beantown); dicyclohexylphenylphosphine (Sigma Aldrich); 2-Dicyclohexylphosphino2′,6′-diisopropoxybiphenyl (RuPhos) (Sigma Aldrich); 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) (Sigma Aldrich); 2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl (BrettPhos) (Sigma Aldrich); 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) (Sigma Aldrich); 4-ethyliodobenzene (Alfa Aesar); iodine (Sigma Aldrich), 3-iodoanisole (Alfa Aesar); iodobenzene (TCI); 3-iodobenzotrifluoride (Sigma Aldrich); 4-iodobiphenyl (Sigma Aldrich); Aldrich); 2-iodonapthalene (Sigma Aldrich); 1-iodo-4-nitrobenzene (Alfa Aesar); 4-(4-iodophenyl)morpholine (Sigma Aldrich); 1-(4-iodophenyl)-pyrrole (Alfa Aesar); 2-iodotoluene (TCI); 4-iodotoluene (TCI); 4-iodothioanisole (Oakwood); 1-iodo-4-chlorobenzene (Oakwood); 5-iodo-2,3-dihydrobenzofuran (Matrix); 4-iodobenzophenone (Matrix); lithium bis(trimethylsilyl)amide (Sigma Aldrich); methyl 4-iodobenzoate (Alfa Aesar); N,N-dimethylformamide (Alfa Aesar),

N,Ndimethyltrifluoroacetamide (Oakwood); potassium fluoride (Alfa Aesar); rac-2-(di-tertbutylphosphino)-1,1′-binaphthyl (TrixiePhos) (Sigma); silver fluoride (>98%) (Alfa Aesar); sodium hydride (Strem); (2R,2′R,5R,5′R)-2,2′,5,5′-tetramethyl-1,1′-(ophenylene)diphospholane (Strem); toluene-d8 (Acros); tosyl chloride (Millipore Sigma); tricyclohexylphosphine (Acros); 2,2,2-trifluoroethylamine hydrochloride (TCI); triphenylphosphine (Alfa Aesar).

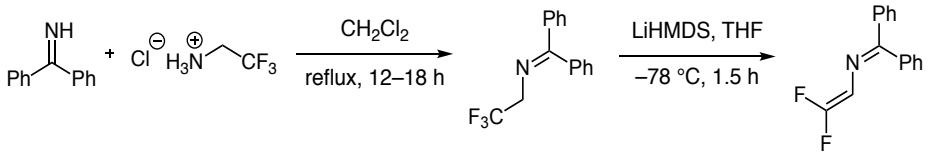
Solvents. Solvents were sparged with dry $N_2$ and purified under a positive pressure of dry $N_2$ by an Innovative Technologies PureSolve solvent purification system: tetrahydrofuran (Sigma-Aldrich), dichloromethane (Sigma-Aldrich), diethyl ether (Sigma-Aldrich), 1,4-dioxane (Sigma-Aldrich), and toluene (Sigma-Aldrich) were passed through two consecutive alumina columns. Anhydrous benzene (Sure/Seal™) was purchased from Sigma-Aldrich and used as received. Cyclohexane was dried over calcium hydride and distilled. Hexanes (Fisher), diethyl ether (Sigma-Aldrich), triethylamine (Sigma-Aldrich), methanol (BDH), ethanol (Fisher), and ethyl acetate (Fisher) for flash column chromatography were used as received.

Instrumentation. $^1$H-NMR spectra were recorded on a Varian INOVA (400 MHz), Varian Unity (500 MHz) or Varian/Agilent VNMRS (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting

from incomplete deuteration ($CDCl_3$: δ 7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). $^{13}$C-NMR spectra were recorded on a Varian Unity (400 MHz), Varian/Agilent VNMRS (500 MHz), or Bruker Avance III (700 MHz) spectrometer with complete proton decoupling but with fluorine coupling except where indicated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from chloroform as the internal reference ($CDCl_3$: $\delta$ 77.16). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). $^{19}$F-NMR spectra were recorded on a Varian/Agilent VNMRS (376 MHz) spectrometer. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). $^{31}$P-NMR spectra were recorded on a Varian/Agilent VNMRS (500 MHz) spectrometer. NMR yields were determined by internal standard (2,2,2-trifluoro-*N,N*-dimethylacetamide and toluene). $^{19}$F-NMR, $^{1}$H-NMR, and $^{31}$P-NMR experiments examining the structure of azaallyl–silver Intermediate were conducted on a Varian/Agilent VNMRS (500 MHz) with coupling and decoupling as indicated. High-resolution mass spectrometry was performed on an Agilent (1200 Series) LCMS-TOF-DART at the Duke University Mass Spectrometry Facility (HRMS data values reported as an average of four runs). Infrared (IR) spectra were collected on a Nicolet 6700 FT-IR spectrometer, $\upsilon_{max}$ in $cm^{-1}$. Bands are

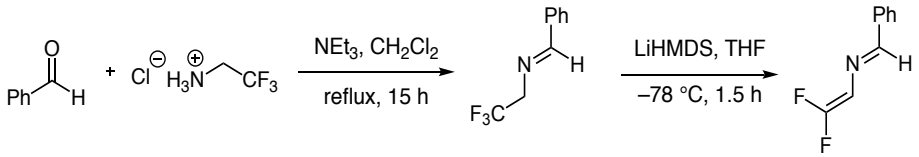
characterized as broad (br), strong (s), medium (m), or weak (w). Teledyne Isco, Nextgen 300+ system was used for automated column chromatography. For characterization of azaallyl–silver intermediate as well as [(XPhos)AgF], NMR spectra were obtained on an Agilent Direct Drive 500 MHz NMR spectrometer equipped with two high band RF channels. A 5 mm HFCN probe with high-band coil double-tuned for 500 MHz and 470 MHz was used for $^{1}$H, $^{19}$F, $^{19}$F-decoupled $^{1}$H and $^{1}$Hdecoupled $^{19}$F NMR experiments. The $^{1}$H 90° pulse was ~9.2 μs at 58 db and the $^{19}$F 90° pulse was ~14 μs at 58 dbpower. A 5 mm indirect detect probe with tunable high band coil was used for $^{1}$H, $^{1}$H-decoupled $^{31}$P, $^{19}$F, $^{19}$F-decoupled $^{31}$P, and $^{31}$Pdecoupled $^{19}$F NMR experiments. The $^{1}$H 90° pulse was ~8 μs at 58 db, the $^{19}$F 900 pulse was ~13 μs at 58 db power and the $^{31}$P 90° pulse was ~24 μs at 58 db power. Experiments were carried out at 25 °C.

### 2.6.2 Preparation of Azadiene Substrates




*N*-(2,2-difluorovinyl)-1,1-diphenylmethanimine (**2.2**). A flame-dried 250-mL round-bottom flask, equipped with stir bar, was charged with benzophenone imine (8.39 mL, 50.0 mmol, 1.00 equiv), dichloromethane (50 mL), and 2,2,2-trifluoroethylamine hydrochloride (8.13 g, 60.0 mmol, 1.20 equiv) and fitted with a reflux condenser. The mixture was allowed to stir and heat under reflux for 17 h. Upon cooling to room temperature, the mixture was filtered, and the filtrate was washed with one equal

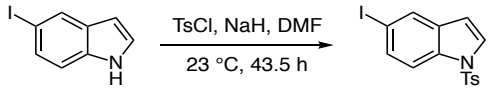
portion of saturated brine, dried over $Na_2SO_4$, filtered and concentrated to afford 2.1 as a white solid (10.5 g, 39.7 mmol, 79.0 %). **$^1$H NMR** (400 MHz, $CDCl_3$). δ 7.65 (2H, d, *J* = 6.8 Hz), 7.46–7.56 (3H, m), 7.41 (1H, d, *J* = 7.3 Hz), 7.34 (2H, t, *J* = 7.3 Hz), 7.15 (2H, dd, *J* = 2.1, 7.7 Hz), 3.85 (1H, q, *J* = 9.4 Hz). Spectral data matched those previously reported.[188] A portion of the solid (3.90 g, 15.0 mmol, 1.00 equiv) was dissolved in THF (45 mL) and the mixture cooled to –78 °C. A solution of LiHMDS (45 mL, 45 mmol, 1.0 M in THF, 3.0 equiv) was transferred by cannula to the cooled solution and the reaction mixture was allowed to stir at –78 °C for 1.5 h. The mixture was then filtered through celite (rinsed with ethyl acetate). The filtrate was concentrated and the resulting oil purified by flash column chromatography (100% hexanes to 49:1 hexanes:ethyl acetate) to afford the title compound as a white solid (2.45 g, 10.1 mmol, 67.0% yield). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 6.8 Hz), 7.53–7.43 (3H, m), 7.41–7.28 (4H, m), 7.18 (1H, dd, *J* = 7.6, 2.0 Hz), 5.97 (1H, d, *J* = 17.3 Hz). Spectral data matched those previously reported.[176]




(*E*)-*N*-(2,2-difluorovinyl)-1-phenylmethanimine (**2.29**). A flame-dried 250-mL round-bottom flask, equipped with stir bar, was charged with benzaldehyde (5.10 mL, 50.0 mmol, 1.00 equiv), dichloromethane (25 mL), 2,2,2-trifluoroethylamine hydrochloride (8.13 g, 60.0 mmol, 1.20 equiv), triethylamine (8.36 mL, 60.0 mmol, 1.20 equiv) and fitted with a reflux condenser. The mixture was allowed to heat under reflux

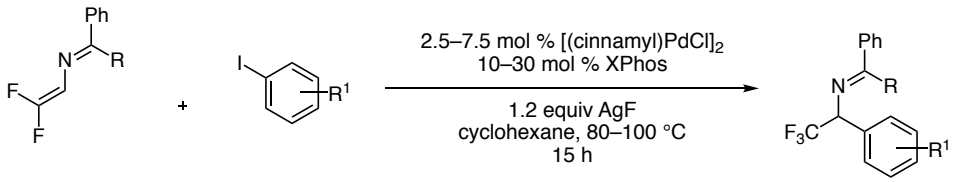
for 17 h. Upon cooling to room temperature, the mixture was filtered, and the filtrate was washed with one equal portion of saturated brine, dried over $Na_2SO_4$, filtered and concentrated to afford the title compound as a yellow oil (5.44 g, 29.1 mmol, 58.2% yield). **$^1$H NMR** (400 MHz, $CDCl_3$). δ 8.34 (1H, s), 7.77 (2H, d, J = 6.8 Hz), 7.41–7.47 (3H, m), 4.11 (1H, q, *J* = 9.1 Hz). Spectral data matched those previously reported.[189] A portion of the compound (1.90 g, 10.0 mmol, 1.00 equiv) was dissolved in THF (30 mL) and cooled to –78 °C. A solution of LiHMDS (30 mL, 30 mmol, 1.0 M in THF, 3 equiv) was transferred by cannula to the cooled solution, which was allowed to stir at –78 °C for 1.5 h. The mixture was filtered through celite (rinsed with ethyl acetate). The filtrate was concentrated and purified by vacuum distillation, affording 2.29 as a yellow oil (736 mg, 4.40 mmol, 44.0% yield). **IR** (thin film) 3066 (w), 2998 (w), 2876 (w), 1720 (s), 1609 (w), 1577 (w) $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.17 (1H, s), 7.77 (2H, dd, *J* = 7.2, 2.3 Hz), 7.47–7.35 (3H, m), 6.12 (1H, dd, *J* = 16.9, 1.4 Hz). **$^{13}$C NMR** (176 MHz, $CDCl_3$) δ 159.4 (dd, *J* = 12.4, 2.9 Hz), 157.8 (d, *J* = 16.9 Hz), 135.8, 131.2, 128.7, 128.3, 101.0 (dd, *J* = 42.9, 12.6 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ –85.27 (dd, *J* = 24.3, 17.0 Hz), 98.24 (d, *J* = 24.4 Hz); **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_9H_7F_2N$: 168.0619, found: 168.0622. Spectral data matched those previously reported.[190]

## 2.6.3 Preparation of Aryl Iodide Substrates



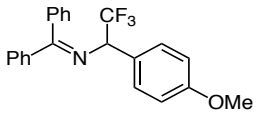

5-iodo-1-tosyl-1H-indole (**2.37**). A flame-dried 100-mL round-bottom flask, equipped with stir bar, was charged with 5-iodoindole (972 mg, 4.00 mmol, 1.00 equiv) and DMF (10.2 mL). NaH (60% in mineral oil) (240 mg, 6.00 mmol, 1.50 equiv) was added and the reaction mixture was allowed to stir 40 min at ambient temperature. A solution of tosyl chloride (991 mg, 5.20 mmol, 1.30 equiv) in DMF (5.2 mL) was added by cannula and the mixture was allowed to stir at ambient temperature for 44 h. The reaction was quenched with 5 mL of deionized water and diluted with ethyl acetate (10 mL). The organic layer was washed with five portions of deionized water, dried over $MgSO_4$, filtered and concentrated to afford 2.37 as an orange solid (695 mg, 1.75 mmol, 43.7% yield). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.84 (1H, s), 7.72 (3H, t, *J* = 8.0 Hz), 7.54 (1H, d, *J* = 8.7 Hz), 7.50 (1H, d, *J* = 3.4 Hz), 7.20 (2H, d, *J* = 7.9 Hz), 6.55 (1H, d, *J* = 7.9 Hz), 2.32 (3H, s). Spectral data matched those previously reported.[191]

## 2.6.4 Fluoroarylation of Difluoroazadienes



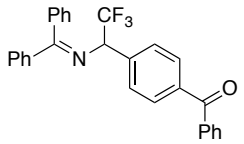

General Method A. In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial, equipped with stir bar, was charged with [(cinnamyl)PdCl]$_2$, XPhos, and

cyclohexane (250 μL). The mixture was allowed to stir 15 min at ambient temperature. Azadiene (0.15 mmol, 1.00 equiv), aryl iodide (0.15 mmol, 1.00 equiv), and silver fluoride (0.18 mmol, 1.20 equiv) were added sequentially, followed by cyclohexane (250 μL) to rinse the sides of the vial. The vial was sealed, removed from the glovebox and heated at the indicated temperature for 15 h while covered in aluminum foil. The reaction was then allowed to cool, filtered through a celite plug and rinsed with three volume portions of ethyl acetate. The solution was concentrated, and the residue purified by flash column chromatography with deactivated silica gel or by combiflash column chromatography with silica gel.

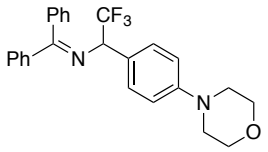



1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)methanimine (**2.16**). Title compound 2.16 prepared according to general method A (reaction at 100 °C with 2.5 mol % [(cinnamyl)PdCl]$_2$, 10 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a yellow solid (44.2 mg, 0.120 mmol, 79.7% yield). **IR** (thin film) 3061 (w), 2905 (w), 2837 (w), 2158 (w), 1625 (m), 1249 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.73–7.69 (2H, m), 7.45–7.38 (3H, m), 7.34 (2H, dd, $J$ = 8.3, 6.6 Hz), 7.28–7.24 (3H, m), 6.97 (2H, d, $J$ = 6.9 Hz), 6.86–6.82 (2H, m), 4.74 (1H, q, $J$ = 7.5 Hz), 3.78 (3H, s); **$^{13}$C NMR** (176 MHz, $CDCl_3$) $\delta$ 172.1, 156.6, 139.1, 136.3, 130.7, 130.3, 129.4, 128.9, 128.5, 128.2, 128.1, 127.5, 125.5 (q, $J_{CF}$ = 280.6 Hz), 124.6, 120.7, 110.4, 59.3 (q, $J_{CF}$ = 29.4 Hz), 55.3; **$^{19}$F**

**NMR** (376 MHz, $CDCl_3$) $\delta$ –74.11 (3F, d, $J_{HF}$ = 7.5 Hz); **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3NO$: 370.1413, found: 370.1416.

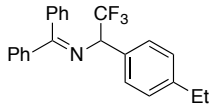



(4-(1-((diphenylmethylene)amino)-2,2,2-trifluoroethyl)phenyl)(phenyl)methanone (**2.17**). Title compound **2.17** prepared according to general method A (reaction at 80 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a white solid (49.6 mg, 0.112 mmol, 74.6% yield). **IR** (thin film) 3060 (w), 2361 (w), 1660 (m), 1126 (s) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.81–7.71 (6H, m), 7.60–7.56 (1H, m), 7.50–7.44 (8H, m), 7.38–7.34 (2H, m), 7.02–6.96 (2H, d, $J$ = 6.3 Hz), 4.90 (1H, q, $J$ = 7.3 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 196.2, 172.9, 139.9, 138.7, 137.8, 137.3, 135.4, 132.6, 131.1, 130.12, 130.1, 129.1, 129.1, 128.8, 128.7, 128.3, 128.2, 127.4, 124.7 (q, $J_{CF}$ = 281.0 Hz), 67.7 (q, $J_{CF}$ = 28.6 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.43 (3F, d, $J_{HF}$ = 7.3 Hz); **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{28}H_{20}F_3NO$: 444.1570, found: 444.1574.

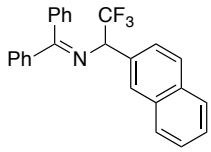



1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(4-morpholinophenyl)ethyl)methanimine (**2.18**). Title compound **2.18** prepared according to general method A (reaction at 100 °C with 5 mol % $[(cinnamyl)PdCl]_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow solid (28.5 mg, 0.0670 mmol, 44.8% yield). **IR** (thin

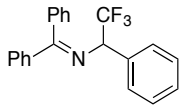
film) 3674 (br), 2971 (br), 2160 (br), 2056 (br), 1613 (w), 1517 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.73–7.66 (2H, m), 7.46–7.29 (6H, m), 7.27–7.22 (2H, m), 7.01–6.94 (2H, m), 6.87–6.81 (2H, m), 4.72 (1H, q, $J$ = 7.5 Hz), 3.84 (4H, t, $J$ = 4.8 Hz), 3.15 (5 H, dd, $J$ = 5.9, 3.4 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 171.7, 151.3, 139.0, 135.7, 130.7, 129.6, 129.0, 128.9, 128.5, 128.1, 127.6, 126.8, 125.1 (q, $J_{CF}$ = 280.3 Hz), 115.1, 67.4 (q, $J_{CF}$ = 28.9 Hz), 66.9, 48.9; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –74.03 (3F, d, $J_{HF}$ = 7.5 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 425.1835, found: 425.1833.




*N*-(1-(4-ethylphenyl)-2,2,2-trifluoroethyl)-1,1-diphenylmethanimine (**2.19**). Title compound **2.19** prepared according to general method A (reaction at 80 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a white solid (35.2 mg, 0.0977 mmol, 65.1% yield). **IR** (thin film) 3059 (w), 2966 (w), 1713 (w), 1625 (s) $cm^{-1}$, **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.73 (2H, dd, $J$ = 8.3, 1.5 Hz), 7.46–7.41 (4H, m), 7.37–7.33 (2H, m), 7.29 (2H, d, $J$ = 8.3 Hz), 7.15 (2H, d, $J$ = 8.0 Hz), 7.00 (2 H, dd, $J$ = 7.5, 1.8 Hz), 4.79 (1H, q, $J$ = 7.5 Hz), 2.64 (2H, q, $J$ = 7.5 Hz), 1.23 (3H, t, $J$ = 7.5 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 171.9, 144.7, 139.0, 135.6, 132.9, 130.8, 129.0, 128.9, 128.7, 128.5, 128.1, 127.9, 127.6, 125.1 (q, $J_{CF}$ = 280.6 Hz), 67.8 (q, $J_{CF}$ = 28.5 Hz), 28.6, 15.4; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.80 (3F, d, $J_{HF}$ = 7.5 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 368.1625, found: 368.1625.

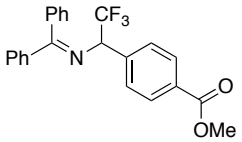


1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethyl)methanimine (**2.20**). Title compound **2.20** prepared according to general method A (reaction at 100 °C with 5 mol % [(cinnamyl)PdCl]$_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow oil (51.0 mg, 0.131 mmol, 87.3% yield). **IR** (thin film) 3059 (br), 1713 (w), 1625 (w); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.86–7.68 (5H, m), 7.58–7.31 (10H, m), 6.97 (2H, d, $J$ = 7.3 Hz), 4.96 (1H, q, $J$ = 7.9 Hz); **$^{13}$C NMR** (176 MHz, $CDCl_3$) $\delta$ 172.4, 138.9, 135.6, 133.4, 133.2, 133.1, 130.9, 129.1, 129.0, 128.6, 128.5, 128.3, 128.2, 128.2, 127.7, 127.6, 126.4, 126.2, 125.8, 125.1 (q, $J_{CF}$ = 280.6 Hz), 68.11 (q, $J_{CF}$ = 28.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.51 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{25}H_{18}F_3N$: 390.1464, found: 390.1460.

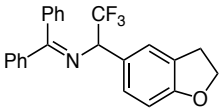


1,1-diphenyl-*N*-(2,2,2-trifluoro-1-phenylethyl)methanimine (**2.21**). Title compound **2.21** prepared according to general method A (reaction at 80 °C with 2.5 mol % [(cinnamyl)PdCl]$_2$, 10 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as yellow crystals (39.7 mg, 0.117 mmol, 78.0% yield). **IR** (thin film) 3063 (w), 1626 (m) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.89–7.61 (2H, m), 7.46–7.30 (11H, m), 6.98 (2H, d, $J$ = 6.1 Hz), 4.81 (1 H, q, $J$ = 7.4 Hz); **$^{13}$C NMR** (176 MHz, $CDCl_3$) $\delta$ 172.2,

138.9, 135.7, 135.6, 130.9, 129.0, 129.0, 128.8, 128.7, 128.6, 128.4, 128.2, 127.5, 125.0 (q, $J_{CF}$ = 280.7 Hz), 67.98 (q, $J_{CF}$ = 28.5 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.77 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 340.1308, found: 340.1314.

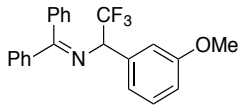



methyl 4-(1-((diphenylmethylene)amino)-2,2,2-trifluoroethyl)benzoate (**2.22**). Title compound **2.22** prepared according to general method A (reaction at 80 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow oil (43.0 mg, 0.108 mmol, 72.2% yield). **IR** (thin film) 2341 (m), 1726 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.99 (2H, d, $J$ = 8.3 Hz), 7.73 (2 H, d, $J$ = 6.9 Hz), 7.45–7.36 (8H, m), 6.95 (2H, d, $J$ = 6.7 Hz), 4.86 (1H, q, $J$ = 7.3 Hz), 3.91 (3H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 172.9, 166.7, 140.5, 138.6, 135.4, 131.1, 130.5, 129.7, 129.1, 129.0, 128.9, 128.7, 128.2, 127.4, 124.7 (q, $J_{CF}$ = 280.9 Hz), 68.7 (q, $J_{CF}$ = 29.5 Hz), 52.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.58 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{23}H_{18}F_3NO_2$: 398.1362, found: 398.1358.



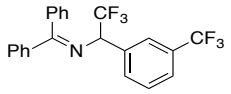

*N*-(1-(2,3-dihydrobenzofuran-5-yl)-2,2,2-trifluoroethyl)-1,1-diphenylmethanimine (**2.23**). Title compound **2.23** prepared according to general method A (reaction at 80 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, deactivated silica gel column

chromatography: 100% hexanes) and isolated as a white solid (38.3 mg, 0.100 mmol, 66.9% yield). **IR** (thin film) 3060 (w), 2896 (w), 1625 (m), 1156 (m) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.74–7.68 (2H, m), 7.46–7.39 (4H, m), 7.37–7.32 (2H, m), 7.27 (1H, m), 7.02–6.95 (3H, m), 6.69 (1H, d, $J$ = 8.2 Hz), 4.72 (1H, q, $J$ = 7.4 Hz), 4.56 (2H, t, $J$ = 8.8 Hz), 3.18 (2H, t, $J$ = 8.7 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 171.7, 160.4, 139.0, 135.6, 130.8, 129.0, 128.9, 128.7, 128.5, 128.1, 127.6, 127.6, 127.3, 125.3, 125.1 (q, $J_{CF}$ = 280.3 Hz), 109.0, 71.4, 67.5 (q, $J_{CF}$ = 28.6 Hz), 29.6; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –74.10 (3F, q, $J_{HF}$ = 7.5 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{23}H_{18}F_3NO$: 382.1413, found: 382.1418.

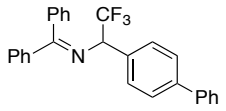



1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(3-methoxyphenyl)ethyl)methanimine (**2.24**). Title compound **2.24** prepared according to general method A (reaction at 100 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a yellow solid (48.6 mg, 0.131 mmol, 87.6% yield). **IR** (thin film) 3062 (w), 2837 (w), 1626 (m), 1260 (s), 1125 (s) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.75–7.71 (1H, m), 7.47–7.32 (7H, m), 7.27–7.18 (1H, m), 7.01–6.95 (3H, m), 6.91 (1H, d, $J$ = 7.6 Hz), 6.87 (1H, ddd, $J$ = 8.3, 2.8, 1.0 Hz), 4.78 (1H, q, $J$ = 7.4 Hz), 3.78 (3H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 172.2, 159.5, 138.9, 137.0, 135.6, 130.9, 129.4, 129.0, 129.0, 128.6, 128.1, 127.6, 124.9 (q, JCF = 280.7 Hz), 121.1, 114.5, 114.1, 67.9 (q, $J_{CF}$ = 28.2 Hz), 55.2; **$^{19}$F NMR**

(376 MHz, $CDCl_3$) $\delta$ –73.64 (3F, d, $J_{HF}$ = 7.5 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3NO$: 370.1413, found: 370.1416.

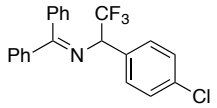



1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)ethyl)methanimine (**2.25**). Title compound **2.25** prepared according to general method A (reaction at 80 °C with 5 mol % $[(cinnamyl)PdCl]_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow oil (40.6 mg, 0.0997 mmol, 66.3% yield). **IR** (thin film) 3725 (w), 3628 (w), 2341 (s), 1626(m), 1166 (s) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.74–7.72 (2H, m), 7.59 (3H, m), 7.47–7.41 (5H, m), 7.39–7.35 (2H, m), 6.96 (2H, d, $J$ = 6.4 Hz), 4.87 (1H, q, $J$ = 7.3 Hz); **$^{13}$C NMR** (176 MHz, $CDCl_3$) $\delta$ 173.2, 138.6, 136.6, 135.4, 132.2, 131.2, 130.9 (q, $J_{CF}$ = 32.5 Hz), 129.2, 129.2, 129.0, 128.8, 127.3, 125.7 (dq, $J_{CF}$ = 22.8, 3.9 Hz), 124.7 (d, $J_{CF}$ = 281.0 Hz), 124.7, 123.1, 67.5 (q, $J_{CF}$ = 29.0 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.76 (3F, d, $J_{HF}$ = 7.2 Hz), –62.65 (3F, s); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{15}F_6N$: 408.1182, found: 408.1190.

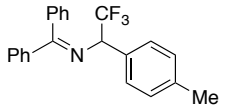



*N*-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)-1,1-diphenylmethanimine (**2.26**). Title compound **2.26** prepared according to general method A (reaction at 100 °C with 5 mol % $[(cinnamyl)PdCl]_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow oil (51.0 mg, 0.123 mmol, 81.8% yield). **IR** (thin film)

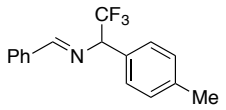
3059 (w), 1968 (w), 1626 (w) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.82–7.75 (m, 7H), 7.52–7.35 (m, 10H), 6.97 (2H, d, $J$ = 7.4 Hz), 4.97 (1 H, q, $J$ = 7.5 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 172.2, 141.5, 140.6, 138.9, 135.6, 134.7, 130.9, 129.2, 129.2, 129.0, 128.8, 128.6, 128.2, 127.6, 127.5, 127.2, 127.11, 125.0 (q, $J_{CF}$ = 280.7 Hz), 67.7 (q, $J_{CF}$ = 28.6 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.67 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{27}H_{20}F_3N$: 416.1621, found: 416.1622.




*N*-(1-(4-chlorophenyl)-2,2,2-trifluoroethyl)-1,1-diphenylmethanimine (**2.27**). Title compound **2.27** prepared according to general method A (reaction at 80 °C with 5 mol % $[(cinnamyl)PdCl]_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a white solid (38.2 mg, 0.102 mmol, 68.0% yield). **IR** (thin film) 3061 (w), 2907 (w), 1625 (m), 1126 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.78–7.69 (2H, m), 7.52–7.33 (7H, m), 7.31 (3H, s), 6.98 (2H, d, $J$ = 6.2 Hz), 4.79 (1H, q, $J$ = 7.3 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 172.6, 138.7, 135.4, 134.6, 134.1, 131.0, 130.4, 130.1, 129.1, 129.0, 128.7, 128.2, 127.4, 124.7 (q, $J_{CF}$ = 280.4 Hz), 67.3 (q, $J_{CF}$ = 28.7 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.91 (3F, d, $J_{HF}$ = 7.3 Hz); **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{21}H_{15}ClF_3N$: 374.0918, found: 374.0922.

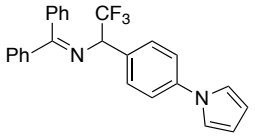



1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(p-tolyl)ethyl)methanimine (**2.38**). Title compound **2.38** prepared according to general method A (reaction at 100 °C with 2.5 mol % [(cinnamyl)PdCl]$_2$, 10 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a white solid (43.0 mg, 0.122 mmol, 81.1% yield). **IR** (thin film) 3059 (w), 2924 (w), 1626 (m), 1160 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.73 (2H, d, $J$ = 8.0 Hz), 7.46–7.41 (4H, m), 7.37–7.34 (2H, m), 7.26 (2H, d, $J$ = 8.0 Hz ), 7.13 (2H, d, $J$ = 8.0 Hz), 7.00 (2H, d, $J$ = 6.3 Hz), 4.78 (1H, q, $J$ = 7.5 Hz), 2.34 (3H, s). **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 171.9, 139.0, 138.4, 135.6, 132.7, 130.8, 129.1, 129.0, 128.9, 128.6, 128.5, 128.1, 127.6, 125.1 (q, $J_{CF}$ = 279.5 Hz), 67.7 (q, $J_{CF}$ = 27.8 Hz), 21.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.86 (3F, d, $J_{HF}$ = 7.5 Hz); **HRMS** (ESI$^+$) [M+H]$^+$ calc'd for $C_{22}H_{18}F_3N$: 354.1464, found: 354.1462.

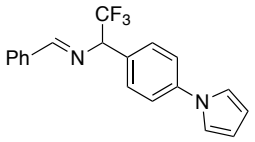



(*E*)-1-phenyl-*N*-(2,2,2-trifluoro-1-(p-tolyl)ethyl)methanimine (**2.39**). Title compound **2.39** prepared according to general method A (reaction at 100 °C with 2.5 mol % [(cinnamyl)PdCl]$_2$, 10 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a yellow oil (32.0 mg, 0.115 mmol, 76.9% yield). **IR** (thin film) 3031 (w), 2925 (w), 2867 (w), 1647 (m), 1581 (s), 1513 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.36 (1H, s), 7.82 (2H, dd, $J$ = 7.8, 1.6 Hz), 7.46–7.40 (5H, m), 7.19 (2H, d, $J$ = 8.0

Hz), 4.76 (1 H, q, $J$ = 7.6 Hz), 2.35 (3H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.6, 138.8, 135.4, 132.04, 131.6, 129.3, 128.8, 128.6, 124.7 (q, $J_{CF}$ = 281.2 Hz), 74.8 (q, $J_{CF}$ = 28.5 Hz), 21.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –74.00 (d, $J_{HF}$ = 7.7 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{16}H_{14}F_3N$: 278.1151, found: 278.1149.

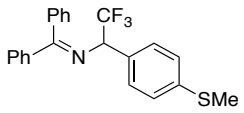



*N*-(1-(4-(1H-pyrrol-1-yl)phenyl)-2,2,2-trifluoroethyl)-1,1-diphenylmethanimine (**2.40**). Title compound **2.40** prepared according to general method A (reaction at 100 °C with 7.5 mol % $[(cinnamyl)PdCl]_2$, 30 mol % XPhos) and not isolated (63% conversion by internal standard).

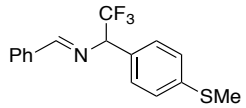



(*E*)-*N*-(1-(4-(1H-pyrrol-1-yl)phenyl)-2,2,2-trifluoroethyl)-1-phenylmethanimine (**2.41**). Title compound **2.41** prepared according to general method A (reaction at 100 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a yellow solid (43.0 mg, 0.131 mmol, 87.3% yield). **IR** (thin film) 2872 (br), 1646 (w), 1522 (m) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.41 (1H, s) 7.85 (2H, dd, $J$ = 7.9, 1.5 Hz), 7.62 (2H, d, $J$ = 8.4 Hz), 7.48–7.40 (5H, m), 7.09 (2H, t, $J$ = 2.2 Hz), 6.35 (2H, t, $J$ = 2.2 Hz), 4.82 (1 H, q, $J$ = 7.5 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 166.0, 141.1, 135.2, 132.2, 131.8, 130.0, 128.8, 128.7, 124.5 (q, $J_{CF}$ = 281.0 Hz), 120.4,

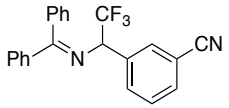
119.2, 110.7, 74.7 (q, $J_{CF}$ = 28.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.99 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 329.1260, found: 329.1258.



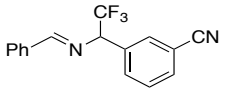

1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(4-(methylthio)phenyl)ethyl)methanimine (**2.42**). Title compound **2.42** prepared according to general method A (reaction at 100 °C with 5 mol % [(cinnamyl)PdCl]$_2$, 20 mol % XPhos) and not isolated (85% conversion by internal standard).




(*E*)-1-phenyl-*N*-(2,2,2-trifluoro-1-(4-(methylthio)phenyl)ethyl)methanimine (**2.43**). Title compound **2.43** prepared according to general method A (reaction at 100 °C with 5 mol % [(cinnamyl)PdCl]$_2$, 20 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as an orange oil (40.5 mg, 0.131 mmol, 87.3% yield). **IR** (thin film) 2924 (br), 1626 (s), 1560 cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.36 (1H, s), 7.82 (2H, dd, $J$ = 8.0, 1.7 Hz), 7.52–7.37 (5H, m), 7.25 (2H, d, $J$ = 8.2 Hz), 4.75 (1H, q, $J$ = 7.5 Hz), 2.47 (2 H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.8, 139.6, 135.3, 131.7, 131.6, 129.1, 128.8, 128.7, 126.4, 124.6 (q, $J_{CF}$ = 281.5 Hz), 74.6 (q, $J_{CF}$ = 28.7 Hz), 15.6; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –74.02 (3F, d, JHF = 7.6 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 310.0872, found: 310.0869.

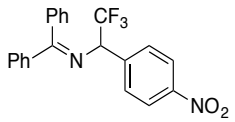


3-(1-((diphenylmethylene)amino)-2,2,2-trifluoroethyl)benzonitrile (**2.44**). Title compound **2.44** prepared according to general method A (reaction at 100 °C with 7.5 mol % [(cinnamyl)PdCl]$_2$, 30 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow oil (29.6 mg, 0.0812 mmol, 54.1% yield). **IR** (thin film) 3062 (w), 2926 (w), 2231 (w), 2032 (w), 1626 (m), 1171 (m) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.73–7.68 (3H, m), 7.64–7.60 (2H, m), 7.48–7.42 (5H, m), 7.39–7.35 (2H, m), 6.95 (2H, d, $J$ = 6.4 Hz), 4.83 (1H, q, $J$ = 7.2 Hz); **$^{13}$C NMR** (176 MHz, $CDCl_3$) $\delta$ 173.6, 138.4, 137.2, 135.3, 133.2, 132.5, 132.4, 131.4, 129.4, 129.3, 129.1, 128.9, 128.3, 127.3, 124.5 (q, $J_{CF}$ = 280.8 Hz), 118.4, 112.8, 67.2 (q, $J_{CF}$ = 29.2 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.75 (3F, d, $J_{HF}$ = 7.2 Hz); **HRMS** (ESI$^+$) [M+H]$^+$ calc'd for $C_{22}H_{15}F_3N_2$: 365.1260, found: 365.1265.

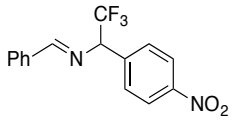


(*E*)-3-(1-(benzylideneamino)-2,2,2-trifluoroethyl)benzonitrile (**2.45**). Title compound **2.45** prepared according to general method A (reaction at 100 °C with 2.5 mol % [(cinnamyl)PdCl]$_2$, 10 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a yellow oil (37.0 mg, 0.130 mmol, 86.7% yield). **IR** (thin film) 3065 (w), 2873 (w), 2231 (m), 1646 (s), 1127 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.41 (1H, s), 7.92 (1H, s), 7.86–7.80 (3H, m), 7.64 (1H, dt, $J$ = 7.8, 1.4 Hz), 7.52–7.43 (4H, m), 4.81 (1H, q, $J$ = 7.3 Hz ); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 166.9, 136.5, 134.9, 133.2, 132.5,

132.5, 132.1, 129.41, 129.0, 128.8, 125.2, 124.0 (q, $J_{CF}$ = 281.1 Hz), 118.4, 112.9, 74.4 (q, $J_{CF}$ = 29.1 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –74.02 (3F, d, $J_{HF}$ = 7.3 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{16}H_{11}F_3N_2$: 289.0947, found: 289.0944.

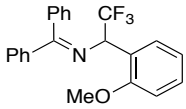



1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(4-nitrophenyl)ethyl)methanimine (**2.46**). Title compound **2.46** prepared according to general method A (reaction at 80 °C with 5 mol % $[(cinnamyl)PdCl]_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow oil (21.3 mg, 0.0552 mmol, 36.8% yield). **IR** (thin film) 3061 (w). 2907 (w), 1625 (w), 1169 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.18 (2H, d, $J$ = 8.9Hz), 7.72 (2H, m ), 7.56 (2H, d, $J$ = 8.5 Hz), 7.50–7.41 (4H, m), 7.39–7.35 (2H, m), 6.95 (2H, d, $J$ = 7.2 Hz), 4.91 (1H, q, $J$ = 7.2 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 173.7, 148.2, 142.5, 138.4, 135.2, 131.4, 129.8, 129.3, 129.1, 128.9, 128.3, 127.3, 124.4 (d, $J_{CF}$ = 280.7 Hz), 123.6, 67.3 (q, $J_{CF}$ = 29.2 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.47 (3F, d, $J_{HF}$ = 7.2 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{21}H_{15}F_3N_2O_2$: 385.1158, found: 385.1167.

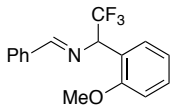



(*E*)-1-phenyl-*N*-(2,2,2-trifluoro-1-(4-nitrophenyl)ethyl)methanimine (**2.47**). Title compound **2.47** prepared according to general method A (reaction at 100 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, deactivated silica gel column chromatography:

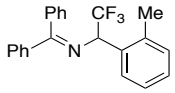
100% hexanes) and isolated as a yellow oil (38.0 mg, 0.123 mmol, 82.2% yield). **IR** (thin film) 3064 (br), 2876 (br), 2209 (w), 2039 (w), 1976 (w), 1646 (m), 1604 (m), 1526 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.25 (2H, d, J = 8.2 Hz), 7.86–7.83 (2H, m), 7.78 (2H, d, $J$ = 8.6 Hz), 7.56–7.39 (3H, m), 4.88 (1H, q, $J$ = 7.2 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 167.0, 148.3, 141.7, 134.8, 132.2, 129.8, 129.0, 128.8, 124.1(q, $J_{CF}$ = 281.1 Hz), 123.7, 74.5 (q, $J_{CF}$ = 29.2 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.70 (3F, d, $J_{HF}$ = 7.3 Hz); **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{15}H_{11}F_3N_2O_2$: 309.0845, found: 309.0846.




1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(2-methoxyphenyl)ethyl)methanimine (**2.48**). Title compound **2.48** prepared according to general method A (reaction at 100 °C with 5 mol % $[(cinnamyl)PdCl]_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as an off-white solid (25.0 mg, 0.0600 mmol, 40.1% yield). **IR** (thin film) 3060 (w), 2935 (w), 1625 (w) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.74–7.69 (3H, m), 7.41–7.30 (7H, m), 6.96–6.87 (3H, m), 6.75 (1H, d, J = 8.4), 5.47 (1H, d, J = 7.6 Hz), 3.50 (3H, s); **$^{13}$C NMR** (176 MHz, $CDCl_3$) $\delta$ 172.1, 156.6, 139.1, 136.3, 130.7, 130.3, 129.4, 128.9, 128.5, 128.2, 128.1, 127.5, 125.5 (q, $J_{CF}$ = 280.6 Hz), 124.6, 120.7, 110.4, 59.4 (q, $J_{CF}$ = 29.3 Hz), 55.3; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –74.08 (3F, d, $J_{HF}$ = 7.6 Hz); **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3NO$: 370.1413, found: 370.1424.

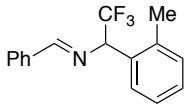


(*E*)-1-phenyl-*N*-(2,2,2-trifluoro-1-(2-methoxyphenyl)ethyl)methanimine (**2.49**). Title compound **2.49** prepared according to general method A (reaction at 100 °C with 2.5 mol % [(cinnamyl)PdCl]$_2$, 10 mol % XPhos, flash column chromatography with deactivated silica gel: 100% hexanes) and isolated as a yellow solid (39.5 mg, 0.135 mmol, 89.8% yield). **IR** (thin film) 2938 (w), 2160 (br), 2028 (br), 1975 (br), 1645 (m), 1602 (s), 1585 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.30 (1H, s), 7.73 (2H, dd, $J$ = 7.8, 1.8), 7.66 (1H, d, $J$ =7.7 Hz), 7.37–7.30 (3H, m), 7.24 (1H, ddd, $J$ = 8.8, 7.6, 1.8 Hz), 6.92 (1H, t, $J$ = 7.1 Hz), 6.84 (1H, d, $J$ = 8.3 Hz), 5.44 (1H, q, $J$ = 7.7 Hz), 3.79 (3H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.7, 157.0, 135.6, 131.4, 130.0, 129.7, 128.7, 128.6, 123.4, 125.1 (q, $J_{CF}$ = 281.0 Hz), 120.9, 110.7, 66.3 (q, $J_{CF}$ = 28.5 Hz), 55.7; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.63 (3F, d, $J_{HF}$ = 7.7 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 294.1100, found: 294.1095.

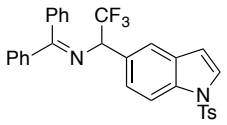


1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(o-tolyl)ethyl)methanimine (**2.50**). Title compound **2.50** prepared according to general method A (reaction at 100 °C with 5 mol % [(cinnamyl)PdCl]$_2$, 20 mol % XPhos, combiflash column chromatography: 100% hexanes) and isolated as a yellow oil (31.0 mg, 0.0830 mmol, 55.5% yield). **IR** (thin film) 3734 (w), 3061 (w), 2931 (w), 2159 (w), 2025 (w), 1625 (w) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.79–7.69 (3H, m), 7.44–7.31 (6H, m), 7.23–7.14 (3H, m), 7.07–7.01 (1H, m), 6.90 (1H, d, $J$ = 7.1

Hz), 5.08 (1H, q, $J$ = 7.4 Hz), 1.76 (3H, s); **$^{13}$C NMR** (176 MHz, $CDCl_3$) $\delta$ 171.9, 138.8, 136.3, 136.3, 134.5, 130.8, 130.1, 129.7, 128.9, 128.8, 128.7, 128.2, 128.1, 127.3, 126.2, 125.6 (d, $J_{CF}$ = 280.7 Hz), 63.2 (q, $J_{CF}$ = 28.9 Hz), 18.9; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.78, $J_{HF}$ = 7.3); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 354.1464, found: 354.1472.

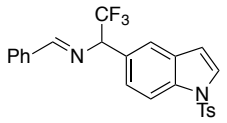



(*E*)-1-phenyl-*N*-(2,2,2-trifluoro-1-(o-tolyl)ethyl)methanimine (**2.51**). Title compound **2.51** prepared according to general method A (reaction at 100 °C with 2.5 mol % $[(cinnamyl)PdCl]_2$, 10 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a white solid (33.6 mg, 0.121 mmol, 80.7% yield). **IR** (thin film) 3854 (w), 3750 (w), 2872 (w),), 2049 (s), 1646 (m), 1129 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.35 (1H, s), 7.81 (2H, dd, $J$ = 7.5, 1.3 Hz), 7.75 (1H, m), 7.45–7.39 (3H, m), 7.24–7.21 (3H, m) 5.13 (1H, q, $J$ = 7.5 Hz), 2.45 (3H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.5, 136.4, 135.4, 133.5, 131.6, 130.6, 129.5, 128.7, 128.6, 128.5, 126.3, 125.1 (q, $J_{CF}$ = 280.9 Hz), 70.6 (q, $J_{CF}$ = 28.2 Hz), 19.9; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.46 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{18}F_3N$: 278.1151, found: 278.1143.



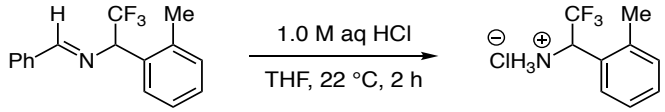

1,1-diphenyl-*N*-(2,2,2-trifluoro-1-(1-tosyl-1H-indol-5-yl)ethyl)methanimine (**2.52**). Title compound **2.52** prepared according to general method A (reaction at 100 °C with 7.5 mol

% [(cinnamyl)PdCl]$_2$, 30 mol % XPhos) and not isolated (17% conversion by internal standard).

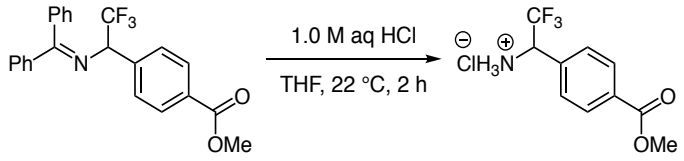



(*E*)-1-phenyl-*N*-(2,2,2-trifluoro-1-(1-tosyl-1H-indol-5-yl)ethyl)methanimine (**2.53**). Title compound **2.53** prepared according to general method A (reaction at 100 °C with 7.5 mol % [(cinnamyl)PdCl]$_2$, 30 mol % XPhos, deactivated silica gel column chromatography: 100% hexanes) and isolated as a colorless film (31.0 mg, 0.0679 mmol, 45.3% yield). **IR** (thin film) 2924 (br), 2362 (br), 1646 (m), 1597 (w), 1581 (w) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.36 (s, 1H), 7.97 (1H, d, $J$ = 8.6 Hz), 7.82 (2H, dd, $J$ = 7.8, 1.5 Hz), 7.76–7.74 (3H, m), 7.57 (1H, d, $J$ = 3.7 Hz), 7.50–7.38 (4H, m), 7.21 (2H, d, $J$ = 8.2 Hz), 6.65 (1H, d, $J$ = 3.6 Hz), 4.84 (1H, q, $J$ = 7.5 Hz), 2.32 (3H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.8, 145.1, 135.3, 135.2, 134.9, 131.7, 130.8, 130.1, 130.0, 128.8, 128.7, 127.0, 126.8, 125.1, 124.7 (q, $J_{CF}$ = 280.9 Hz), 121.9, 113.5, 108.9, 75.0 (q, $J_{CF}$ = 28.7 Hz), 65.87, 21.56; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –73.92 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) [M+H]$^+$ calc'd for $C_{24}H_{19}F_3N_2O_2S$: 457.1192, found: 457.1191.

## 2.6.5 Hydrolysis of Imines in Products



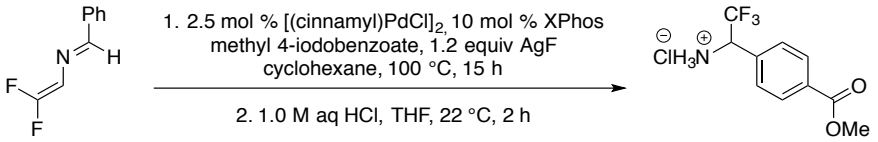

2,2,2-trifluoro-1-(*m*-tolyl)ethan-1-aminium chloride (**2.57**). A 2-dram vial, equipped with stir bar, was charged with imine (33.1 mg, 0.119 mmol, 1.00 equiv), THF (0.750 mL), and 1.0 M aq HCl (0.750 mL). The mixture was allowed to stir for 2 h at 22 °C whereupon it was diluted with an additional 0.750 mL of 1.0 M aq HCl. The solution was diluted with diethyl ether (2 mL) and the layers partitioned. The aqueous layer was washed with additional diethyl ether (2 x 2 mL). The aqueous layer was collected and concentrated to afford **2.57** as a white solid (21.3 mg, 0.0944 mmol, 79.3% yield). **IR** (solid) 2965 (w), 2107 (br), 1498 (w) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CD_3OD$) $\delta$ 7.57 (1H, d, $J$ = 7.1 Hz), 7.38–7.46 (3H, m), 5.55 (1H, q, $J$ = 7.3 Hz), 2.48 (3H, s); **$^{13}$C NMR** (126 MHz, $CD_3OD$) $\delta$ 138.1, 131.3, 130.5, 126.8, 126.6, 126.5, 123.7 (q, $J_{CF}$ = 281.4 Hz) 51.4 (q, $J_{CF}$ = 32.4 Hz), 18.2; **$^{19}$F NMR** (376 MHz, $CD_3OD$) $\delta$ –76.26 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_9H_{11}F_3N$: 190.0838, found: 190.0834.




2,2,2-trifluoro-1-(4-(methoxycarbonyl)phenyl)ethan-1-aminium chloride (**2.58**). A 2-dram vial, equipped with stir bar, was charged with imine (59.6 mg, 0.150 mmol, 1.00 equiv), THF (0.75 mL), and 1.0 M aq HCl (0.750 mL). The mixture was allowed to stir for 2 h at

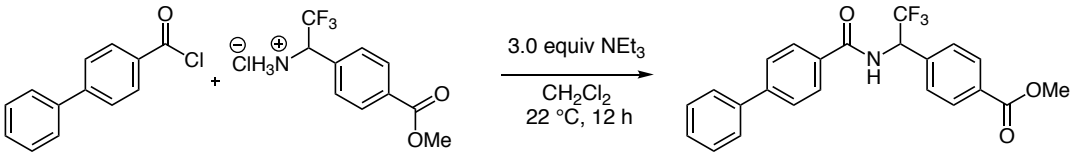
22 °C whereupon it was diluted with an additional 0.750 mL of 1.0 M aq HCl. The solution was diluted with diethyl ether (2 mL) and the layers partitioned. The aqueous layer was washed with additional diethyl ether (2 x 2 mL). The aqueous layer was collected and concentrated to afford **2.58** as a white solid (33.0 mg, 0.122 mmol, 81.6% yield). **IR** (solid) 2798 (br), 1726 (m), 1573 (w), 1519 (m) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CD_3OD$) $\delta$ 8.16 (2H, d, $J$ = 8.4 Hz), 7.71 (2H, d, $J$ = 8.1 Hz), 5.52 (1H, q, $J$ = 7.4 Hz), 3.92 (3H, s); **$^{13}$C NMR** (126 MHz, $CD_3OD$) $\delta$ 165.9, 132.8, 132.4, 130.0, 128.6, 123.2 (q, $J_{CF}$ = 280.6 Hz), 54.9 (q, $J_{CF}$ = 33.0 Hz), 51.6; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –74.61 (3F, d, $J_{HF}$ = 7.4 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{10}H_{11}F_3NO_2$: 234.0736, found: 234.0735.

### 2.6.6 Synthesis of HDAC6 Inhibitor



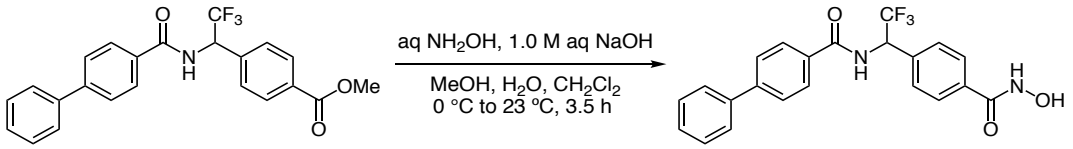

2,2,2-trifluoro-1-(4-(methoxycarbonyl)phenyl)ethan-1-aminium chloride (**2.58**). In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial, equipped with stir bar, was charged with $[(cinnamyl)PdCl]_2$ (51.8 mg, 0.100 mmol, 0.0250 equiv), XPhos (191 mg, 0.400 mmol, 0.100 equiv), and cyclohexane (6.67 mL). The mixture was allowed to stir 15 min at ambient temperature. Azadiene **2.29** (669 mg, 4.00 mmol, 1.00 equiv), methyl 4-iodobenzoate (1.05 g, 4.00 mmol, 1.00 equiv), and silver fluoride (609 mg, 4.80 mmol, 1.20 equiv) were added sequentially, followed by cyclohexane (6.67 mL) to rinse the sides of the vial. The vial was sealed, removed from the glovebox and heated at 100 °C

for 15 h while covered in aluminum foil. The reaction was then allowed to cool, filtered through a celite plug, and rinsed with three portions (3 x 10 mL) of ethyl acetate. The solution was concentrated, and the residue was dissolved in THF (10.0 mL) and 1.0 M aq HCl (10.0 mL). The mixture was allowed to stir for 2 h at 22 °C whereupon it was diluted with an additional 10.0 mL of 1.0 M aq HCl. The solution was diluted with diethyl ether (10 mL) and the layers partitioned. The aqueous layer was washed with additional diethyl ether (2 x 20 mL). The aqueous layer was collected and concentrated to afford 2.58 as a yellow solid (912 mg, 3.38 mmol, 84.6% yield).




methyl 4-(1-([1,1'-biphenyl]-4-carboxamido)-2,2,2-trifluoroethyl)benzoate. An oven-dried (120 °C) microwave vial, equipped with stir bar, was charged with ammonium salt 2.58 (912 mg, 3.38 mmol, 1.00 equiv), $NEt_3$ (1.40 mL, 10.2 mmol, 3.00 equiv), and $CH_2Cl_2$ (11.3 mL). To this solution was added the acid chloride (732 mg, 3.38 mmol, 1.00 equiv) and $CH_2Cl_2$ (11.3 mL). Upon completion, the mixture was dissolved in water (10.0 mL) and dichloromethane (10.0 mL). The organic layer was washed with saturated aqueous ammonium chloride (2 x 10.0 mL), water (2 x 10.0 mL), and brine (10.0 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the title compound as an off-white solid (1.09 g, 2.63 mmol, 77.8%). **IR** (thin film) 2360 (m), 1533 (w), $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$ + 1 drop of $CD_3OD$ for solubility) $\delta$ 8.08 (2H, d, $J$ = 8.2 Hz), 7.87

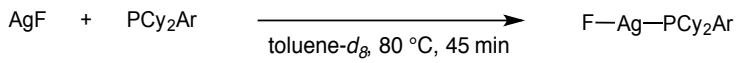
(2H, d, $J$ = 8.2 Hz), 7.69 (2H, d, $J$ = 8.3 Hz), 7.59 (2H, d, $J$ = 7.2 Hz), 7.55 (2H, d, $J$ = 8.1 Hz), 7.46 (t, 2H, $J$ = 7.4 Hz), 7.39 (1H, t, $J$ = 7.3 Hz), 6.72 (1H, d, $J$ = 9.5 Hz), 6.08–5.96 (1H, m); **$^{13}$C NMR** (176 MHz, $CDCl_3$ + 1 drop of $CD_3OD$ for solubility) $\delta$ 167.7, 166.7, 145.0, 139.7, 137.9, 131.7, 130.7, 130.0, 128.9, 128.2, 128.1, 128.0, 127.1, 127.1, 124.4 (q, $J_{HF}$ = 281.0 Hz), 54.6 (q, $J_{HF}$ = 31.6 Hz), 52.3; **$^{19}$F NMR** (376 MHz, $CDCl_3$ + 1 drop of $CD_3OD$ for solubility) $\delta$ –73.16 (3F, d, JHF = 8.0 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{23}H_{18}F_3NO_3$: 414.1312, found: 414.1311.



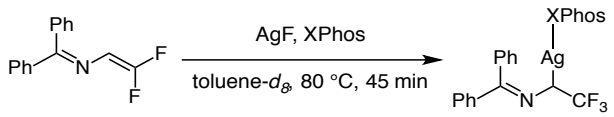

*N*-(2,2,2-trifluoro-1-(4-(hydroxycarbamoyl)phenyl)ethyl)-[1,1'-biphenyl]-4-carboxamide (**2.59**). A flame-dried 100-mL round-bottom flask, equipped with stir bar, was charged with ester (207 mg, 0.500 mmol, 1.00 equiv), dichloromethane (5.0 mL), and methanol (6.5 mL). The mixture was allowed to cool to 0 °C and hydroxylamine (2.0 mL, 0.030 mol, 60. equiv) and sodium hydroxide (100 mg, 2.5 mmol, 5.0 equiv) were added. The mixture was allowed to stir 15 min at 0 °C and then allowed to warm to room temperature. After 1.5 h, the mixture was concentrated, and the resulting residue partially dissolved in ethyl acetate (10.0 mL) and diluted with 1.0 M aq HCl (10.0 mL). The layers were separated. The organic layer was washed with brine and then concentrated. The solid was rinsed with dichloromethane and **2.59** was collected as a pale pink solid (95.5 mg, 0.229 mmol, 45.9%). **IR** (solid) 3281 (br), 2468 (w), 1641 (m),

1610 (m), 1573 (m), 1536 (m), 1511 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 11.23 (1H, s), 9.56 (1H, d, J = 8.9 Hz), 9.08 (1H, s), 7.98 (2H, d, $J$ = 8.4 Hz), 7.82–7.74 (6H, m), 7.73–7.68 (3H, m), 7.47 (2H, dd, $J$ = 6.6 Hz), 7.39 (1H, dd, $J$ = 8.6 Hz), 6.26–5.98 (1H, m); **$^{13}$C NMR** (126 MHz, DMSO-$d_6$, $^1$H and $^{19}$F decoupled) $\delta$ 166.7, 163.7, 143.5, 139.0, 136.1, 133.5, 132.0, 129.1, 128.8, 128.7, 128.2, 127.2, 127.0, 126.6, 124.8, 53.7, 40.0, 39.9, 39.7, 39.5, 39.4, 39.2, 39.0; **$^{19}$F NMR** (376 MHz, DMSO-$d_6$) $\delta$ –71.75 (3F, d, $J_{HF}$ = 8.9 Hz); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{17}F_3N_2O_3$: 415.1264, found: 415.1260.

### 2.6.7 NMR Studies: Characterization of Azaallyl–Silver Intermediate

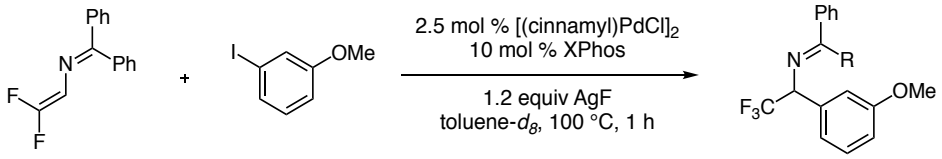



Procedure for generation of Silver Fluoride Monophosphine Complex **2.62.** In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial, equipped with stir bar, was charged with AgF (6.3 mg, 0.050 mmol, 1.0 equiv), XPhos (23.8 mg, 0.0500 mmol, 1.00 equiv) and toluene-$d_8$ (500 μL). The vial was sealed and covered in aluminum foil. The mixture was then heated to 80 °C for 45 min. The reaction was then allowed to cool and transferred to an NMR tube, which was sealed for analysis at 25 °C.




Procedure for generation of Azaallyl-Silver Intermediate **2.60** In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial, equipped with stir bar, was charged with AgF (6.3 mg, 0.050 mmol, 1.0 equiv), XPhos (23.8 mg, 0.0500 mmol, 1.00 equiv) and toluene-$d_8$

(250 μL). The mixture was allowed to stir 15 min at ambient temperature. Azadiene 2.2 (12.3 mg, 0.050 mmol, 1.00 equiv) and toluene-$d_8$ (250 μL) were added. The vial was sealed and covered in aluminum foil. The mixture was then heated to 80 °C for 45 min. The reaction was then allowed to cool and transferred to an NMR tube, which was sealed for analysis at 25 °C.




<u>Procedure for *in situ* NMR monitoring of reaction progress.</u> In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial, equipped with stir bar, was charged with [(cinnamyl)PdCl]$_2$ (1.9 mg, 0.0040 mmol, 0.025 equiv), XPhos (7.2 mg, 0.015 mmol, 0.10 equiv) and toluene-$d_8$ (250 μL). The mixture was allowed to stir 15 min at ambient temperature. Azadiene **2.2** (36.5 mg, 0.150 mmol, 1.00 equiv), 3-iodoanisole (35.1 mg, 0.150 mmol, 1.00 equiv), and silver fluoride (22.8 mg, 0.180 mmol, 1.20 equiv) were added sequentially, followed by toluene-$d_8$ (250 μL) to rinse the sides of the vial. The vial was sealed and covered in aluminum foil. The mixture was then heated to 100 °C for 1 h. The reaction was then allowed to cool and transferred to an NMR tube, which was sealed for analysis at 25 °C. Intermediate **2.60** was not observed in a detectable quantity, and a number of unidentifiable products were formed in this reaction.

# 3. Enantio- and Diastereoselective Synthesis of α-Trifluoromethyl Homoallylic Amines by Catalytic Hydroalkylation of Dienes

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Onyeagusi, C. I.; Shao, X.; Malcolmson, S. J. Enantio- and Diastereoselective Synthesis of α-Trifluoromethyl Homoallylic Amines by Catalytic Hydroalkylation of Dienes. *Org Lett.* **2020**, *22*, 1681–1685.

This work was done in collaboration with Xinxin Shao.

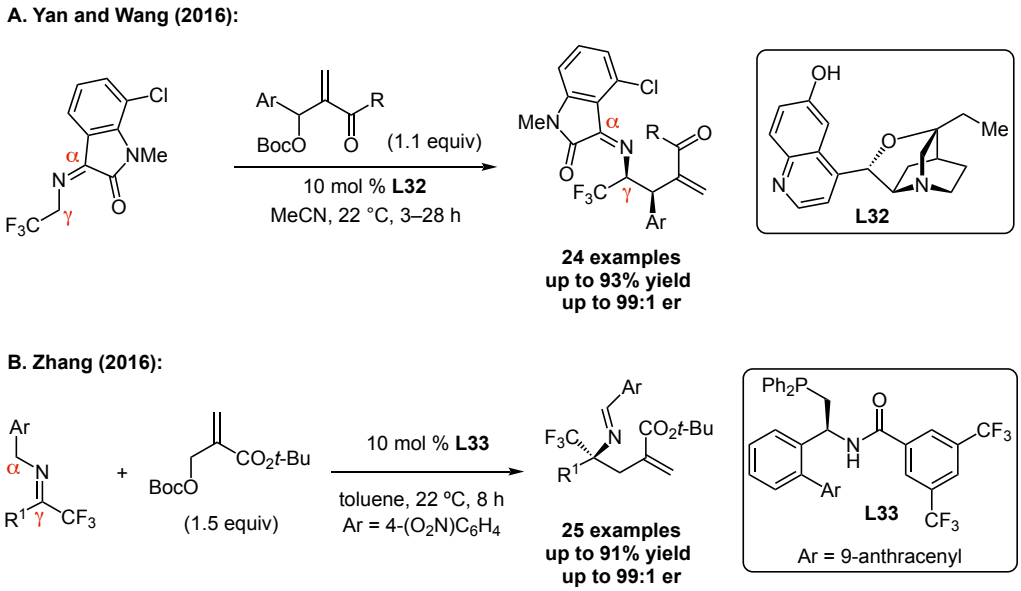
## *3.1 Introduction*

Chiral homoallylic amines are valuable building blocks for biologically relevant compounds.[192-193] They are synthetically useful as precursors for α-amino acids,[194] heterocycles,[195] as well as intermediates in the synthesis of complex natural products. While approaches for preparing chiral homoallylic amines are abundant, methods of accessing the fluorinated versions of this moiety represent an underexplored area. The need to bridge this gap in synthetic organic chemistry is bolstered because the importance of organofluorine compounds has been established in medicinal chemistry.[2-3, 165] For instance, the incorporation of the trifluoromethyl group influences the chemical and biological properties of compounds (see section **1.1**).[1-3] As a result, trifluoromethyl-containing scaffolds become heavily sought after for use in medicinal applications. Therefore, we aim to develop new methodologies for preparing a subset of this amine class: α-trifluoromethyl homoallylic amines.

## 3.2 Background

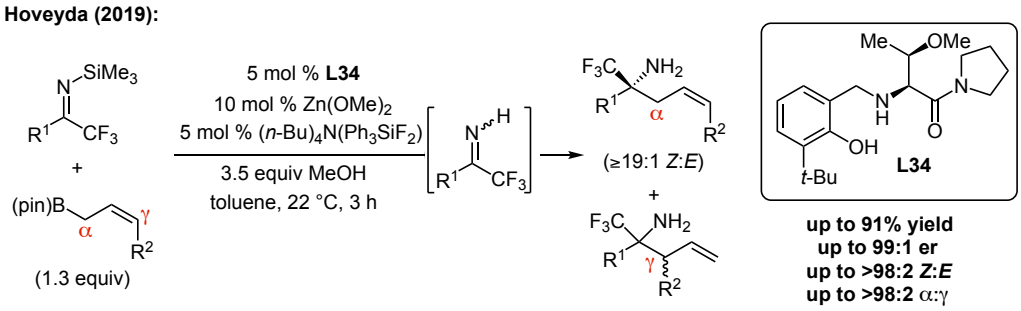
Chiral homoallylic amines are an important scaffold that is heavily sought in medicinal chemistry and hence, a number of strategies have been developed to access them.[17, 34, 196-198] A valuable subset of these compounds is α-trifluoromethyl homoallylic amines because of the chemical properties of the fluorine group. These amines bear a pendant allylic group which can be utilized as a handle for downstream functionalization.[199] Recently, a number of research groups have initiated efforts towards the synthesis of different α-trifluoromethyl homoallylic amines. Most of these strategies have relied on allylation between allylic carbonates and imines through allylic substitution using organocatalysts as well as transition metal catalysts. In 2016, the Yan and Wang laboratories showed the coupling of highly electrophilic allylic carbonates that bear an ester moiety (i.e. Morita–Baylis–Hillman MBH carbonates, Scheme 32A).[200] These carbonates undergo coupling with $CF_3$-substituted imines to generate α-secondary amine-substituted stereogenic centers. This reaction is aided by a chiral amine catalyst; however, the electrophile scope is limited to these MBH carbonates. These carbonates couple with the azadienolate generated from the deprotonation of the imine bearing a chloro-substituted isatin-based activating group. The isatin group is carefully chosen as the azadienolate generated *in situ* benefits from conjugation with the carbonyl group. This azadienolate offers two modes of nucleophilic attack: α-addition and γ-addition (addition from the $CF_3$-substituted carbon), however only the γ-addition

product is observed. The reaction is efficient and generates homoallylic amines containing vicinal trisubstituted stereogenic centers bearing a *syn* relationship as the major product. Following that work, Zhang and coworkers showed the coupling of $CF_3$-substituted ketimines bearing a *para*-nitrobenzyl activating group with an allylic carbonate derived from a primary alcohol to deliver the desired α-trifluoromethyl homoallylic amines in excellent yields and enantioselectivities (Scheme 32B).[201] However, attempts to employ secondary alcohol-derived carbonates lead to exclusive azaallyl anion addition from the activating group side of the ambidentate nucleophile (α′-addition). The products in this reaction only bear a single stereogenic center. The Shi group has also pursued a similar approach for homoallylic amines.[202]




**Scheme 32: Organocatalytic Methods for Synthesis of α-Trifluoromethyl Homoallylic Amines**

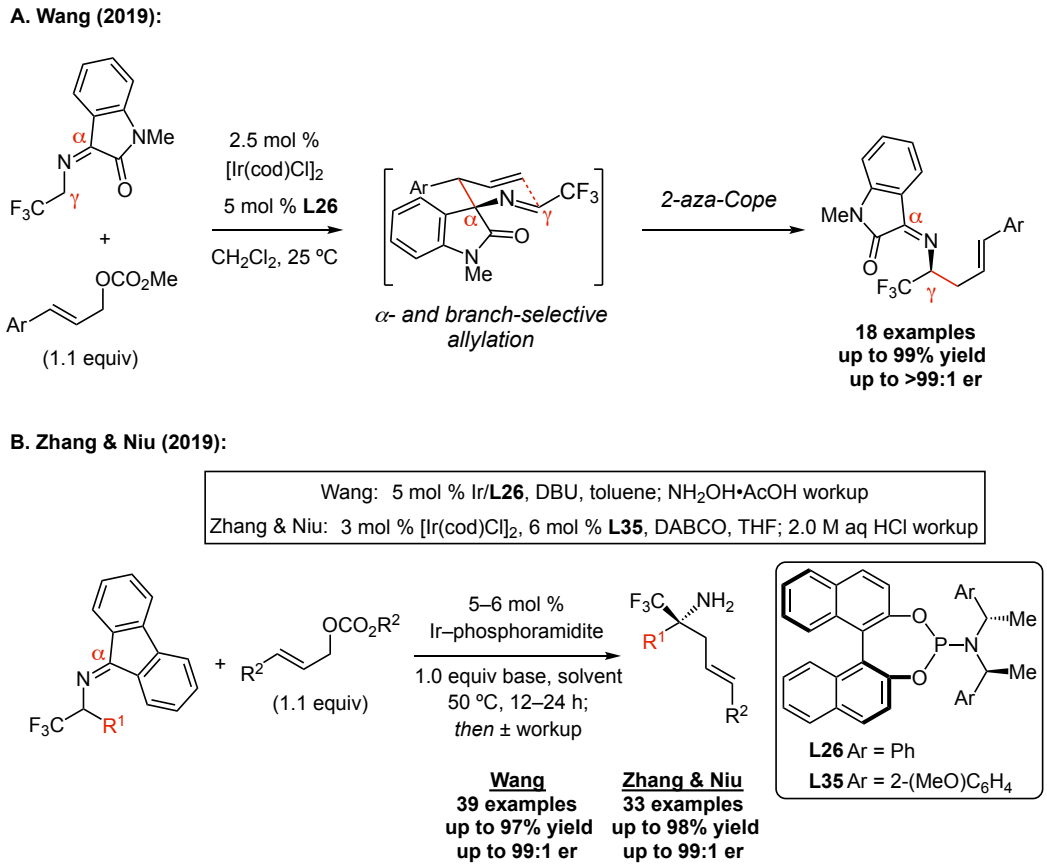
In addition to organocatalyzed methods for accessing α-trifluoromethyl homoallylic amines, transition-metal approaches have been employed by a number of groups. The Hoveyda group has shown the construction of (*Z*)-substituted α-trifluoromethyl amines through the coupling of $CF_3$-substituted N–H ketimines and (*Z*)-disubstituted allylboron reagents using an aminophenol catalyst (Scheme 33).[203] The reaction is stereoretentive, delivering predominantly the (*Z*)-alkene after α-alkylation by the allyl boronate.




**Scheme 33: Hoveyda's Synthesis of (*Z*)-Substituted Homoallylic Amines**

Recently, the Wang group added another contribution to this area by constructing quaternary α,α-disubstituted amino acids through an enantioselective allylation of α-trifluoromethyl aldimine esters followed by an unprecedented kinetic resolution.[204] Furthermore, Wang and coworkers have also disclosed an iridium-catalyzed allylation of isatin-derived azadienolates with allylic carbonates (Scheme 34A).[205] In this reaction, the azadienolate undergoes α-addition to the Ir–π-allyl, forming a branched α-product kinetically. However, this branched product is thermodynamically poised to undergo a stereoselective aza-Cope rearrangement to form

the linear net γ-allylation product. This phenomenon is due to the congestion of the tri- and tetrasubstituted centers and rehybridization of imine carbon from $sp^2$ to $sp^3$, while forming an olefin that is conjugated with the arene. Additionally, the imine formed is also conjugated with the carbonyl again.

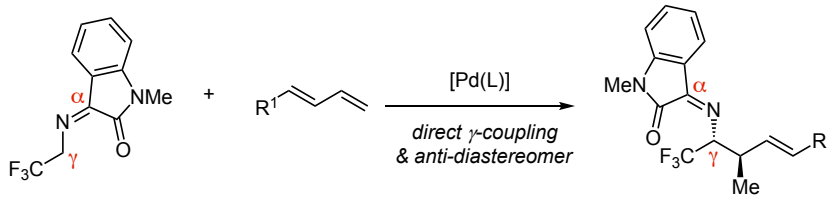



**Scheme 34: Ir-Catalyzed Methods for Synthesis of (*E*)-Substituted Homoallylic Amines**

Other efforts using iridium catalysts have been explored by the Wang group[206] and the team of Zhang and Niu[207] who used imines with a fluorenyl-activating group for coupling with allylic carbonates (Scheme 34B). With the aid of a phosphoramidite ligand, the α-addition products (not shown) are formed in the reaction first but

subsequent stereoselective aza-Cope rearrangement at elevated temperatures deliver the net γ-allylation products at the end of the reaction. The desired homoallylic amines bear one stereogenic center and an (*E*)-1,2-disubstituted alkene.

Our group has made considerable efforts in imine umpolung[161, 164, 208-209] and diene hydrofunctionalization strategies[210-214], and we envisioned the merging of these two methods for the enantio-, diastereo-, and regioselective construction of α-$CF_3$ homoallylic amines that bear two vicinal stereogenic centers and an (*E*)-alkene (Scheme 35). In addition, given that these α-$CF_3$ homoallylic amines have been previously only prepared with the *syn* selectivity (see Scheme 32A),[200] we hoped that we could potentially develop a route to the *anti*-diastereomer.



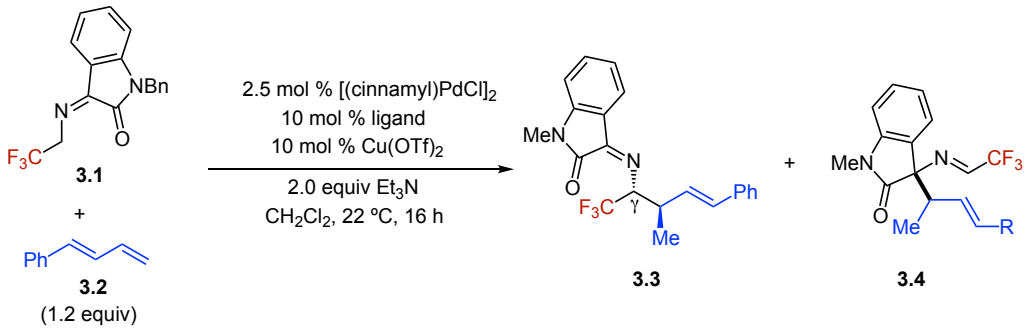

**Scheme 35: Enabling Strategy for Synthesis of α-Trifluoromethyl Homoallylic Amines**

## *3.3 Results and Discussion*

We began by examining the coupling between *N*-benzyl trifluoroethylisatin **3.1** and phenylbutadiene **3.2** (Table 6). Using our previously disclosed fluoroarylation reaction conditions[215], we initially used 2.5 mol% $[(cinnamyl)PdCl]_2$ as the palladium source and 10 mol% XPhos as the ligand. Triethylamine (2 equivalents) was selected as the base, 10 mol% of $Cu(OTf)_2$ as a Lewis acid co-catalyst, and dichloromethane as the

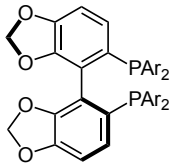
solvent (0.3 M) Under this condition, we observed 14% conversion of the starting materials to coupled product at room temperature (entry 1). However, we obtained the undesired α-alkylation isomer **3.3** rather than the γ-alkylation product **3.4**. We hypothesized that a different ligand might be able to favor the γ-alkylation product.

**Table 6: Initial Reaction Optimization**[a]

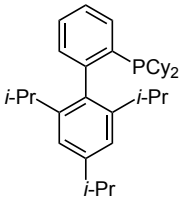



| entry | ligand | yield of **3.3/3.4** (%) |
|---|---|---|
| 1 | XPhos | <2/14 |
| 2 | DPEPhos | 4/23 |
| 3 | (*S*,*S*)-Ph-BPE | 4/9 |
| 4 | PHOX | <2/8 |
| 5 | (*S*)-(+)-DTBM-SEGPHOS | 57/<2 |

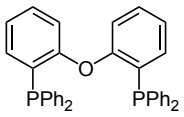
[a]Reaction concentration of 0.15 M under $N_2$ atmosphere. [b]Yield was determined by 376 MHz $^{19}$F NMR spectroscopy with 2,2,2-trifluoro-*N*,*N*-dimethyl acetamide as an internal standard.



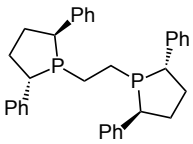

Ar = -3,5-di-*tert*-butyl-4-methoxyphenyl
(*S*)-(+)-DTBM-SEGPHOS



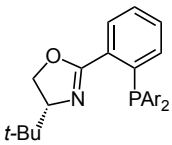

XPhos




DPEPhos




(*S*,*S*)-Ph-BPE

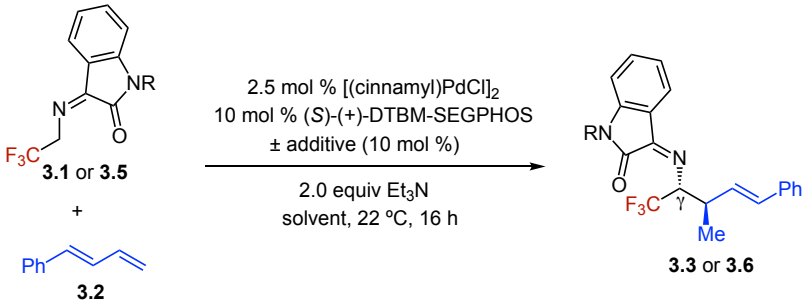



Ar = 3,5-$(CF_3)_2C_6H_3$
PHOX

Inspired by our prior hydrofunctionalization technology,[214] we explored our PHOX ligand system to promote favorable coupling. However, PHOX ligands as well as DPEPhos and Ph-BPE lead to inefficient catalysts that still deliver the α-alkylation

isomer in this reaction (entries 2–4). Owing to the congested quaternary stereogenic center generated during the formation of the α-alkylation product, we hypothesized that switching to a bulky bis-phosphine comprised of 3,5-di-*tert*-butyl-4-methoxy (DTBM) groups could hinder the formation of this product and lead to γ-selective alkylation. To our delight, (*S*)-DTBM-SegPhos provided the exclusive formation of the desired γ-alkylation isomer in 57% yield, 7:1 dr, and 92:8 er (Table 7, entry 1).

**Table 7: Solvent/Additive and Substituent Effects on Hydroalkylation with DTBM–SegPhos**[a]




| entry | R | solvent | additive | yield (%)[b] | dr[c] | er[d] |
|---|---|---|---|---|---|---|
| 1[e,f] | Bn | $CH_2Cl_2$ | - | 57 | 7.1:1 | 92:8 |
| 2[f] | Bn | $CH_2Cl_2$ | - | 81 | 8:1 | 92.5:7.5 |
| 3[e] | Bn | $CH_2Cl_2$ | - | 71 | 6:1 | 89:11 |
| 4 | Bn | $CH_2Cl_2$ | $NaBAr^F{}_4$ | 73 | 7:1 | 93.5:6.5 |
| 5 | Bn | $Et_2O$ | $NaBAr^F{}_4$ | 86 | 11:1 | 92.5:7.5 |
| 6 | Bn | $Et_2O$ | $NaBF_4$ | 69 | 7.6:1 | 85:15 |
| 7[g] | Bn | $Et_2O$ | - | <2 | n.a. | n.a. |
| 8[e,h] | Bn | $CH_2Cl_2$ | - | 34 | 7.5:1 | 90:10 |
| 9[i] | Bn | $CH_2Cl_2$ | - | 71 | 6:1 | 88:12 |
| 10 | Me | $Et_2O$ | $NaBAr^F{}_4$ | 96 | 11:1 | 94.5:5.5 |
| 11[j] | Me | $Et_2O$ | $NaBAr^F{}_4$ | <2 | n.a. | n.a. |

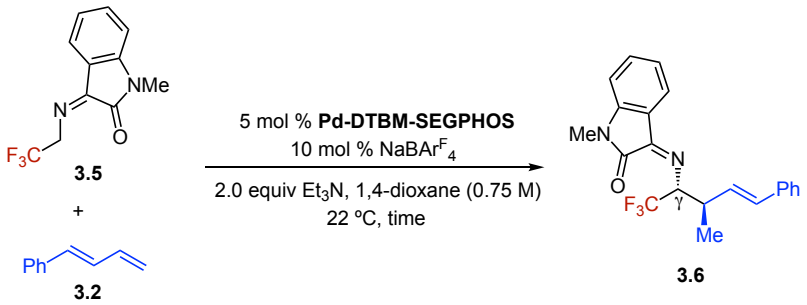
[a]Reaction run at 0.3 M unless otherwise noted with 1.5 equiv isatin and 1.0 equiv diene. [b]Yield determined by 376 MHz $^{19}F$ NMR spectroscopy in comparison to an internal standard. [c]Enantiomeric ratios determined using an authenthic racemic standard.[d]Diastereomeric ratios determined from 376 MHz $^{19}F$ NMR spectroscopy of the unpurified mixture. [e]1.0 equiv isatin and 1.2 equiv diene. [f]10 mol % $Cu(OTf)_2$ used. [g]No $NEt_3$ used. [h]Reaction run at 0 °C. [i]Reaction run at 0.75 M. [j]Reaction run for 2 h.

We focused our efforts using DTBM-SegPhos as a ligand (Table 7). Subsequently, we discovered that without the Cu co-catalyst, the reaction proceeds with negligible impact to yield or stereoselectivity (entries 1–3). Furthermore, we observed that the inclusion of $NaBAr^{F}_{4}$ as an additive improved the er (entry 4). Switching from dichloromethane to ethereal solvent was important for improving product yield, without significantly eroding enantio- or diastereoselectivity (entry 5). The use of base for this reaction is also crucial as no product is observed without triethylamine (entry 7). We discovered that switching from the *N*-benzyl derived isatin **3.1** to the *N*-methyl analogue **3.5** enhanced NMR yield from 86% to 96% yield and er from 92.5:7.5 er to 94.5:5.5 er (entry 10). We then attempted to shorten reaction time and observed that using $[(cinnamyl)PdCl]_2$ and DTBM-SegPhos to generate catalyst *in situ* led to a longer induction period: after 2 hours, we observed no product (entry 11).

We then hypothesized that using an isolated Pd complex for the reaction might lead to faster activation of catalyst, leading to better yields at shorter times (Table 8). Switching to the isolated Pd complex (Pd-DTBM-SegPhos) for the reaction at 0.75 M, allowed the formation of 42% product in 2 hours (entry 1), compared to our initial result with the *in situ* formed catalyst. We also examined the effect of different additives (such as $LiBF_4$, $AgBF_4$, $Zn(OTf)_2$, or $Et_3NHBAr^{F}_{4}$) in the hydroalkylation reaction (not shown in the table): most additives have a negligible impact on the reaction and do not positively affect conversion rates or levels of er and dr. However, the use of $NaBAr^{F}_{4}$ allows for full

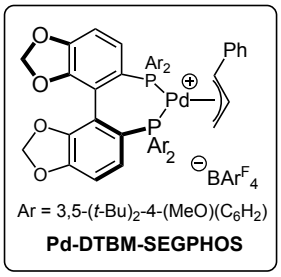
conversion of starting material to product and an increase in er from 91.5:8.5 er to 95:5 er with 1,4-dioxane as the solvent. Although $NaBAr^{F}_{4}$ is beneficial for higher levels of er in this case, it drastically retards reaction rate (56% conversion observed in 6 h compared to full conversion without the use of $NaBAr^{F}_{4}$). Nevertheless, we decided to use $NaBAr^{F}_{4}$ as full conversion can still be attained in 12 h (entries 2–6). The reaction proceeds smoothly at room temperature, however, decreasing the reaction temperature in an attempt to enhance enantioselectivity proved unfruitful (entry 7).

**Table 8: Reaction Optimization**[a]




| entry | time (h) | conv to **3.6** (%)[b] | dr[c] | er[d] |
|---|---|---|---|---|
| 1[e] | 2 h | 42 | 8:1 | n.d |
| 2 | 6 h | 56 | 8:1 | 95:5 |
| 3[f] | 6 h | >98 | 9:1 | 91.5:8.5 |
| 4 | 12 h | >98 | 8:1 | 95:5 |
| 5 | 16 h | >98 | 8:1 | 95:5 |
| 6[f] | 16 h | >98 | 8:1 | 94:6 |
| 7[e,g] | 16 h | 93 | 8:1 | 94:6 |

[a]Reaction run at 0.75 M under $N_2$ atmosphere with 1.5 equiv isatin and 1.0 equiv diene. [b]Conversion was determined by 376 MHz $^{19}$FNMR spectroscopy with 2,2,2-trifluoro-*N,N*-dimethylacetamide as internal standard. [c]Determined by 376 MHz $^{19}$F NMR spectroscopy of the unpurified mixture. [d]Determined by HPLC analysis of purified 3a. [e]$Et_2O$ used as solvent. [f]No $NaBAr^{F}_{4}$ used. [g]Reaction run at 4 °C. n.d. = not determined. n.a. = not applicable.



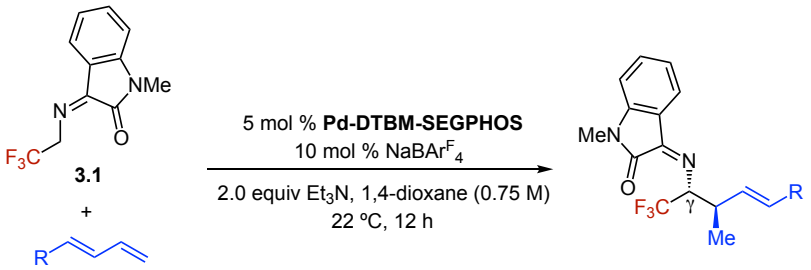

We decided to investigate other Pd pre-catalysts supporting alternative ligand architectures; however, they provide a mixture favoring the formation of α-alkylation

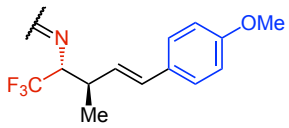
product. Notably, the diastereomeric ratio obtained for the product is considerably lower with these non-selective catalysts. Ultimately, using 5 mol % Pd-DTBM-SegPhos and 10 mol% $NaBAr^{F_4}$ in 1,4-dioxane (0.75 M) allowed the full conversion of **3.5** to **3.6** in 95:5 er and 8:1 dr (entry 4). This product is also furnished with the two stereogenic centers bearing an *anti* relationship and an internal (*E*)-alkene.

### 3.3.1 Substrate Scope

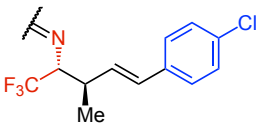
Upon determination of our optimal reaction conditions for this methodology, we explored a substrate scope of both aryl- and alkyl-substituted terminal dienes to access a new homoallylic amine scaffold. In the case of aryl dienes, the homoallylic amine products **3.16**–**3.24** are furnished in up to 86% yield, 10:1 dr, and 95:5 er. Both electron-donating (for products **3.16**, **3.21**, and **3.22**) and electron-withdrawing (for products **3.17** and **3.18**) aryl dienes undergo successful coupling with the azadienolates at room temperature with moderate to good enantioselectivity. Heterocycles are also tolerated in the reaction — both furyl- and pyridyl-substituted dienes **3.23** and **3.24** deliver the desired products with good yield and stereoselectivity. Although most dienes favor the γ-alkylation product exclusively, an *ortho* substituent on the arene leads to not only a slower reaction (44% conversion in 12 h) but also the formation of the α-alkylation product (ca. 10%). To improve reaction efficiency, $NaBAr^{F_4}$ was excluded from the reaction. The removal of additive lowered the diastereoselectivity but still allowed for reasonable enantioselectivity in **3.20** (92.5:7.5 er).

**Table 9: Substrate Scope for Aryl-Substituted 1,3-Dienes**[a]

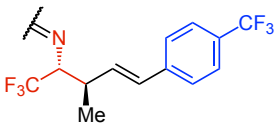


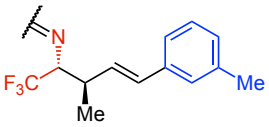

**3.16**
68% yield
**94:6 er, 10:1 dr**



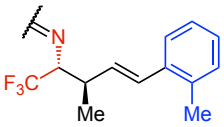

**3.17**
75% yield
**90:10 er, 8:1 dr**



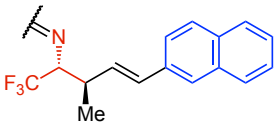

**3.18**
74% yield
**90:10 er, 8:1 dr**



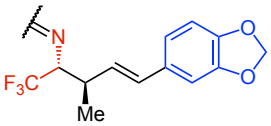

**3.19**
72% yield
**93:7 er, 6:1 dr**



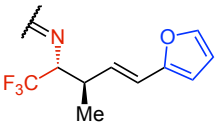

**3.20**[d,e]
59% yield
**92.5:7.5 er, 2:1 dr**



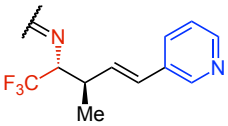

**3.21**
62% yield
**94:6 er, 8:1 dr**




**3.22**
86% yield
**91.5:8.5 er, 10:1 dr**




**3.23**
59% yield
**93:7 er, 8:1 dr**



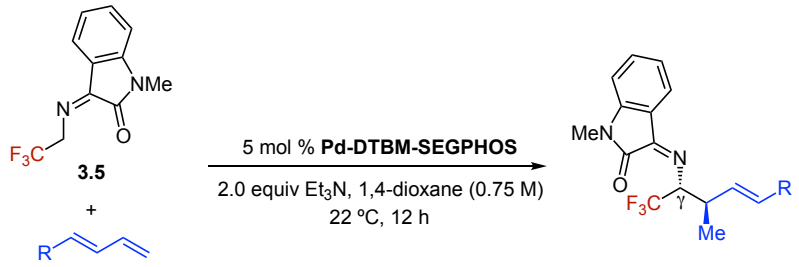

**3.24**
82% yield
**94:6 er, 7:1 dr**

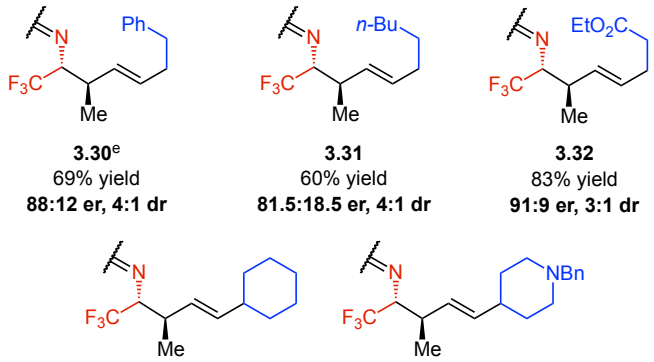
[a]Reaction run under $N_2$ with 0.15 mmol of diene (0.75 M). [b]Diastereomeric ratio determined by 376 MHz $^{19}$F NMR or 400 MHz $^{1}$H NMR spectroscopy of the unpurified mixture. [c]Enantiomeric ratios (er) determined by HPLC in comparison with an authentic racemic standard. [d]Reaction run without $NaBAr^F_4$. [e]Isolated yield is a mixture of regioisomers.

More challenging alkyl-substituted dienes are amenable substrates in this reaction. Moderate to good yields of the corresponding products are obtained by raising the reaction temperature (50 °C) and excluding $NaBAr^F_4$. Both linear and α-branched

alkyl-substituted dienes participate in the reactions, affording homoallylic amines **3.26**–**3.30** in 43–84% yield in up to 4:1 dr and 91:9 er.

**Table 10: Substrate Scope for Alkyl-Substituted 1,3-Dienes**[a]




| **3.30**[e] | **3.31** | **3.32** |
|---|---|---|
| 69% yield | 60% yield | 83% yield |
| **88:12 er, 4:1 dr** | **81.5:18.5 er, 4:1 dr** | **91:9 er, 3:1 dr** |

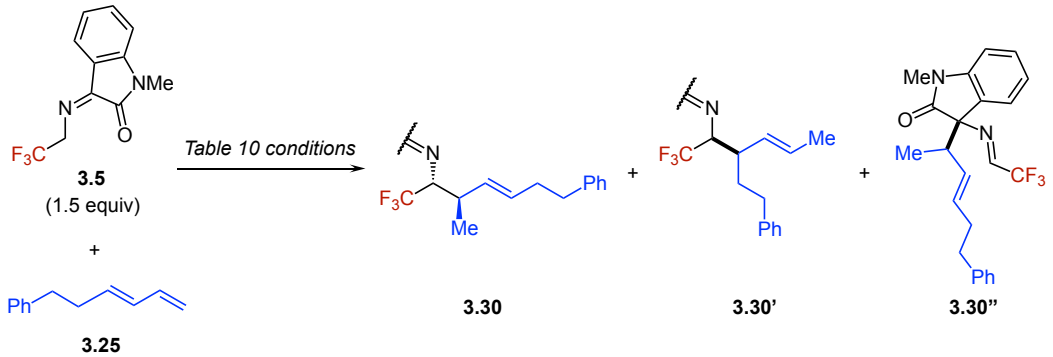
| **3.33** | **3.34**[e] |
|---|---|
| 43% yield | 83% yield |
| **90:10 er, 3:1 dr** | **86.5:13.5 er, 3:1 dr** |

[a]Reaction run under $N_2$ with 0.15 mmol of diene (0.75 M). [b]Diastereomeric ratio determined by 376 MHz $^{19}$F NMR or 400 MHz $^{1}$H NMR spectroscopy of the unpurified mixture. [c]Enantiomeric ratios (er) determined by HPLC in comparison with an authentic racemic standard. [e]Isolated yield is a mixture of regioisomers.

Reactions with alkyl-substituted dienes lead exclusively to the desired γ-alkylation product although the phenethyl-derived diene afforded a regioisomeric mixture of products **3.30**:**3.30″** (Table 11). Product **3.30″** bears a different connectivity with respect to the diene-derived fragment, and we were able to ascertain through

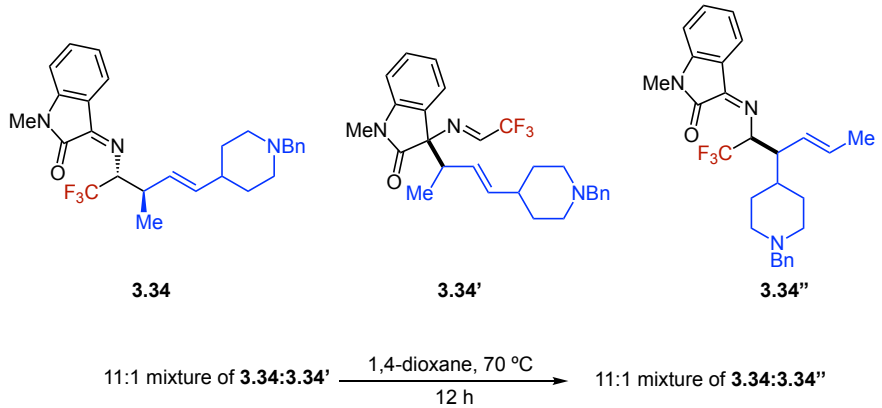
additional experimentation (Table 11) that **3.30″** is formed from the aza-Cope rearrangement of **3.30′**, in agreement with earlier studies by Wang.[206]

**Table 11: Mechanistic Studies on Regioisomers Generated from Hydroalkylation with Certain Alkyl Dienes**[a]




| entry | temp (ºC) | conv to **3.30**:**3.30'**:**3.30''** (%)[b] |
|---|---|---|
| 1 | 50 | 82:<2:8 |
| 2 | 35 | 52:14:4 |

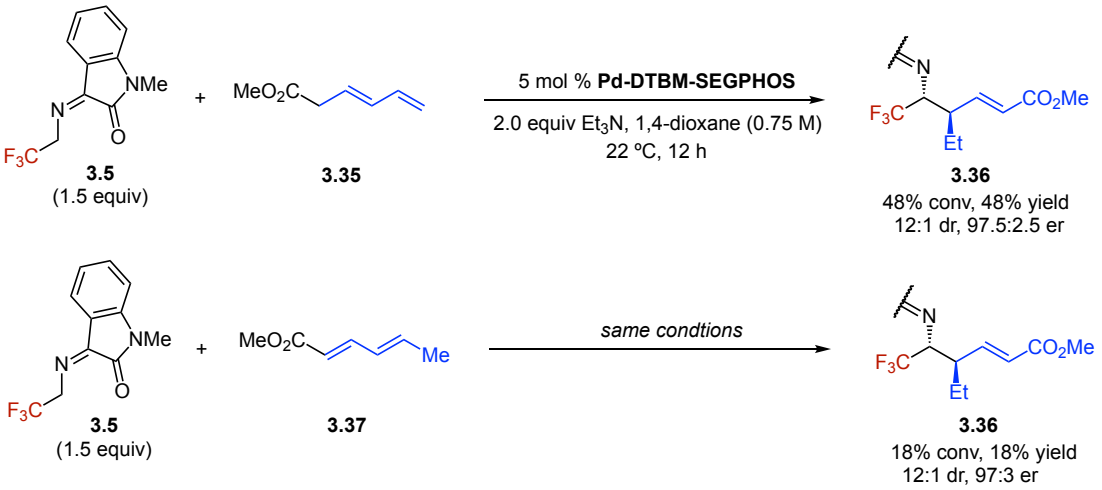
[a]Reaction run at [0.75 M] under $N_2$ atmosphere. [b]Conversion was determined by 376 MHz $^{19}$F NMR spectroscopy with 2,2,2-trifluoro-N,N-dimethyl acetamide as internal standard.




Additionally, piperidine-substituted diene leads to the formation of an 11:1 mixture of γ-alkylation to α-alkylation products **3.34**:**3.34′**. We have shown that in these cases where a mixture of regioisomers is formed, **3.30** and **3.30′** are formed initially in

the reaction mixture, and then a subsequent aza-Cope rearrangement of **3.30′** gives rise to **3.30″**. When an 11:1 mixture of **3.34**:**3.34′** is heated in 1,4-dioxane at 70 °C, we observe the disappearance of **3.34′** in the mixture and concomitant formation of **3.34″** after 12 h.

Products derived from isomerization of the diene (i.e. "chain walking" along the alkyl chain) prior to enolate addition were not detected with any substrate. Conversely, we observed that hexadienoate **3.36** undergoes diene isomerization into conjugation with the ester functionality prior to coupling with **3.5**, affording an ethyl-substituted stereogenic center in **3.36** in 48% yield, 12:1 dr, and 97.5:2.5 er. Comparatively, its internal diene analogue **3.37** can undergo the same coupling with **3.1** but furnishes a lower yield of **3.36** without affecting stereoselectivity (Scheme 36).




**Scheme 36: Isomerization/Alkylation of 3,5-Hexadienoate and Comparison to its Internal Diene Isomer**

We embarked on synthesizing amine scaffolds that are currently circuitous to access via existing technology. We evaluated coupling partners **3.38** and **3.39** (Figure 8),

which would furnish α-difluoromethyl amines and amines bearing tetrasubstituted stereogenic centers, respectively, upon reaction with terminal dienes. Unfortunately, these substrates could not participate in the reactions as **3.38** undergoes decomposition while **3.39** is completely unreactive with the diene electrophile. We then examined electrophiles that could enable the formation of fluorinated amino alcohol products. However, alcohol and TBS-ether containing aliphatic dienes **3.40** and **3.41** were also unproductive leading to a myriad of products arising from the desired γ-alkylation, the undesired α-alkylation, as well as the aza-Cope rearrangement product, all in diastereomeric mixtures. Surprisingly, no chain walking products were observed with these couplings.

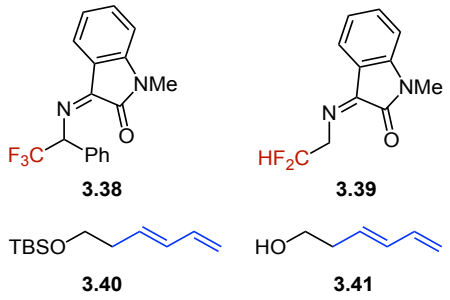
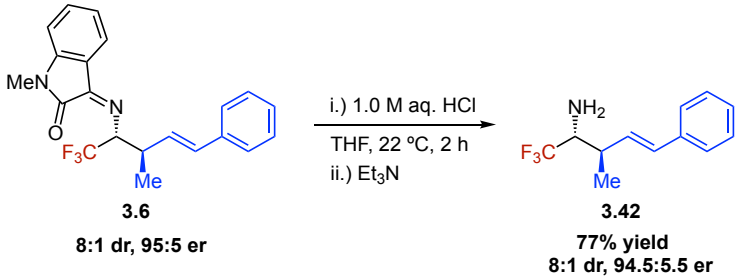



**Figure 8: Incompatible Substrates in Hydroalkylation Methodology**

### 3.3.2 Hydrolysis of Product Imines to Deliver Primary Amines

The direct products obtained from the hydroalkylation reaction are present as isatin-protected forms of primary amines. The isatin group is readily cleaved under mild conditions (1.0 M aq HCl at room temperature in 2 hours, then excess $Et_3N$) to liberate primary amine **3.42** in 77% yield without significant erosion of er or dr (Scheme 37).




**Scheme 37: Imine Hydrolysis in Products**

## *3.4 Conclusions and Outlook*

We developed a method for the diastereo- and enantioselective hydroalkylation of acyclic terminal 1,3-dienes. Isatin-derived *N*-trifluoroethyl imines undergo deprotonation by triethylamine to form azadienolates. These azadienolates then take part in selective γ-alkylation with aryl- and alkyl-substituted dienes to form homoallylic α-trifluoromethyl amines bearing vicinal stereogenic centers in an *anti*-relationship. Crucial to the success of this reaction is the bulky ligand DTBM-SegPhos, as it efficiently controls the regioselectivity with respect to both the isatin and diene components, delivering γ-alkylation products exclusively in high enantioselectivity.

It should be noted that there are only a handful of examples where the relative and absolute configuration of vicinal stereogenic centers can be controlled in a single catalytic step via an olefin hydrofunctionalization approach.[160, 216-220] Additionally, this transformation is the first instance of an enantioselective hydroalkylation using an umpolung carbon nucleophile. Accessing α-$CF_2H$ amines or α-$CF_3$ amines bearing tetrasubstituted stereogenic centers using this technology proved elusive. With this

challenge in mind, we anticipate that the modification of the catalyst system might address these issues.

## *3.5 Experimental Details*

Additional supporting information, including NMR spectra for new compounds can be found in the supporting information published online for:

Onyeagusi, C. I.; Shao, X.; Malcolmson, S. J. Enantio- and Diastereoselective Synthesis of α-Trifluoromethyl Homoallylic Amines by Catalytic Hydroalkylation of Dienes. *Org Lett.* **2020**, *22*, 1681–1685.

### 3.5.1 General Information

General Procedures. All reactions were carried out in oven- (120 °C) or flame-dried glassware under an inert atmosphere of dry $N_2$ unless otherwise noted. 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.

Reagents. Triethylamine (Sigma Aldrich) was distilled from $CaH_2$ prior to use. Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F{}_4$) was prepared according to a previously reported procedure.[221]

The following chemicals were used as received: $[(allyl)PdCl]_2$ (Strem); benzyl bromide (Alfa Aesar); (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (Alfa Aesar) ((*R*)-BINAP) (Strem); (*R*)-(+)-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl, ((*R*)-

MeO-BIPHEP) (Strem); (*R*)-(+)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole ((*R*)-SEGPHOS) (Strem); (*S*)-(+)-5,5′-bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (*S*)-(+)-DTBM-SEGPHOS (Strem); (*R*)-(−)-5,5′-bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole ((*R*)-DM-SEGPHOS) (Strem); bis[(2-diphenylphosphino)phenyl] ether (DPEPhos) (Strem); (+)-(5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl)-2,2′-diyl-bis(diphenylphosphine) ((*R*)-Cl-MeO-BIPHEP) (Strem); (*R*)-[6,6′-dimethoxy(1,1′-biphenyl)-2,2′-diyl]bis(bis[3,5-bis(1,1-dimethylethyl)-4-methoxyphenyl]phosphine) ((*R*)-DTBM-OMe-BIPHEP) (Strem); $[(cinnamyl)PdCl]_2$ (Sigma Aldrich); iodomethane (Sigma Aldrich); isatin (Alfa Aesar); lithium tetrafluroborate (Fisher); morpholine (Sigma Aldrich); palladium acetate (Strem); silver tetrafluroborate (Strem); sodium hydride (Strem); tetrakis(acetonitrile)palladium(II) tetrafluoroborate (Strem); tris(pentafluorophenyl)borane (TCI); 2,2,2-trifluoroethylamine hydrochloride (Matrix); zinc trifluoromethanesulfonate (Sigma Aldrich).

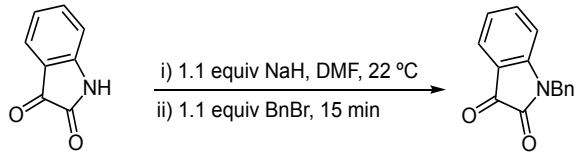
<u>Solvents.</u> Solvents were sparged with dry $N_2$ and purified under a positive pressure of dry $N_2$ by an Innovative Technologies PureSolve solvent purification system: tetrahydrofuran (Sigma-Aldrich), dichloromethane (Sigma-Aldrich), diethyl ether (Sigma-Aldrich), 1,4-dioxane (Sigma-Aldrich), and toluene (Sigma-Aldrich) were passed through two consecutive alumina columns. Methanol (Sigma-Aldrich) and *N,N*-dimethylformamide (Sigma-Aldrich) were used as received. HPLC-grade hexanes

(Sigma-Aldrich) and methanol (Sigma-Aldrich) for reactions were distilled over $CaH_2$ prior to use. Hexanes (Fisher) and ethyl acetate (Fisher) were used for flash column chromatography as received. HPLC-grade hexanes (Sigma-Aldrich) and isopropanol (Sigma-Aldrich) for chromatography were used as received.

Instrumentation. $^1$H NMR spectra were recorded on a Varian INOVA (400 MHz) or Bruker (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration (CDCl3: $\delta$ 7.26) as the internal reference. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). $^{13}$C NMR spectra were recorded on a Varian/Agilent VNMRS (500 MHz) or Bruker (500 MHz) spectrometer with complete proton decoupling but with fluorine coupling except where indicated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from chloroform as the internal reference ($CDCl_3$: $\delta$ 77.16). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). $^{19}$F NMR spectra were recorded on a Varian INOVA (400 MHz) or Bruker (500 MHz) spectrometer. Chemical shifts are reported in ppm using (2,2,2-trifluoro-*N*,*N*-dimethylacetamide: $\delta$ –69.56) as the internal reference Data are reported as follows: chemical shift, integration, multiplicity (s =

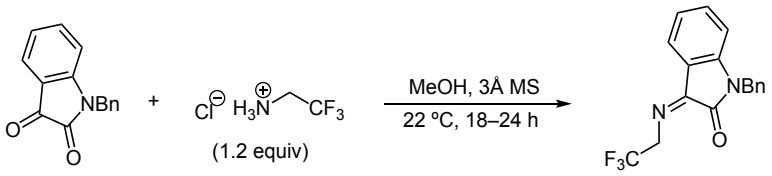
singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). $^{31}$P NMR spectra were recorded on a Bruker (500 MHz) spectrometer with complete proton decoupling. Conversions were determined by $^{19}$F NMR by product ratio to an internal standard (2,2,2-trifluoro-*N,N*-dimethylacetamide). Enantiomer ratios (er) were determined by HPLC (PhenomenexTM Lux® Cellulose I, Cellulose II, Cellulose III, Amylose I, or Chiralpak™ 1A-3 columns) in comparison with authentic racemic materials on a Shimadzu Prominence Modular HPLC. High-resolution mass spectrometry was performed on an Agilent (1200 Series) LCMS-TOF-DART at the Duke University Mass Spectrometry Facility (HRMS data values reported as an average of four runs). Infrared (IR) spectra were collected on a Nicolet 6700 FT-IR spectrometer, $\upsilon_{max}$ in cm$^{-1}$; bands are characterized as broad (br), strong (s), medium (m), or weak (w). All X-ray crystallography measurements were made in the Molecular Education, Technology, and Research Innovation Center (METRIC) at NC State University. X-ray crystallography data can be found on the Cambridge Crystallographic Data Centre (ref: CCDC 1978720).

### 3.5.2 Preparation of *N*-Trifluoroethyl Imine Substrate



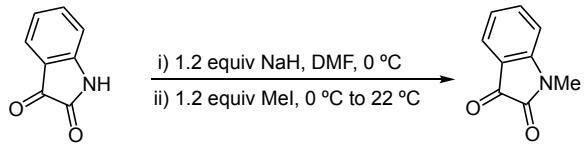

1-benzylindoline-2,3-dione. A flame-dried 250-mL round-bottom flask, equipped with stir bar, was charged with isatin (4.41 g, 30.0 mmol, 1.00 equiv) and *N,N*-

dimethylformamide (50 mL). NaH (60% in mineral oil) (1.32 g, 33.0 mmol, 1.10 equiv) was added in one portion to the flask and the resulting mixture was allowed to stir for 10 minutes. Benzyl bromide (3.93 mL, 33.0 mmol, 1.10 equiv) was slowly added to the flask and the reaction mixture was allowed to stir at room temperature for an additional 15 minutes. The mixture was poured into ice cold swirling saturated brine (200 mL). The orange precipitate was then filtered by vacuum filtration and washed with water (100 mL) and hexanes (150 mL) to afford the title compound as an orange solid (5.31 g, 21.1 mmol, 70.4% yield). **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.60 (1H, d, $J$ = 7.4 Hz), 7.46 (1H, t, $J$ = 7.8 Hz), 7.36–7.27 (5H, m), 7.07 (1H, t, $J$ = 7.5 Hz), 6.76 (1H, d, $J$ = 7.9 Hz), 4.92 (2H, s). Spectral data matched those previously reported.[222]

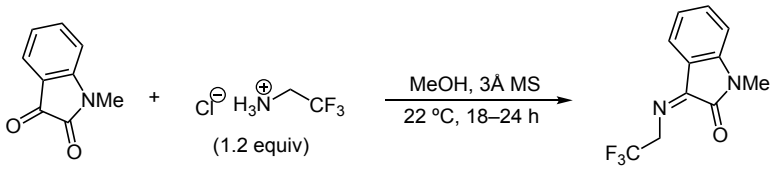



(*Z*)-1-benzyl-3-((2,2,2-trifluoroethyl)imino)indolin-2-one (**3.1**). A flame-dried 250-mL round-bottom flask, equipped with stir bar, was charged with 1-benzylindoline-2,3-dione (1.26g, 5.00 mmol, 1.00 equiv), 2,2,2-trifluoroethylamine hydrochloride (813 mg, 6.00 mmol, 1.20 equiv), and 3Å molecular sieves. Methanol (50 mL) was added to the reaction flask and the resulting mixture was allowed to stir at room temperature for 18–24 h. The mixture was filtered through celite (rinsed with diethyl ether) and concentrated. The yellow residue was purified by flash column chromatography (4:1 hexanes:ethyl acetate) to afford the title compound as a yellow solid (1.02 g, 3.06 mmol,

61.3% yield). **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.72 (1H, d, $J$ = 7.6 Hz), 7.36–7.28 (6H, m), 7.08 (1H, t, $J$ = 7.6 Hz), 6.73 (1H, d, $J$ = 7.9 Hz), 4.91–4.83 (4H, m); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –71.91 (3F, t, $J_{HF}$ = 9.7 Hz). Spectral data matched those previously reported.[223]




1-methylindoline-2,3-dione. A flame-dried 100-mL round-bottom flask, equipped with stir bar, was charged with isatin (5.00 g, 34.0 mmol, 1.00 equiv) and *N,N*-dimethylformamide (35 mL) and then cooled to 0 °C. NaH (60% in mineral oil, 1.67 g, 40.7 mmol, 1.20 equiv) was added in three portions, and the resulting mixture was allowed to stir for 30 min. Methyl iodide (2.53 mL, 40.7 mmol, 1.20 equiv) was added to the reaction flask at 0 °C, and the reaction mixture was allowed to stir for 2 h at 0 °C and for an additional 1 h at room temperature. The reaction was quenched with saturated aq. ammonium chloride (100 mL) and diluted with ethyl acetate (100 mL). The organic layer was washed with three portions of deionized water (50 mL), dried over $Na_2SO_4$, filtered, and concentrated. The orange residue was purified by flash column chromatography (3:1 hexanes:ethyl acetate) to afford the title compound as an orange solid (4.93 g, 30.6 mmol, 90.2% yield); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.61–7.57 (2H, m), 7.11 (1H, t, $J$ = 7.5 Hz), 6.88 (1H, d, $J$ = 8.0 Hz), 3.24 (3H, s). Spectral data matched those previously reported.[222]



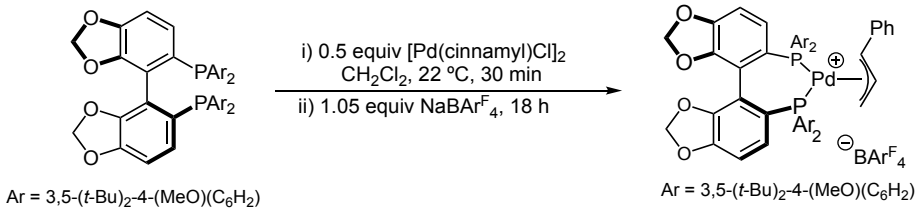

(*Z*)-1-methyl-3-((2,2,2-trifluoroethyl)imino)indolin-2-one (**3.5**). A flame-dried 250-mL round-bottom flask, equipped with stir bar, was charged with 1-methylindoline-2,3-dione (1.21g, 7.50 mmol, 1.00 equiv), 2,2,2-trifluoroethylamine hydrochloride (1.22 g, 9.00 mmol, 1.20 equiv), and 3Å molecular sieves. Methanol (50 mL) was added to the reaction flask and the resulting mixture was allowed to stir at room temperature for 18–24 h. The mixture was filtered through celite (rinsed with diethyl ether) and concentrated. The yellow residue was purified by flash column chromatography (4:1 hexanes:ethyl acetate) to afford the title compound as a yellow solid (1.11 g, 4.58 mmol, 61.1% yield). $^{1}$**H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.70 (1H, d, $J$ = 7.5 Hz), 7.45 (1H, t, $J$ = 7.9 Hz), 7.11 (1H, t, $J$ = 7.6 Hz), 6.82 (1H, d, $J$ = 7.8 Hz), 4.82 (2H, q, $J$ = 9.7 Hz), 3.21 (3H, s); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –71.93 (3F, t, $J_{HF}$ = 9.8 Hz). Spectral data matched those previously reported.[223]

### 3.5.3 Preparation of Diene Substrates

The following 1,3-dienes substrates were prepared as previously described[213-214, 224-227]: (*E*)-buta-1,3-dien- 1-ylbenzene (**3.2**), (*E*)-1-(buta-1,3-dien-1-yl)-4-methoxybenzene (**3.7**), (*E*)-1-(buta-1,3-dien-1-yl)-4-chlorobenzene (**3.8**), (*E*)-1-(buta-1,3-dien-1-yl)-4-(trifluoromethyl)benzene (**3.9**), (*E*)-1-(buta-1,3-dien-1-yl)-3-methylbenzene (**3.10**), (*E*)-1-(buta-1,3-dien-1-yl)-2-methylbenzene (**3.11**), (*E*)-2-(buta-1,3-dien-1-yl)naphthalene (**3.12**),

(*E*)-5-(buta-1,3-dien-1-yl)benzo[d][1,3]dioxole (**3.13**), (*E*)-2- (buta-1,3-dien-1-yl)furan (**3.14**), (*E*)-3-(buta-1,3-dien-1-yl)pyridine (**3.15**), (*E*)-hexa-3,5-dien-1-ylbenzene (**3.25**), (*E*)-deca-1,3-diene (**3.26**), ethyl (*E*)-hepta-4,6-dienoate (**3.27**), (*E*)-buta-1,3-dien-1-ylcyclohexane (**3.28**), (*E*)-1-benzyl-4-(buta-1,3-dien-1-yl)piperidine (**3.29**), methyl (*E*)-hexa-3,5-dienoate (**3.35**), methyl (2*E*,4*E*)-hexa-2,4-dienoate (**3.37**), (*E*)-tert-butyl(hexa-3,5-dien-1-yloxy)dimethylsilane (**3.40**), and (*E*)-hexa-3,5-dien-1-ol (**3.41**).

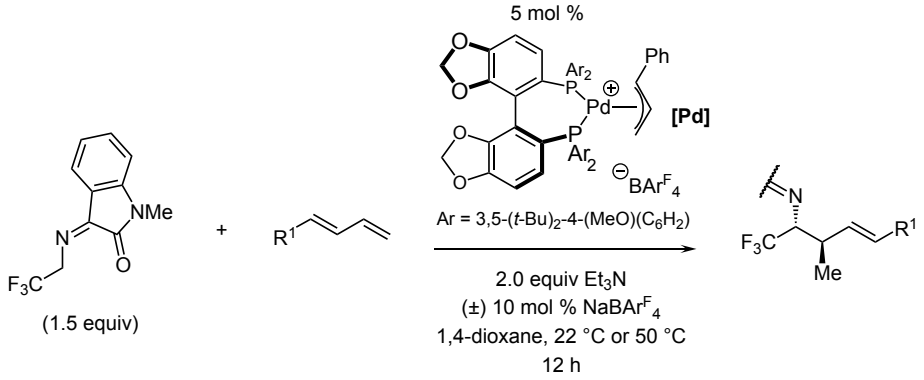
### 3.5.4 Preparation of Pd–DTBM–SEGPHOS Catalyst




[**Pd–DTBM-SEGPHOS**]. To an oven-dried 25-mL round-bottom flask, equipped with a magnetic stirring rod, inside an $N_2$-filled glovebox was added Pd(cinnamyl)Cl]$_2$ (104 mg, 0.200 mmol, 0.500 equiv), (*S*)-(+)-DTBM-SEGPHOS (472 mg, 0.400 mmol, 1.00 equiv), and $CH_2Cl_2$ (4 mL). The resulting yellow solution was allowed to stir at ambient temperature for ca. 30 min before $NaBAr^{F}_4$ (372 mg, 0.420 mmol, 1.05 equiv) was added and the flask was removed from the glovebox. The reaction was allowed to stir vigorously for 18 h. The reaction mixture was filtered through a pad of celite (rinsing with 3 X 5 mL $CH_2Cl_2$), concentrated in vacuo and purified by flash column chromatography (100% $CH_2Cl_2$) to afford the title compound as a yellow solid (877 mg, 0.384 mmol, 95.9% yield). The complex was isolated as a ca. 4:1 diastereomeric mixture.

**IR** (thin film) 2965 (br), 1610 (w), 1440 (w), 1353 (s), 1162 (m), 1121 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.62 (10 H, s, major + minor), 7.42 (5 H, s, major + minor), 7.11–7.06 (3H, m, major + minor), 7.00–6.88 (3H, m, major + minor), 6.82–6.79 (3H, m, major + minor) , 6.59–6.57 (4H, m, major + minor), 6.48–6.39 (2H, m, major + minor), 5.96 (1H, dt, $J$ = 13.4, 6.7 Hz, major + minor), 5.57 (1H, s, major + minor), 5.49 (2H, d, $J$ = 1.8 Hz, major + minor), 5.43 (1H, s, major + minor), 4.19 (1H, t, $J$ = 11.9 Hz, major + minor), 3.74 (3H, s, major), 3.68 (3H, s, major), 3.62 (3H, s, major), 3.54 (3H, s, major), 3.32 (1H, t, $J$ = 6.3 Hz, major + minor), 1.32 (36H, s, major), 1.28 (36H, s, major); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 163.5, 163.4, 162.4, 162.0, 161.9, 161.9, 161.6, 161.2, 150.1, 150.1, 149.6, 149.6, 147.8, 147.7, 147.6, 145.3, 145.2, 145.1, 145.1, 144.3, 144.3, 134.9, 132.3, 131.8, 131.7, 131.4, 131.3, 129.4, 129.3, 129.1, 128.8, 128.6, 128.5, 127.9, 127.3, 126.8, 126.8, 126.6, 126.5, 126.4, 126.1, 126.0, 125.7, 124.7, 124.3, 123.5, 123.0, 122.6, 122.4, 122.0, 121.4, 121.2, 120.8, 120.0, 119.3, 118.0, 117.4, 108.3, 108.2, 108.0, 107.9, 101.1, 101.1, 93.1, 93.0, 92.8, 92.7, 77.3, 77.0, 76.8, 64.6, 64.5, 64.3, 36.2, 36.1, 36.0, 35.9, 35.8, 31.9, 31.8, 31.7 (note: spectrum is complex due to mixture of diastereomeric species and $^{31}$P splitting and accordingly all observable peaks are simply listed as if they were singlets); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –62.47 (24F, s, major + minor); **$^{31}$P NMR** (162 MHz, $CDCl_3$) $\delta$ 22.76 (d, $J_{PP}$ = 59.5 Hz, minor), 21.95 (d, $J_{PP}$ = 61.2 Hz, major), 19.20 (d, $J_{PP}$ = 61.5 Hz, major), 16.82 (d, $J_{PP}$ = 60.0 Hz, minor); **HRMS** ($ESI^+$) [M]+ calc'd for $C_{83}H_{109}O_8P_2Pd$: 1401.6627, found: 1401.6647.

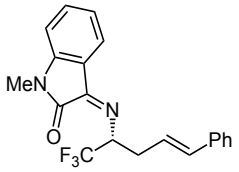
### 3.5.5 Hydroalkylation of Dienes



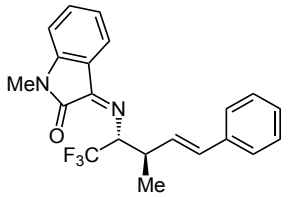

General Method A. In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial, equipped with stir bar, was charged with [**Pd**] (17.1 mg, 7.50 μmol, 0.0500 equiv), *N*-trifluoroethyl imine 1 (54.5 mg, 0.225 mmol, 1.50 equiv), (±) $NaBAr^{F_4}$ (13.3 mg, 15.0 μmol, 0.100 equiv), and dioxane (200 μL). Diene (0.150 mmol, 1.00 equiv) and triethylamine (41.8 μL, 0.300 mmol, 2.00 equiv) were added to the reaction vial. The vial was sealed, removed from the glovebox and allowed to stir at 22 °C or 50 °C in a heating block for 12 h. The reaction mixture was then filtered through a celite plug and rinsed with ethyl acetate (3 X 10 mL). The solution was concentrated, and the residue purified by flash column chromatography with silica gel or by combiflash automated column chromatography.

**Note:** Isolated yields reported are an average of 2 runs. Only peaks for the major product diastereomer are reported for clarity. For some products, the regioisomers could not be separated. Yields for all products represent isolated yields of a single regioisomer unless otherwise noted. Some samples contain <5% of a byproduct of catalyst initiation

that could not be separated. In entries with large discrepancy in conversion to desired product and isolated yield (as seen in manuscript), this is due to difficulty in separation of desired product and unreacted starting material imine by silica gel flash column chromatography. Authentic racemic standards were prepared using a 1:1 mixture of R:S enantiomers of the isolated Pd catalyst



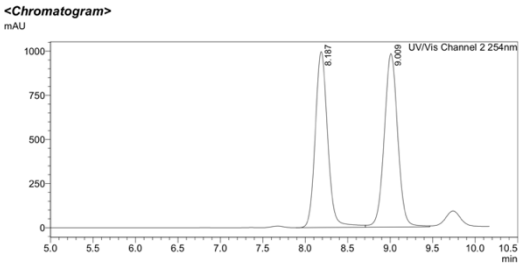

"catalyst initiation byproduct"




(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methyl-5-phenylpent-4-en-2-yl)imino)indolin-2-one (**3.6**). Title compound **3.6** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.6** as a yellow solid (44.5 mg, 0.119 mmol, 79.6% yield). Note: contains 2% catalyst initiation byproduct. **IR** (thin film) 2938 (w), 1712 (s), 1661 (w), 1611 (s), 1491 (w), 1471 (s), 1334 (m), 1263 (s), 1147 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.69 (1H, d, $J$ = 7.2 Hz), 7.40 (1H, t, $J$ = 8.3 Hz), 7.27–7.16 (5H, m), 7.08 (1H, t, $J$ = 7.4 Hz), 6.69 (1H, d, $J$ = 7.7 Hz), 6.33–6.15 (2H, m), 6.12–6.05 (1H, m), 3.04 (3H, s), 3.01–2.90 (1H, m), 1.28 (3H, d, $J$ = 6.3 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.03 (3F, d, $J_{HF}$ = 7.2 Hz); **$^{13}$C**

**NMR** (126 MHz, $CDCl_3$) $\delta$ 159.0, 156.2, 145.7, 137.3, 133.6, 131.4, 131.1, 128.4, 127.2, 126.1, 125.3 (q, $J_{CF}$ = 282.0 Hz), 123.3, 122.8, 120.9, 108.5, 63.8 (q, $J_{CF}$ = 26.3 Hz), 39.9, 25.6, 17.3; **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{21}H_{20}F_3N_2O$: 373.1522, found: 373.1529.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 95:5.

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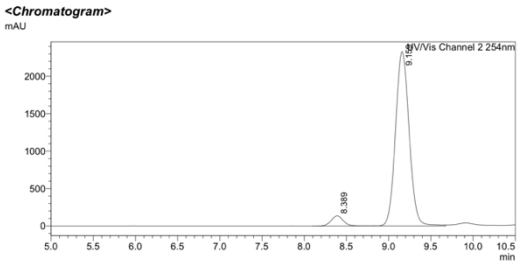


<Peak Table>
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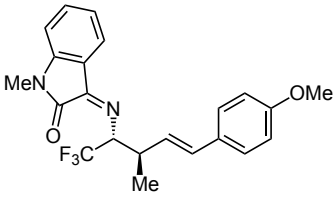
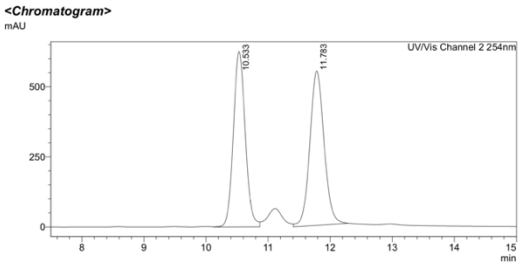



(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-5-(4-methoxyphenyl)-3-methylpent-4-en-2-yl)imino)indolin-2-one (**3.16**). Title compound **3.16** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.16** as a yellow oil (41.0 mg, 0.102 mmol, 67.9% yield). **IR** (thin film) 2934 (w), 1717 (m), 1613 (m), 1251 (s) $cm^{-1}$; **$^1$H NMR** (400

MHz, $CDCl_3$) $\delta$ 7.67 (1H, d, $J$ = 6.9 Hz), 7.40 (1H, td, $J$ = 7.8, 1.3 Hz), 7.18–7.11 (2H, d, $J$ = 8.7 Hz), 7.07 (1H, t, $J$ = 7.4 Hz), 6.76 (2H, d, $J$ = 8.7 Hz), 6.70 (1H, d, $J$ = 7.8 Hz), 6.18 (1H, d, $J$ = 15.9 Hz), 6.06–5.93 (2H, m), 3.76 (3H, s), 3.05 (3H, s), 2.95–2.81 (1H, m), 1.25 (3H, d, $J$ = 7.0 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.02 (3F, d, $J_{HF}$ = 7.9 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 159.0, 158.9, 156.0, 145.7, 133.5, 130.5, 130.1, 129.2, 127.2, 125.3 (q, $J_{CF}$ = 281.5 Hz), 123.3, 122.8, 120.9, 113.8, 108.5, 63.9 (q, $J_{CF}$ = 26.7 Hz), 55.3, 39.9, 25.6, 17.4; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{22}F_3N_2O_2$: 403.1628, found: 403.1620.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 94:6.

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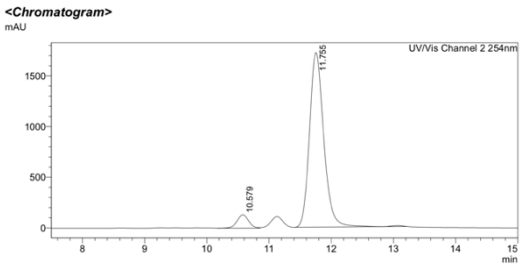


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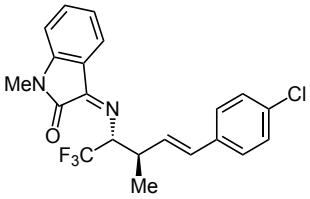
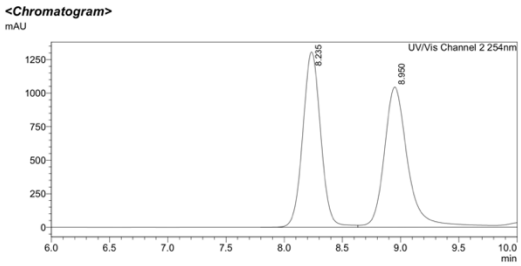



(*Z*)-3-(((*E*)-5-(4-chlorophenyl)-1,1,1-trifluoro-3-methylpent-4-en-2-yl)imino)-1-methylindolin-2-one (**3.17**). Title compound **3.17** was prepared according to general

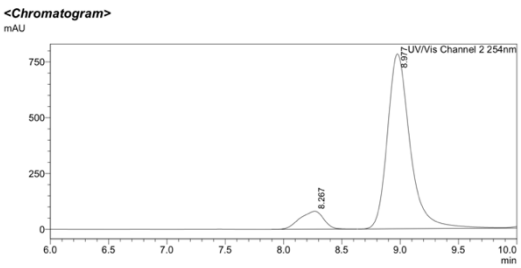
method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.17** as a yellow solid (45.5 mg, 0.112 mmol, 74.6% yield). **IR** (thin film) 2929 (w), 1715 (s), 1663 (w), 1613 (s), 1491 (w), 1472 (s), 1270 (m), 1151 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.67 (1H, d, $J$ = 7.4 Hz), 7.41 (1H, t, $J$ = 7.8 Hz), 7.23–7.11 (4H, m), 7.08 (1H, t, $J$ = 7.6 Hz), 6.72 (1H, d, $J$ = 7.8 Hz), 6.24–6.15 (2H, m), 6.11–6.01 (1H, m), 3.07 (3H, s), 2.98–2.89 (1H, m), 1.25 (3H, d, $J$ = 6.9 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.13 (3F, d, $J_{HF}$ = 7.6 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 158.9, 156.2, 145.7, 135.8, 133.7, 132.7, 132.0, 129.8, 128.5, 127.3, 125.2 (q, $J_{CF}$ = 281.72 Hz), 123.4, 122.8, 120.9, 108.6, 63.7 (q, $J_{CF}$ = 27.0 Hz), 39.8, 25.6, 17.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{19}ClF_3N_2O$: 407.1133, found: 407.1140. See section 3.5.8 for X-ray crystallography data for **3.17**.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er= 90.5:9.5.



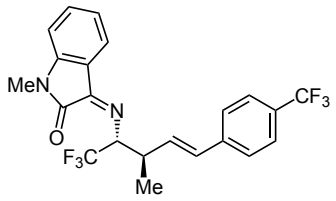

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.235 | 14007186 | 46.924 |
| 2 | 8.950 | 15843868 | 53.076 |
| Total | | 29851054 | 100.000 |



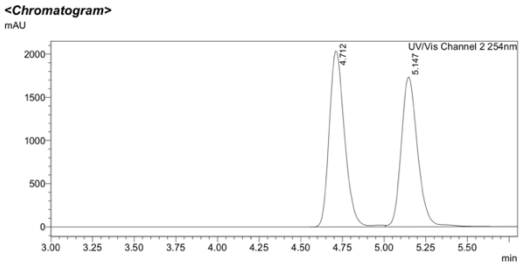

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.267 | 1128722 | 9.488 |
| 2 | 8.977 | 10767598 | 90.512 |
| Total | | 11896320 | 100.000 |



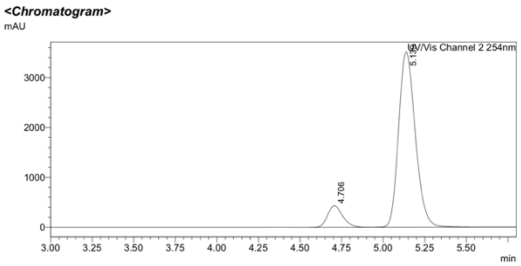

(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methyl-5-(4-(trifluoromethyl)phenyl)pent-4-en-2-yl)imino)indolin-2-one (**3.18**). Title compound **3.18** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.18** as a yellow solid (48.2 mg, 0.110 mmol, 73.6% yield). **IR** (thin film) 2940 (w), 1716 (m), 1614 (m), 1490 (w), 1472 (w), 1370 (w), 1324 (s), 1165 (m), 1123 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.68 (1H, d, $J$ = 7.5 Hz), 7.48 (2H, d, $J$ = 8.0 Hz), 7.42 (1H, t, $J$ = 7.8 Hz), 7.31 (2H, d, $J$ = 8.1 Hz), 7.09 (1H, t, $J$ = 7.6 Hz), 6.72 (1H, d, $J$ = 7.8 Hz), 6.33–6.31 (2H, m), 6.15–6.03 (1H, m), 3.07 (1H, s), 3.02–2.95 (1H, m), 1.26 (3H, d, $J$ = 6.9 Hz); **$^{19}$F NMR** (376 MHz, CDCl3) $\delta$ –62.50 (3F, s), –70.22 (3F, d, $J_{HF}$ = 7.7 Hz); **$^{13}$C{$^{19}$F} NMR** (126 MHz, $CDCl_3$) $\delta$ 158.9, 156.3, 145.7, 140.7, 134.0, 133.8, 129.7, 129.0, 126.2, 125.3, 125.2, 125.1, 123.4, 122.8, 120.8, 108.6, 63.6, 39.7, 25.6, 17.2; **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{22}H_{19}F_6N_2O$: 441.1396, found: 441.1407.

**HPLC**: Column: Cellulose-2 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 90:10.



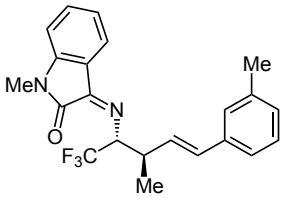

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 4.712 | 13028679 | 52.397 |
| 2 | 5.147 | 11836453 | 47.603 |
| Total | | 24865132 | 100.000 |



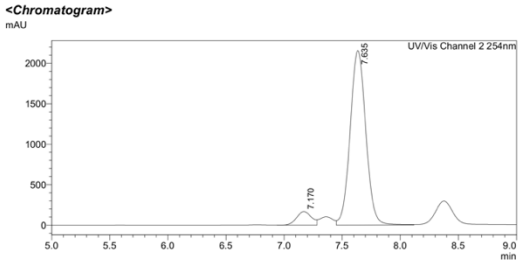

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 4.706 | 2722753 | 9.959 |
| 2 | 5.139 | 24616208 | 90.041 |
| Total | | 27338962 | 100.000 |



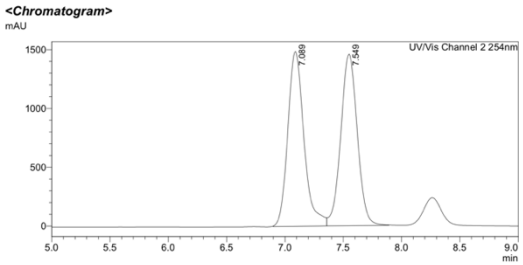

(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methyl-5-(m-tolyl)pent-4-en-2-yl)imino)indolin-2-one (**3.19**). Title compound **3.19** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.19** as a yellow oil (42.1 mg, 0.109 mmol, 72.4% yield). Note: contains 3% catalyst initiation byproduct. **IR** (thin film) 2934 (br), 1716 (s), 1490 (s), 1157 (s) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.69 (1H, d, $J$ = 7.4 Hz), 7.40 (1H, t, $J$ = 8.5 Hz), 7.13–7.06 (3H, m), 6.99 (3H, m), 6.69 (1H, d, $J$ = 7.8 Hz), 6.23–6.19 (1H, m), 6.17–6.13 (1H, m), 6.09–6.02 (m, 1H), 3.04 (s, 3H), 2.95–2.90 (1H, m), 2.27 (s, 3H), 1.27 (d, $J$ = 6.9 Hz, 3H); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.02 (3F, d, $J_{HF}$ = 7.8 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 159.0, 156.1, 145.7, 137.9, 137.2, 133.56, 131.3, 131.2, 128.3, 127.9, 126.9, 125.3 (q, $J_{CF}$ = 280.6 Hz), 123.3, 123.2, 122.8, 120.93, 108.50, 63.8 (q, $J_{CF}$ = 27.1 Hz), 39.9, 25.5, 21.4, 17.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{22}F_3N_2O$: 387.1679, found: 387.1690.

**HPLC**: Column: Cellulose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 93:7.



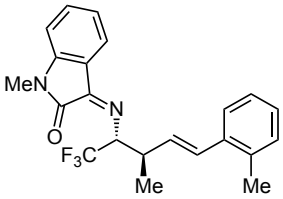

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 7.170 | 1508911 | 6.944 |
| 2 | 7.635 | 20221469 | 93.056 |
| Total | | 21730381 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

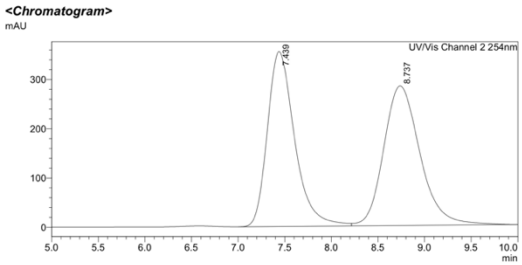
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 7.089 | 14365571 | 50.038 |
| 2 | 7.549 | 14343532 | 49.962 |
| Total | | 28709103 | 100.000 |




(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methyl-5-(*o*-tolyl)pent-4-en-2-yl)imino)indolin-2-one (**3.20**). Title compound **3.20** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.20** as a yellow oil (38.4 mg, 0.100 mmol, 66.2% yield). Note: contains 9:1 mixture of regioisomers **3.20**:**3.20′** with 3.20 in 59.6% yield and **3.20′** in 6.62% yield. **IR** (thin film); 2935 (w), 1715 (s), 1662 (w), 1268 (m) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 7.5 Hz), 7.40 (1H, t, *J* = 7.2 Hz), 7.34–7.29 (1H, m), 7.06 (4H, m), 6.71 (1H, d, *J* = 7.7 Hz), 6.45 (1H, d, *J* = 15.7 Hz), 6.15–5.94 (2H, m), 3.06 (3H, s), 2.10 (3H, s), 1.28 (3H, d, *J* = 7.1 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) *δ* –70.05 (3F, d, $J_{HF}$ = 7.5 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 159.0, 156.1, 145.7, 136.3, 135.2, 133.6, 132.6, 130.0, 129.0, 127.1,

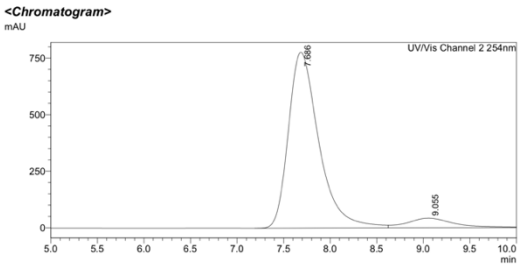
125.9, 125.6, 123.3, 122.8, 120.9, 108.5, 63.8 (q, $J_{CF}$ = 26.9 Hz), 40.1, 25.6, 19.5, 17.5; HRMS (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{22}F_3N_2O$: 387.1679, found: 387.1684.

**HPLC**: Column: Cellulose-3 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 92.5:7.5.



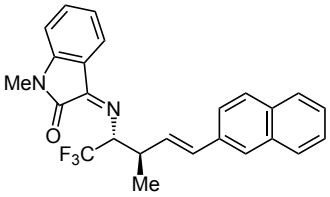

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 7.439 | 7225918 | 48.460 |
| 2 | 8.737 | 7685268 | 51.540 |
| Total | | 14911186 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

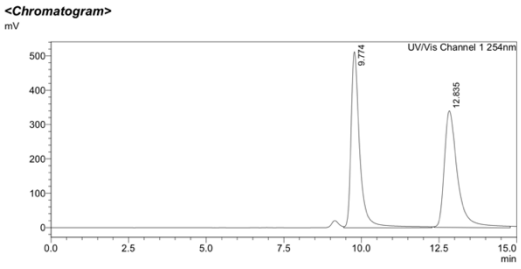
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 7.686 | 17716617 | 92.312 |
| 2 | 9.055 | 1475529 | 7.688 |
| Total | | 19192147 | 100.000 |




(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methyl-5-(naphthalen-2-yl)pent-4-en-2-yl)imino)indolin-2-one (**3.21**). Title compound **3.21** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.21** as a yellow solid (39.0 mg, 0.0920 mmol, 61.5% yield). Note: contains 3% catalyst initiation byproduct. **IR** (thin film) 3057 (w), 2938 (w), 1714 (s), 1661 (w), 1490 (m), 1370 (m), 1268 (m), 1124 (s) cm$^{-1}$ ; **$^1$H NMR** (400

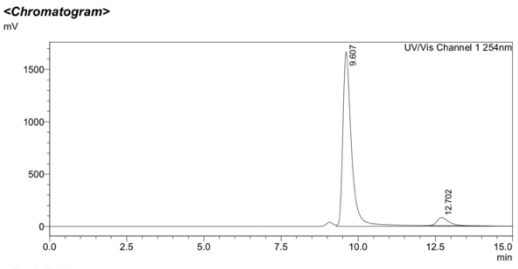
MHz, $CDCl_3$) δ 7.73 (4H, m), 7.55–7.32 (5H, m), 7.08 (1H, t, *J* = 7.3 Hz), 6.60 (1H, d, *J* = 7.7 Hz), 6.40 (1H, d, *J* = 15.8 Hz), 6.37–6.25 (1H, m), 6.17–6.07 (1H, m), 3.07–2.97 (1H, m), 2.96 (3H, s), 1.34 (3H, d, *J* = 6.3 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ –69.92 (3F, d, $J_{HF}$ = 7.2 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 159.1, 156.2, 145.7, 134.7, 133.6, 133.6, 132.8, 131.9, 131.3, 128.0, 127.9, 127.6, 126.2, 125.7, 125.7, 125.4 (q, $J_{CF}$ = 281.74 Hz), 123.6, 123.3, 122.8, 120.9, 108.6, 63.9 (q, $J_{HF}$ = 26.9 Hz), 40.0, 25.5, 17.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{25}H_{22}F_3N_2O$: 423.1679, found: 423.1689.

**HPLC**: Column: Amylose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 94:6.



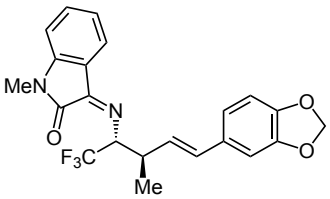

<Peak Table>
UV/Vis Channel 1 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 9.774 | 10077595 | 50.089 |
| 2 | 12.835 | 10041870 | 49.911 |
| Total | | 20119465 | 100.000 |




<Peak Table>
UV/Vis Channel 1 254nm

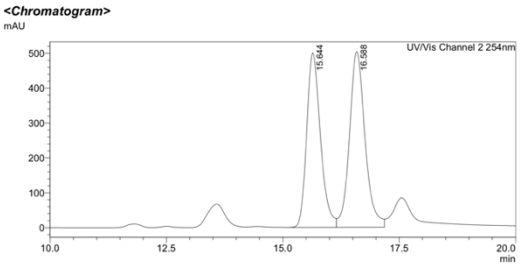
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 9.607 | 33332704 | 94.114 |
| 2 | 12.702 | 2084751 | 5.886 |
| Total | | 35417455 | 100.000 |




(*Z*)-3-(((E)-5-(benzo[d][1,3]dioxol-5-yl)-1,1,1-trifluoro-3-methylpent-4-en-2-yl)imino)-1-methylindolin-2-one (**3.22**). Title compound **3.22** was prepared according to general

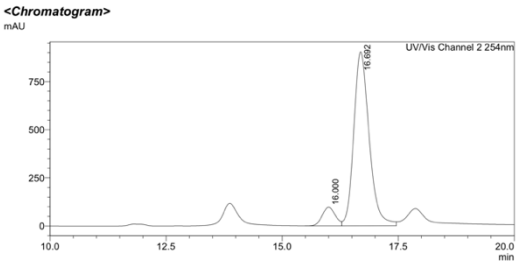
method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.22** as a yellow solid (51.2 mg, 0.123 mmol, 82.0% yield). **IR** (thin film) 2933 (br), 1714 (s), 1491 (s), 1251 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.67 (1H, d, $J$ = 7.4 Hz), 7.41 (1H, t, $J$ = 7.8 Hz), 7.08 (1H, t, $J$ = 7.6 Hz), 6.79–6.78 (1H, m), 6.72 (1H, d, $J$ = 7.8 Hz), 6.68–6.58 (2H, m), 6.17 (1H, d, $J$ = 15.8 Hz), 6.06–6.02 (2H, m), 5.90 (s, 2H), 3.09 (s, 3H), 2.91 (1H, m), 1.24 (3H, d, $J$ = 6.9 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.09 (3F, d, $J_{HF}$ = 7.6 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 159.0, 156.1, 147.9, 146.8, 145.7, 133.6, 131.8, 130.6, 129.6, 125.3 (q, $J_{CF}$ = 282.0 Hz), 123.3, 122.8, 120.9, 120.6, 108.5, 108.1, 105.6, 100.9, 63.8 (q, $J_{CF}$ = 26.6 Hz), 39.8, 25.6, 17.4; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{22}H_{20}F_3N_2O_3$: 417.1421, found: 417.1432.

**HPLC**: Column: Cellulose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99.9:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 91.5:8.5.



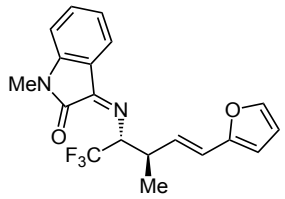

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 15.644 | 10276817 | 46.760 |
| 2 | 16.588 | 11700917 | 53.240 |
| Total | | 21977734 | 100.000 |



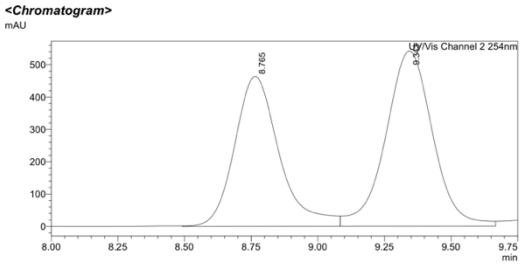

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 16.000 | 1904133 | 8.369 |
| 2 | 16.692 | 20848082 | 91.631 |
| Total | | 22752216 | 100.000 |



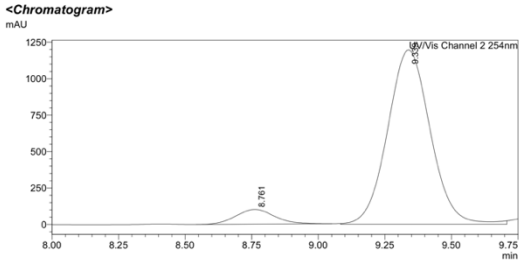

(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-5-(furan-2-yl)-3-methylpent-4-en-2-yl)imino)indolin-2-one (**3.23**). Title compound **3.23** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.23** as a yellow oil (31.5 mg, 0.0867 mmol, 57.8% yield). **IR** (thin film) 2930 (w), 2164 (s), 1714 (m), 1613 (m), 1270 (br) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.68 (1H, d, $J$ = 8.2 Hz), 7.42 (1H, t, $J$ = 7.8 Hz), 7.28 (1H, d, $J$ = 1.6 Hz), 7.08 (1H, t, $J$ = 7.5 Hz), 6.75 (1H, d, $J$ = 7.8 Hz), 6.30–6.29 (1H, m), 6.20–6.17 (2H, m), 6.14–6.07 (2H, m), 3.14 (3H, s), 2.97–2.92 (1H, m), 1.22 (3H, d, $J$ = 6.9 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.20 (3F, d, $J_{HF}$ = 7.5 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 158.8, 156.4, 152.8, 145.8, 141.6, 133.7, 129.8, 125.1 (q, $J_{CF}$ = 282.6 Hz), 123.4, 122.9, 120.9, 119.6, 111.1, 108.5, 107.0, 63.7 (q, $J_{CF}$ = 26.8 Hz), 39.6, 25.7, 17.4; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{19}H_{18}F_3N_2O_2$: 363.1315, found: 363.1306.

**HPLC**: Column: Cellulose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 93:7.



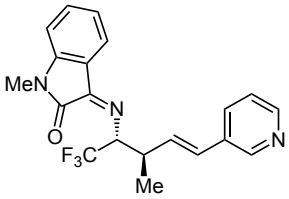

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.765 | 5400134 | 44.901 |
| 2 | 9.343 | 6626624 | 55.099 |
| Total | | 12026758 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

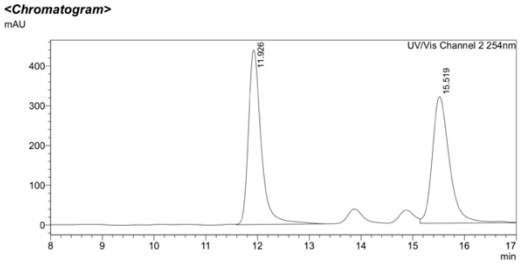
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.761 | 1030326 | 7.179 |
| 2 | 9.339 | 13322397 | 92.821 |
| Total | | 14352722 | 100.000 |




(*Z*)-1-methyl-3-(((2*R*,3*R*,*E*)-1,1,1-trifluoro-3-methyl-5-(pyridin-3-yl)pent-4-en-2-yl)imino)indolin-2-one (**3.24**). Title compound **3.24** was prepared according to general method A at 22 °C. The material was purified by flash column chromatography (100% hexanes to 70:30:1 hexanes:EtOAc:triethylamine) to obtain **3.24** as a yellow oil (46.1 mg, 0.124 mmol, 82.4% yield). **IR** (thin film) 2938 (w), 1714 (s), 1661 (w), 1612 (s), 1491 (s), 1370 (m), 1149 (s), 1124 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.42–8.38 (2H, m), 7.66 (1H, d, $J$ = 7.3 Hz, 1H), 7.56 (1H, d, $J$ = 8.0 Hz), 7.40 (1H, td, $J$ = 7.8, 1.4 Hz), 7.15 (1H, dd, $J$ = 7.9, 4.8 Hz), 7.07 (1H, t, $J$ = 7.5 Hz), 6.72 (1H, d, $J$ = 7.9 Hz), 6.29–6.28 (2H, m), 6.13–6.06 (1H, m), 3.08 (3H, s), 3.01–2.96 (1H, m), 1.25 (3H, d, $J$ = 6.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.23 (3F, d, $J_{HF}$ = 7.7 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 159.0, 156.4, 148.3, 148.0, 145.7, 133.8, 133.7, 132.9, 132.7, 127.5, 125.2 (q, $J_{CF}$ = 280.9 Hz), 123.4, 123.3, 122.9,

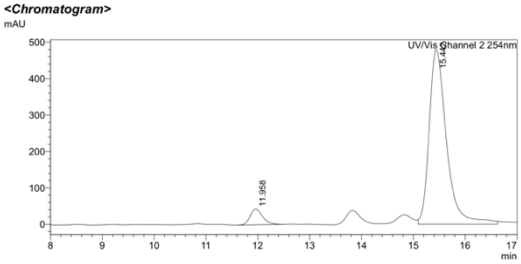
120.8, 108.6, 63.6 (q, $J_{CF}$ = 27.1 Hz), 39.8, 25.7, 17.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{20}H_{19}F_3N_3O$: 374.1475, found: 374.1480.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 90:10 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 94:6.



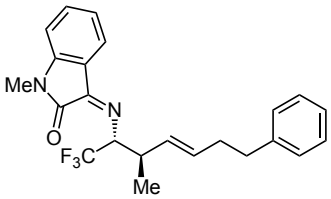

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.926 | 7530559 | 50.645 |
| 2 | 15.519 | 7338726 | 49.355 |
| Total | | 14869284 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

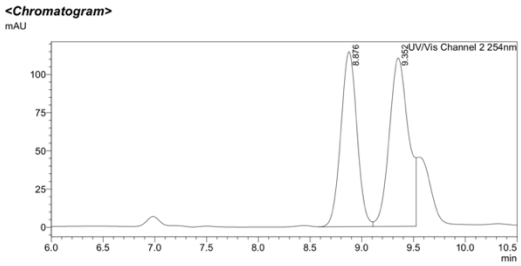
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.958 | 720325 | 6.056 |
| 2 | 15.442 | 11174293 | 93.944 |
| Total | | 11894618 | 100.000 |




(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methyl-7-phenylhept-4-en-2-yl)imino)indolin-2-one (**3.30**). Title compound **3.30** was prepared according to general method A at 50 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.30** as a yellow oil (41.5 mg, 0.104 mmol, 69.1% yield). Note: contains 2% catalyst initiation byproduct. **IR** (thin film) 3028 (w), 2938 (w), 1716 (s), 1613 (s), 1472 (s), 1157 (s) cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.68 (1H, d, $J$ = 7.4 Hz), 7.44 (1H, t, $J$ = 7.7 Hz), 7.24–7.20 (2H, m), 7.15–7.11 (2H, m), 7.09–7.04 (2H, m), 6.80 (d, $J$ = 7.9 Hz,

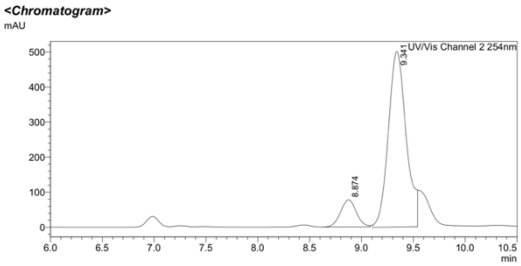
1H), 6.04–5.97 (1H, m), 5.53–5.43 (2H, m), 3.20 (3H, s), 2.81–2.75 (1H, m), 2.53–2.47 (2H, m), 2.24–2.19 (2H, m), 1.15 (3H, d, $J$ = 6.9 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.01 (3F, d, $J_{HF}$ = 7.7 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 158.9, 155.7, 145.7, 141.9, 133.6, 131.5, 131.1, 128.3, 128.2, 125.7, 125.3 (q, $J_{CF}$ = 280.8 Hz), 123.4, 122.9, 121.0, 108.6, 63.8 (q, $J_{CF}$ = 26.7 Hz), 39.4, 35.9, 34.2, 25.8, 17.6; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{23}H_{24}F_3N_2O_2$: 401.1835, found: 401.1838.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 88:12.



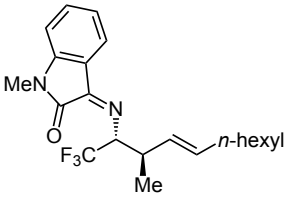

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.876 | 1244967 | 46.696 |
| 2 | 9.352 | 1421147 | 53.304 |
| Total | | 2666114 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

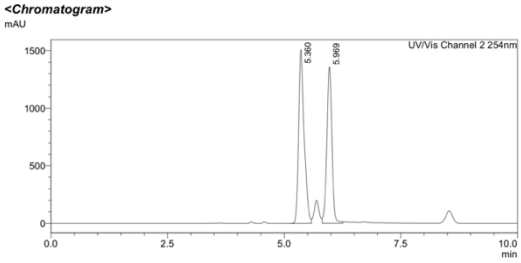
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.874 | 820910 | 12.016 |
| 2 | 9.341 | 6010665 | 87.984 |
| Total | | 6831575 | 100.000 |




(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methylundec-4-en-2-yl)imino)indolin-2-one (**3.31**). Title compound **3.31** was prepared according to general method A at 50 °C. The material was purified by flash column chromatography (100% hexanes to 99:1 hexanes:EtOAc) to

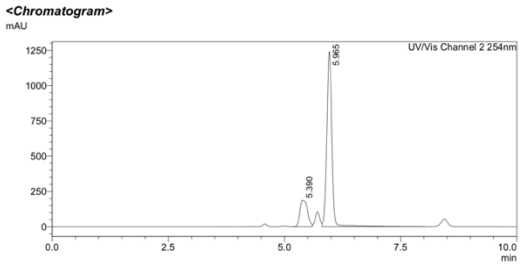
obtain **3.31** as a yellow oil (34.3 mg, 0.0900 mmol, 60.0% yield). **IR** (thin film) 2928 (w), 2856 (w), 1712 (s), 1663 (w), 1472 (s), 1370 (s), 1156 (s), 1123 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.66 (1H, d, $J$ = 7.4 Hz), 7.42 (1H, t, $J$ = 7.8 Hz), 7.08 (1H, t, $J$ = 7.4 Hz), 6.78 (1H, d, $J$ = 7.8 Hz), 6.00–5.92 (1H, m), 5.36–5.33 (2H, m), 3.18 (3H, s), 2.78–2.72 (1H, m), 1.90–1.80 (2H, m), 1.24–1.11 (11H, m), 0.81 (3H, t, $J$ = 7.1 Hz ); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.05 (d, 3F, $J_{HF}$ = 8.0 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 158.9, 155.6, 145.7, 133.5, 132.3, 130.8, 125.4 (q, $J_{CF}$ = 281.3 Hz), 123.3, 122.8, 121.0, 108.5, 63.8 (q, $J_{CF}$ = 26.8 Hz), 39.4, 32.3, 31.7, 29.3, 28.7, 25.7, 22.5, 17.6, 14.1; **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{21}H_{28}F_3N_2O$: 381.2148, found: 381.2154.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 81.5:18.5.



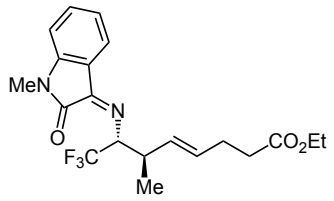

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 5.360 | 12515234 | 55.292 |
| 2 | 5.969 | 10119490 | 44.708 |
| Total | | 22634723 | 100.000 |



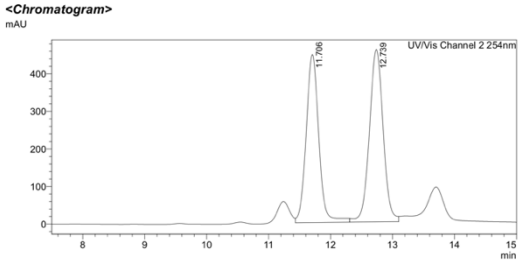

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 5.390 | 2123396 | 18.443 |
| 2 | 5.965 | 9390056 | 81.557 |
| Total | | 11513452 | 100.000 |



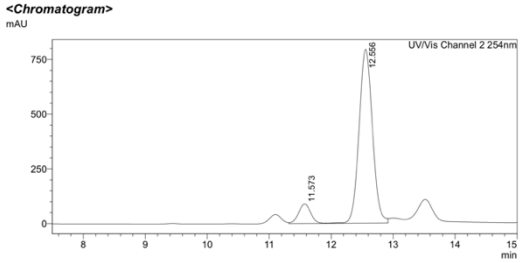

Ethyl (6*R*,7*R*,*E*)-8,8,8-trifluoro-6-methyl-7-(((*Z*)-1-methyl-2-oxoindolin-3-ylidene)amino)oct-4-enoate (**3.32**). Title compound **3.32** was prepared according to general method A at 50 °C. The material was purified by flash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.32** as a yellow oil (49.5 mg, 0.125 mmol, 83.2% yield). **IR** (thin film) 2979 (w), 2882 (w), 1734 (s), 1717 (s), 1491 (m), 1472 (w), 1371 (m), 1159 (m) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.66 (1H, d, $J$ = 7.5 Hz), 7.43 (1H, t, $J$ = 7.8 Hz), 7.09 (1H, t, $J$ = 7.6 Hz), 6.79 (1H, d, $J$ = 7.8 Hz), 6.03–5.95 (1H, m), 5.52–5.46 (1H, m) 5.43–5.36 (1H, m), 4.04 (2H, q, $J$ = 7.8 Hz), 3.19 (3H, s), 2.82–2.75 (1H, m), 2.21 (4H, s), 1.20 (3H, t, $J$ = 7.2 Hz), 1.11 (3H, d, $J$ = 6.9 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.19 (d, 3F, $J_{HF}$ = 7.8 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 173.0, 158.9, 155.9, 145.8, 133.6, 132.0, 129.7, 125.2 (q, $J_{CF}$ = 281.0 Hz), 123.4, 122.8, 120.9, 108.6, 63.6 (q, $J_{CF}$ = 26.9 Hz), 60.2, 39.2, 34.0, 27.7, 25.8, 17.6, 14.2; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{20}H_{24}F_3N_2O_3$: 397.1734, found: 397.1740.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 90.5:9.5.



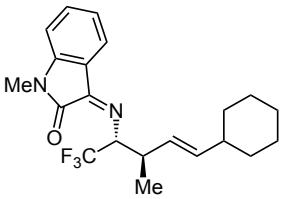

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.706 | 6365415 | 47.287 |
| 2 | 12.739 | 7095891 | 52.713 |
| Total | | 13461305 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

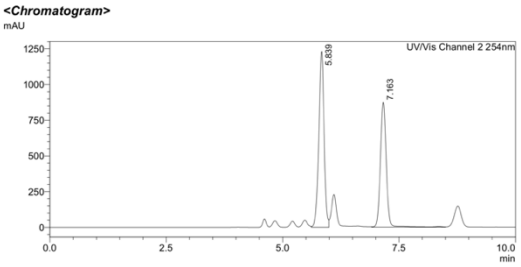
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.573 | 1215780 | 9.239 |
| 2 | 12.556 | 11943436 | 90.761 |
| Total | | 13159215 | 100.000 |




(*Z*)-3-(((2*R*,3*R*,*E*)-5-cyclohexyl-1,1,1-trifluoro-3-methylpent-4-en-2-yl)imino)-1-methylindolin-2-one (**3.33**). Title compound **3.33** was prepared according to general method A at 50 °C. The material was purified by combiflash column chromatography (100% hexanes to 25:1 hexanes:EtOAc) to obtain **3.33** as a yellow oil (24.7 mg, 0.0651 mmol, 43.5% yield). **IR** (thin film) 2924 (m), 2851 (m), 1716 (s), 1612 (s), 1491 (s), 1155 (s), 1123 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.65 (1H, d, $J$ = 7.5 Hz, 1H), 7.42 (1H, t, $J$ = 7.8 Hz), 7.08 (1H, t, $J$ = 7.6 Hz), 6.78 (1H, $J$ = 7.7 Hz), 5.98–5.91 (1H, m), 5.28–5.26 (2H, m), 3.18 (3H, s), 1.73–1.69 (1H, m) 1.59–1.44 (6H, m) , 1.26–1.22 (1H, m), 1.15 (3H, d, $J$ = 6.8 Hz), 0.97–0.77 (4H, m); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.01 (d, 3F, $J_{HF}$ = 7.8 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 159.0, 155.5, 145.7, 138.1, 133.5, 128.4, 125.4 (q, $J_{CF}$ = 281.3 Hz), 123.3, 122.8, 121.0, 108.4, 63.9 (q, $J_{CF}$ = 26.7 Hz), 40.2, 39.5, 32.9, 32.6, 26.2, 25.9, 25.9, 25.7,

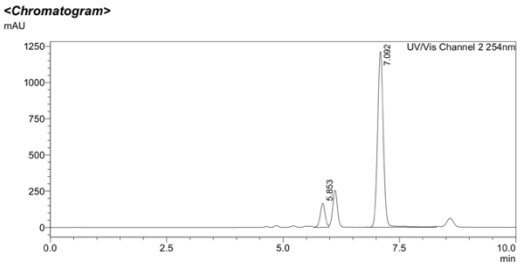
17.6 (One sp3 carbon extra due to different conformations of cyclohexyl substituent); **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{21}H_{26}F_3N_2O$: 379.1992, found: 379.1995.

**HPLC**: Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 90:10.



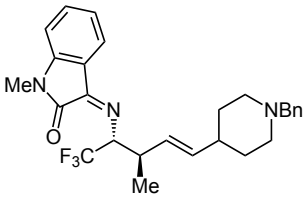

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 5.839 | 9622171 | 55.370 |
| 2 | 7.163 | 7755820 | 44.630 |
| Total | | 17377990 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

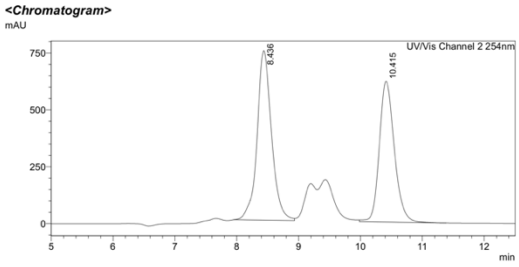
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 5.853 | 1191390 | 10.086 |
| 2 | 7.092 | 10621505 | 89.914 |
| Total | | 11812894 | 100.000 |




(*Z*)-3-(((2*R*,3*R*,*E*)-5-(1-benzylpiperidin-4-yl)-1,1,1-trifluoro-3-methylpent-4-en-2-yl)imino)-1-methylindolin-2-one (**3.34**). Title compound **3.34** was prepared according to general method A at 50 °C. The material was purified by flash column chromatography (100% hexanes to 90:10:1 hexanes:EtOAc:triethylamine) to obtain **3.34** as a yellow oil (58.3 mg, 0.124 mmol, 82.7% yield). Note: contains 11:1 mixture of regioisomers **3.34**: **3.34'** with 3.34 in 75.8% yield and **3.34'** in 6.89% yield. **IR** (thin film) 3028 (w), 2934 (m), 2800 (w), 2756 (w), 1716 (s), 1613 (s), 1492 (w), 1471 (s), 1369 (w), 1144 (s) cm$^{-1}$; **$^1$H NMR**

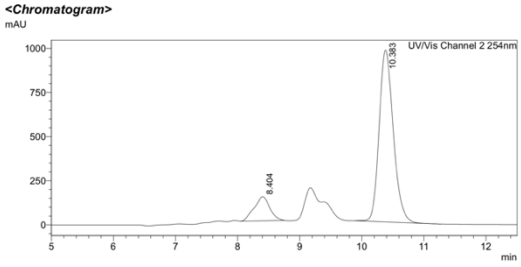
(400 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 7.0 Hz), 7.35 (1H, t, *J* = 8.3 Hz), 7.23–7.16 (5H, m), 7.02 (1H, t, *J* = 7.5 Hz), 6.71 (1H, d, *J* = 7.9 Hz), 5.93–5.87 (1H, m), 5.29–5.21 (2H, m), 3.35 (2H, s), 3.12 (3H, s), 2.69–2.65 (3H, m), 1.84–1.76 (3H, m), 1.43–1.31 (2H, m), 1.19–1.12 (2H, m), 1.09 (3H, d, *J* = 6.9 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) *δ* –70.01 (d, 3F, $J_{HF}$ = 7.8 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) *δ* 159.0, 155.6, 145.7, 138.7, 136.7, 133.5, 129.2, 129.1, 128.1, 126.9, 125.3 (q, $J_{CF}$ = 281.3 Hz), 123.4, 122.8, 121.0, 108.5, 63.8 (q, $J_{CF}$ = 26.7 Hz), 53.5, 39.4, 38.4, 32.0, 31.8, 25.8, 17.6; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{27}H_{31}F_3N_3O$: 470.2414, found: 470.2424.

**HPLC**: Column: Chiralpak 1-A3 (3 μm, 4.6 mm X 150 mm). Mobile phase: 80:20 i-PrOH (with 0.1% $Et_2NH$):MeOH (with 0.1% $Et_2NH$), 0.3 mL/min. Detection wavelength: 254 nm. Er = 86.5:13.5.



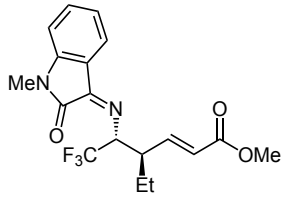

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.436 | 12082158 | 53.612 |
| 2 | 10.415 | 10453931 | 46.388 |
| Total | | 22536089 | 100.000 |



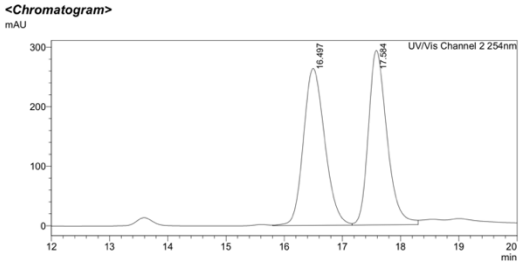

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.404 | 2369642 | 13.315 |
| 2 | 10.383 | 15427589 | 86.685 |
| Total | | 17797231 | 100.000 |



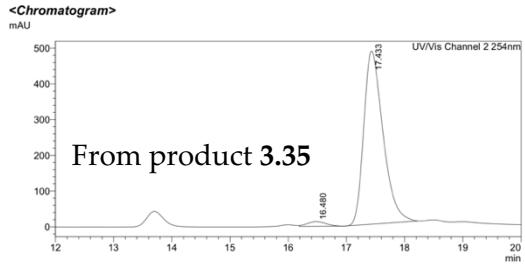

Methyl (4*R*,5*R*,*E*)-4-ethyl-6,6,6-trifluoro-5-(((*Z*)-1-methyl-2-oxoindolin-3-ylidene)amino)hex-2-enoate (**3.36**). Title compound **3.36** was prepared from **3.36** according to general method A at 50 °C. The material was purified by flash column chromatography (100% hexanes to 90:10:1 hexanes:EtOAc:triethylamine) to obtain **3.36** as a yellow oil (26.5 mg, 0.0718 mmol, 47.9% yield). Similarly, **3.36** was also prepared from **3.37** according to general method A at 50 °C to obtain **3.36** as a yellow oil (9.8 mg, 0.027 mmol, 17.7% yield). **IR** (thin film) 2952 (w), 1718 (s), 1660 (w), 1613 (s), 1491 (w), 1472 (s), 1270 (m), 1169 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.63 (1H, d, $J$ = 7.1 Hz), 7.39 (1H, t, $J$ = 7.8 Hz), 7.06–6.99 (2H, m), 6.74 (1H, d, $J$ = 7.8 Hz), 6.28–6.24 (1H, m), 5.84 (1H, d, $J$ = 15.7 Hz), 3.66 (3H, s), 3.14 (3H, s), 2.72–2.66 (1H, m), 1.61–1.53 (1H, m), 1.31–1.23 (1H, m), 0.79 (3H, t, $J$ = 7.4 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ –70.83 (d, 3F, $J_{HF}$ = 7.6 Hz); **$^{13}$C[$^{19}$F] NMR** (126 MHz, $CDCl_3$) $\delta$ 166.6, 158.7, 157.3, 147.1, 145.9, 134.0, 124.6, 123.5, 123.1, 123.1, 120.8, 108.6, 62.1, 51.4, 45.8, 25.8, 24.1, 11.7; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{18}H_{20}F_3N_2O_3$: 369.1421, found: 369.1426.

**HPLC**: Column: Cellulose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 97.5:2.5.



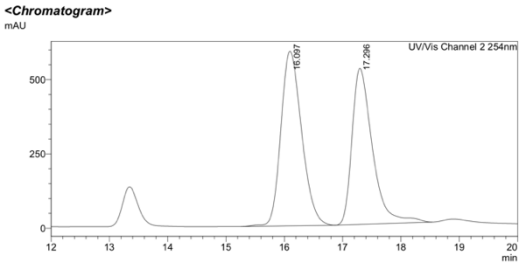

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 16.497 | 6722714 | 50.778 |
| 2 | 17.584 | 6516609 | 49.222 |
| Total | | 13239323 | 100.000 |



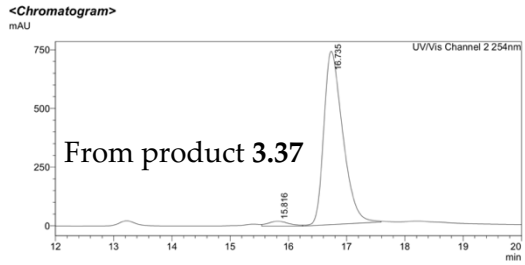

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 16.480 | 292166 | 2.550 |
| 2 | 17.433 | 11167374 | 97.450 |
| Total | | 11459540 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

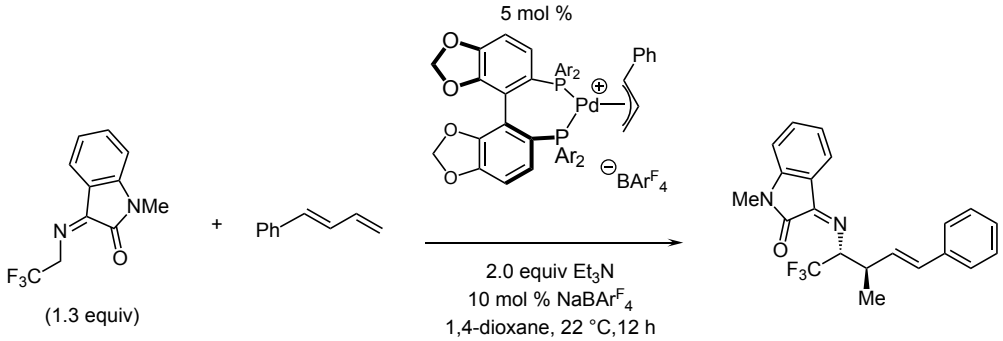
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 16.097 | 14569830 | 53.232 |
| 2 | 17.296 | 12800780 | 46.768 |
| Total | | 27370610 | 100.000 |




<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 15.816 | 512704 | 2.968 |
| 2 | 16.735 | 16763281 | 97.032 |
| Total | | 17275985 | 100.000 |

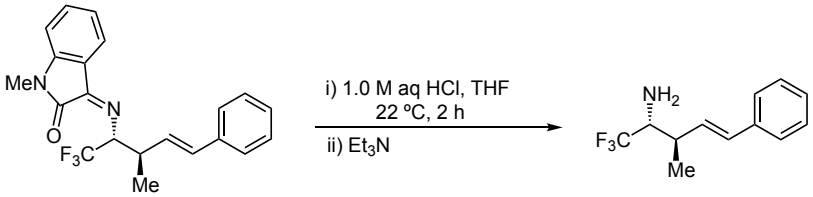
## 3.5.7 Reaction Scale Up




(*Z*)-1-methyl-3-(((*E*)-1,1,1-trifluoro-3-methyl-5-phenylpent-4-en-2-yl)imino)indolin-2-one (**3.6**). In an $N_2$-filled glovebox, a 25-mL round-bottom flask, equipped with stir bar, was charged with **[Pd]** (114 mg, 0.050 mmol), *N*-trifluoroethyl imine **3.5** (315 mg, 1.30 mmol, 1.30 equiv), $NaBAr^{F_4}$ (88.6 mg, 0.100 mmol, 0.100 equiv), and dioxane (1.33 mL). (*E*)-

buta-1,3-dien-1-ylbenzene **3.2** (0.15 mmol, 1.00 equiv) and triethylamine (279 μL, 2.00 mmol, 2.00 equiv) were added to the flask. The flask was removed from the glovebox and allowed to stir at 22 °C for 12 h. The reaction mixture was filtered through a celite plug and rinsed with ethyl acetate (3 X 50 mL). The solution was concentrated, and the residue purified by flash column chromatography to afford **3.6** as a yellow solid (304 mg, 0.816 mmol, 81.6% yield).

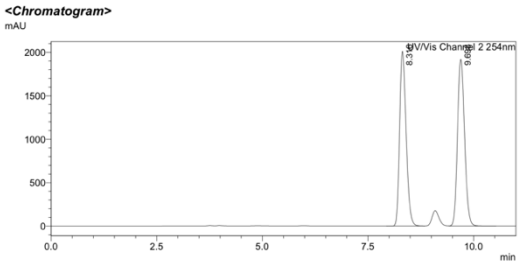
### 3.5.8 Hydrolysis of Imines in Product




(*E*)-1,1,1-trifluoro-3-methyl-5-phenylpent-4-en-2-amine (**3.42**). A 2-dram vial, equipped with stir bar, was charged with imine **3.6** (46.0 mg, 0.123 mmol, 1.00 equiv), THF (1 mL), and 1.0 M aq HCl (0.500 mL). The mixture was allowed to stir for 2 h at 22 °C whereupon it was diluted with triethylamine (1 mL, 7.17 mmol, 58.3 mmol). The solution was concentrated and purified by flash column chromatography with silica gel (50:1 hexanes:EtOAc to 25:1 hexanes: EtOAc) to afford the title compound as a faint yellow oil (21.8 mg, 0.0947 mmol, 77.0% yield). **IR** (thin film) 3408 (br), 3027 (w), 2971 (w), 1599 (w), 1263 (s), 1120 (s) $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.29 (2H, d, $J$ = 7.3 Hz), 7.24 (2H, t, $J$ = 7.6 Hz), 7.16 (1H, t, $J$ = 7.3 Hz), 6.41 (1H, d, $J$ = 15.9 Hz), 6.09 (1H, dd, $J$ = 15.9, 8.0 Hz), 3.10–3.09 (1H, m), 2.75–2.67 (1H, m), 1.20 (3H, d, $J$ = 6.9 Hz); **$^{19}$F NMR** (376

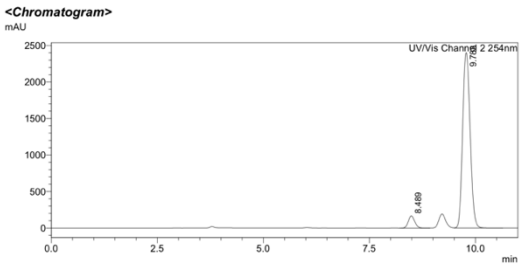
MHz, $CDCl_3$) $\delta$ –74.78 (3F, d, $J_{HF}$ = 7.8 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 137.0, 132.1, 129.1, 128.6, 127.5, 126.6 (q, $J_{CF}$ = 283.0 Hz), 126.3, 57.7 (q, $J_{CF}$ = 27.2 Hz), 37.0, 17.9; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{12}H_{15}F_3N$: 230.1151, found: 230.1165.

**HPLC**: Column: Amylose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:i-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 94.5:5.5.




<Peak Table>
UV/Vis Channel 2 254nm

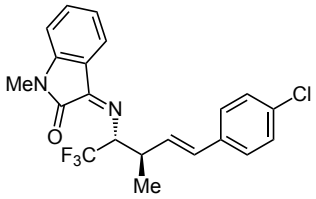
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.316 | 21604846 | 49.162 |
| 2 | 9.698 | 22341105 | 50.838 |
| Total | | 43945951 | 100.000 |



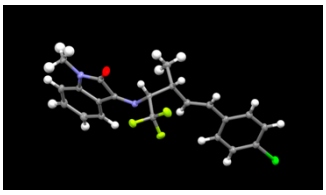

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.489 | 1728714 | 5.550 |
| 2 | 9.783 | 29421033 | 94.450 |
| Total | | 31149747 | 100.000 |

## 3.5.9 X-ray crystallographic data for 3.17




≡



**Sample and crystal data for rds943V**

| | | |
|---|---|---|
| **Identification code** | rds943V | |
| **Chemical formula** | $C_{21}H_{18}ClF_3N_2O$ | |
| **Formula weight** | 406.82 g/mol | |
| **Temperature** | 100(2) K | |
| **Wavelength** | 1.54178 Å | |
| **Crystal size** | 0.058 x 0.125 x 0.198 mm | |
| **Crystal habit** | yellow rod | |
| **Crystal system** | orthorhombic | |
| **Space group** | P 21 21 21 | |
| **Unit cell dimensions** | a = 7.5125(2) Å | $\alpha$ = 90° |
| | b = 11.9615(3) Å | $\beta$ = 90° |
| | c = 21.0233(6) Å | $\gamma$ = 90° |
| **Volume** | 1889.17(9) $Å^3$ | |
| **Z** | 4 | |
| **Density (calculated)** | 1.430 $g/cm^3$ | |
| **Absorption coefficient** | 2.177 $mm^{-1}$ | |
| **F(000)** | 840 | |

**Data collection and structure refinement for rds943V**

| | | |
|---|---|---|
| **Diffractometer** | Bruker D8 VENTURE | |
| **Radiation source** | Incoatec IμS 3.0 microfocus sealed tube (Cu K$\alpha$, $\lambda$ = 1.54178 Å) | |
| **Theta range for data collection** | 4.21 to 79.86° | |
| **Index ranges** | -9<=h<=9, -15<=k<=15, -26<=l<=25 | |
| **Reflections collected** | 34309 | |
| **Independent reflections** | 3990 [R(int) = 0.0237] | |
| **Coverage of independent reflections** | 99.2% | |
| **Absorption correction** | Numerical Mu Calculated | |
| **Max. and min. transmission** | 0.8840 and 0.6720 | |
| **Structure solution technique** | direct methods | |
| **Structure solution program** | XT, VERSION 2014/5 (Sheldrick, 2015) | |
| **Refinement method** | Full-matrix least-squares on $F^2$ | |
| **Refinement program** | SHELXL-2018/3 (Sheldrick, 2015) | |
| **Function minimized** | $\Sigma\ w(F_o^2 - F_c^2)^2$ | |
| **Data / restraints / parameters** | 3990 / 0 / 255 | |
| **Goodness-of-fit on $F^2$** | 1.064 | |
| **$\Delta/\sigma_{max}$** | 0.001 | |
| **Final R indices** | 3954 data; I>2σ(I) | R1 = 0.0214, wR2 = 0.0573 |
| | all data | R1 = 0.0215, wR2 = 0.0575 |
| **Weighting scheme** | $w=1/[\sigma^2(F_o^2)+(0.0278P)^2+0.3940P]$ where $P=(F_o^2+2F_c^2)/3$ | |
| **Absolute structure parameter** | 0.035(2) | |
| **Largest diff. peak and hole** | 0.214 and -0.160 eÅ$^{-3}$ | |
| **R.M.S. deviation from mean** | 0.033 eÅ$^{-3}$ | |

**Atomic coordinates and equivalent isotropic atomic displacement parameters (Å2) for rds943V**

U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | x/a | y/b | z/c | U(eq) |
|---|---|---|---|---|
| Cl1 | 0.59189(6) | 0.80268(3) | 0.33663(2) | 0.02634(10) |
| F1 | 0.19916(13) | 0.18309(8) | 0.43833(5) | 0.0266(2) |
| F2 | 0.21191(14) | 0.06034(10) | 0.36316(4) | 0.0297(2) |
| F3 | 0.13527(13) | 0.01169(8) | 0.45814(5) | 0.0250(2) |
| O1 | 0.4666(2) | 0.82210(9) | 0.49612(5) | 0.0301(3) |
| N1 | 0.55123(19) | 0.83943(11) | 0.60084(6) | 0.0207(3) |
| N2 | 0.46512(18) | 0.08254(10) | 0.50778(6) | 0.0170(3) |
| C1 | 0.4987(2) | 0.87874(13) | 0.54265(7) | 0.0205(3) |
| C2 | 0.4899(2) | 0.00728(12) | 0.54957(7) | 0.0165(3) |
| C3 | 0.5287(2) | 0.02874(13) | 0.61682(7) | 0.0164(3) |
| C4 | 0.5361(2) | 0.12690(13) | 0.65113(7) | 0.0186(3) |
| C5 | 0.5848(2) | 0.12126(14) | 0.71509(7) | 0.0232(3) |
| C6 | 0.6241(2) | 0.01883(15) | 0.74300(7) | 0.0255(4) |
| C7 | 0.6161(2) | 0.91902(14) | 0.70893(7) | 0.0224(3) |
| C8 | 0.5680(2) | 0.92612(13) | 0.64551(7) | 0.0178(3) |
| C9 | 0.4383(2) | 0.05102(12) | 0.44108(7) | 0.0164(3) |
| C10 | 0.5725(2) | 0.11312(12) | 0.39791(7) | 0.0175(3) |
| C11 | 0.5581(2) | 0.23867(12) | 0.39916(7) | 0.0183(3) |
| C12 | 0.5596(2) | 0.30192(13) | 0.34708(7) | 0.0187(3) |
| C13 | 0.56106(19) | 0.42498(12) | 0.34527(7) | 0.0177(3) |
| C14 | 0.6190(2) | 0.47969(13) | 0.29012(7) | 0.0190(3) |
| C15 | 0.6298(2) | 0.59533(13) | 0.28723(7) | 0.0195(3) |
| C16 | 0.5809(2) | 0.65686(12) | 0.34038(7) | 0.0188(3) |
| C17 | 0.5218(2) | 0.60607(13) | 0.39578(7) | 0.0205(3) |
| C18 | 0.5115(2) | 0.49028(13) | 0.39740(7) | 0.0190(3) |
| C19 | 0.5840(3) | 0.72183(13) | 0.61338(8) | 0.0283(4) |
| C20 | 0.2470(2) | 0.07820(14) | 0.42521(7) | 0.0199(3) |
| C21 | 0.7610(2) | 0.07802(15) | 0.41773(8) | 0.0235(3) |

**Bond lengths (Å) for rds943V**

| | | | |
|---|---|---|---|
| Cl1-C16 | 1.7479(15) | F1-C20 | 1.3338(19) |
| F2-C20 | 1.3480(18) | F3-C20 | 1.3478(18) |
| O1-C1 | 1.214(2) | N1-C1 | 1.369(2) |
| N1-C8 | 1.405(2) | N1-C19 | 1.4522(19) |
| N2-C2 | 1.271(2) | N2-C9 | 1.4661(18) |
| C1-C2 | 1.546(2) | C2-C3 | 1.466(2) |
| C3-C4 | 1.379(2) | C3-C8 | 1.399(2) |
| C4-C5 | 1.395(2) | C4-H4 | 0.95 |
| C5-C6 | 1.390(2) | C5-H5 | 0.95 |
| C6-C7 | 1.394(2) | C6-H6 | 0.95 |
| C7-C8 | 1.384(2) | C7-H7 | 0.95 |
| C9-C20 | 1.511(2) | C9-C10 | 1.546(2) |
| C9-H9 | 1.0 | C10-C11 | 1.506(2) |
| C10-C21 | 1.535(2) | C10-H10 | 1.0 |
| C11-C12 | 1.331(2) | C11-H11 | 0.95 |
| C12-C13 | 1.473(2) | C12-H12 | 0.95 |
| C13-C18 | 1.396(2) | C13-C14 | 1.401(2) |
| C14-C15 | 1.387(2) | C14-H14 | 0.95 |
| C15-C16 | 1.387(2) | C15-H15 | 0.95 |
| C16-C17 | 1.387(2) | C17-C18 | 1.388(2) |
| C17-H17 | 0.95 | C18-H18 | 0.95 |
| C19-H19A | 0.98 | C19-H19B | 0.98 |
| C19-H19C | 0.98 | C21-H21A | 0.98 |
| C21-H21B | 0.98 | C21-H21C | 0.98 |

**Bond angles (°) for rds943V**

| | | | |
|---|---|---|---|
| C1-N1-C8 | 111.71(13) | C1-N1-C19 | 122.95(13) |
| C8-N1-C19 | 125.35(13) | C2-N2-C9 | 119.93(12) |
| O1-C1-N1 | 125.85(14) | O1-C1-C2 | 128.49(14) |
| N1-C1-C2 | 105.66(13) | N2-C2-C3 | 124.84(13) |
| N2-C2-C1 | 130.20(14) | C3-C2-C1 | 104.85(12) |
| C4-C3-C8 | 120.86(13) | C4-C3-C2 | 131.40(14) |
| C8-C3-C2 | 107.70(13) | C3-C4-C5 | 118.25(14) |
| C3-C4-H4 | 120.9 | C5-C4-H4 | 120.9 |
| C6-C5-C4 | 120.34(15) | C6-C5-H5 | 119.8 |
| C4-C5-H5 | 119.8 | C5-C6-C7 | 121.94(14) |
| C5-C6-H6 | 119.0 | C7-C6-H6 | 119.0 |
| C8-C7-C6 | 116.98(15) | C8-C7-H7 | 121.5 |
| C6-C7-H7 | 121.5 | C7-C8-C3 | 121.62(14) |
| C7-C8-N1 | 128.48(14) | C3-C8-N1 | 109.91(13) |
| N2-C9-C20 | 106.64(12) | N2-C9-C10 | 110.39(12) |
| C20-C9-C10 | 112.78(12) | N2-C9-H9 | 109.0 |
| C20-C9-H9 | 109.0 | C10-C9-H9 | 109.0 |
| C11-C10-C21 | 109.54(13) | C11-C10-C9 | 114.96(13) |
| C21-C10-C9 | 108.10(12) | C11-C10-H10 | 108.0 |
| C21-C10-H10 | 108.0 | C9-C10-H10 | 108.0 |
| C12-C11-C10 | 123.50(14) | C12-C11-H11 | 118.2 |
| C10-C11-H11 | 118.2 | C11-C12-C13 | 126.13(14) |
| C11-C12-H12 | 116.9 | C13-C12-H12 | 116.9 |
| C18-C13-C14 | 118.11(14) | C18-C13-C12 | 122.47(13) |
| C14-C13-C12 | 119.39(13) | C15-C14-C13 | 121.34(14) |
| C15-C14-H14 | 119.3 | C13-C14-H14 | 119.3 |
| C14-C15-C16 | 118.59(14) | C14-C15-H15 | 120.7 |
| C16-C15-H15 | 120.7 | C17-C16-C15 | 121.92(14) |
| C17-C16-Cl1 | 119.35(12) | C15-C16-Cl1 | 118.72(12) |
| C16-C17-C18 | 118.40(15) | C16-C17-H17 | 120.8 |
| C18-C17-H17 | 120.8 | C17-C18-C13 | 121.63(14) |

| | | | |
|---|---|---|---|
| C17-C18-H18 | 119.2 | C13-C18-H18 | 119.2 |
| N1-C19-H19A | 109.5 | N1-C19-H19B | 109.5 |
| H19A-C19-H19B | 109.5 | N1-C19-H19C | 109.5 |
| H19A-C19-H19C | 109.5 | H19B-C19-H19C | 109.5 |
| F1-C20-F3 | 106.34(12) | F1-C20-F2 | 107.25(13) |
| F3-C20-F2 | 106.37(13) | F1-C20-C9 | 114.39(13) |
| F3-C20-C9 | 110.61(13) | F2-C20-C9 | 111.43(13) |
| C10-C21-H21A | 109.5 | C10-C21-H21B | 109.5 |
| H21A-C21-H21B | 109.5 | C10-C21-H21C | 109.5 |
| H21A-C21-H21C | 109.5 | H21B-C21-H21C | 109.5 |

**Torsion angles (°) for rds943V**

| | | | |
|---|---|---|---|
| C8-N1-C1-O1 | -176.69(17) | C19-N1-C1-O1 | 3.1(3) |
| C8-N1-C1-C2 | 3.27(18) | C19-N1-C1-C2 | -176.94(15) |
| C9-N2-C2-C3 | 176.14(14) | C9-N2-C2-C1 | 0.4(3) |
| O1-C1-C2-N2 | -7.8(3) | N1-C1-C2-N2 | 172.21(16) |
| O1-C1-C2-C3 | 175.79(17) | N1-C1-C2-C3 | -4.17(17) |
| N2-C2-C3-C4 | 4.8(3) | C1-C2-C3-C4 | -178.57(16) |
| N2-C2-C3-C8 | -173.04(15) | C1-C2-C3-C8 | 3.59(16) |
| C8-C3-C4-C5 | 0.4(2) | C2-C3-C4-C5 | -177.22(16) |
| C3-C4-C5-C6 | -0.2(2) | C4-C5-C6-C7 | -0.1(3) |
| C5-C6-C7-C8 | 0.3(3) | C6-C7-C8-C3 | -0.1(2) |
| C6-C7-C8-N1 | 179.51(16) | C4-C3-C8-C7 | -0.2(2) |
| C2-C3-C8-C7 | 177.88(14) | C4-C3-C8-N1 | -179.91(14) |
| C2-C3-C8-N1 | -1.80(17) | C1-N1-C8-C7 | 179.29(16) |
| C19-N1-C8-C7 | -0.5(3) | C1-N1-C8-C3 | -1.06(19) |
| C19-N1-C8-C3 | 179.15(16) | C2-N2-C9-C20 | 111.25(16) |
| C2-N2-C9-C10 | -125.92(15) | N2-C9-C10-C11 | -61.14(16) |
| C20-C9-C10-C11 | 58.03(17) | N2-C9-C10-C21 | 61.56(15) |
| C20-C9-C10-C21 | -179.27(13) | C21-C10-C11-C12 | 103.73(18) |
| C9-C10-C11-C12 | -134.35(16) | C10-C11-C12-C13 | -174.54(14) |
| C11-C12-C13-C18 | -18.4(3) | C11-C12-C13-C14 | 159.63(16) |
| C18-C13-C14-C15 | 0.9(2) | C12-C13-C14-C15 | -177.25(14) |
| C13-C14-C15-C16 | -0.3(2) | C14-C15-C16-C17 | -0.1(2) |
| C14-C15-C16-Cl1 | -179.31(12) | C15-C16-C17-C18 | -0.1(2) |
| Cl1-C16-C17-C18 | 179.04(13) | C16-C17-C18-C13 | 0.8(3) |
| C14-C13-C18-C17 | -1.2(2) | C12-C13-C18-C17 | 176.92(14) |
| N2-C9-C20-F1 | 53.34(16) | C10-C9-C20-F1 | -67.98(16) |
| N2-C9-C20-F3 | -66.69(15) | C10-C9-C20-F3 | 171.98(12) |
| N2-C9-C20-F2 | 175.20(12) | C10-C9-C20-F2 | 53.88(17) |

**Anisotropic atomic displacement parameters (Å²) for rds943V**

The anisotropic atomic displacement factor exponent takes the form:
$-2\pi^2[\ h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

| | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| Cl1 | 0.0368(2) | 0.01699(17) | 0.02519(18) | 0.00066(13) | 0.00720(16) | 0.00346(15) |
| F1 | 0.0238(5) | 0.0229(5) | 0.0331(5) | 0.0030(4) | -0.0009(4) | 0.0064(4) |
| F2 | 0.0252(5) | 0.0484(6) | 0.0156(4) | -0.0006(4) | -0.0042(4) | -0.0020(5) |
| F3 | 0.0227(5) | 0.0281(5) | 0.0244(5) | 0.0017(4) | 0.0037(4) | -0.0049(4) |
| O1 | 0.0544(8) | 0.0177(5) | 0.0183(5) | -0.0028(4) | -0.0009(5) | 0.0004(6) |
| N1 | 0.0278(7) | 0.0154(6) | 0.0189(6) | 0.0017(5) | 0.0006(5) | 0.0026(5) |
| N2 | 0.0197(6) | 0.0164(6) | 0.0150(6) | 0.0001(5) | -0.0004(5) | 0.0005(5) |
| C1 | 0.0272(8) | 0.0163(7) | 0.0179(7) | 0.0019(6) | 0.0034(6) | 0.0017(6) |
| C2 | 0.0171(7) | 0.0163(7) | 0.0161(7) | -0.0013(5) | 0.0009(6) | -0.0001(5) |
| C3 | 0.0161(6) | 0.0183(7) | 0.0150(7) | 0.0020(5) | 0.0008(5) | 0.0001(6) |
| C4 | 0.0200(7) | 0.0186(7) | 0.0173(7) | 0.0001(6) | 0.0005(6) | -0.0009(6) |
| C5 | 0.0268(8) | 0.0232(7) | 0.0195(7) | -0.0028(6) | -0.0015(6) | -0.0044(7) |
| C6 | 0.0288(9) | 0.0313(9) | 0.0166(7) | 0.0022(6) | -0.0044(6) | -0.0049(7) |
| C7 | 0.0243(8) | 0.0233(7) | 0.0196(7) | 0.0063(6) | -0.0031(6) | -0.0012(6) |
| C8 | 0.0170(7) | 0.0183(7) | 0.0183(7) | 0.0015(5) | 0.0012(6) | -0.0003(6) |
| C9 | 0.0215(7) | 0.0148(6) | 0.0130(6) | 0.0004(5) | -0.0011(6) | 0.0013(6) |
| C10 | 0.0193(7) | 0.0177(7) | 0.0154(6) | -0.0001(5) | -0.0002(6) | 0.0009(6) |
| C11 | 0.0206(7) | 0.0177(7) | 0.0166(6) | -0.0012(5) | -0.0003(6) | -0.0008(6) |
| C12 | 0.0208(7) | 0.0186(7) | 0.0167(7) | -0.0024(6) | -0.0004(6) | -0.0013(6) |
| C13 | 0.0177(7) | 0.0178(7) | 0.0176(7) | 0.0010(5) | -0.0027(6) | -0.0011(5) |
| C14 | 0.0202(7) | 0.0223(7) | 0.0146(6) | -0.0009(5) | -0.0004(6) | 0.0001(6) |
| C15 | 0.0206(7) | 0.0223(7) | 0.0157(7) | 0.0026(6) | 0.0006(6) | -0.0026(6) |
| C16 | 0.0185(7) | 0.0169(7) | 0.0211(7) | 0.0004(6) | -0.0011(6) | -0.0020(5) |
| C17 | 0.0233(8) | 0.0213(7) | 0.0168(7) | -0.0017(6) | 0.0008(6) | -0.0010(6) |
| C18 | 0.0213(7) | 0.0206(7) | 0.0150(7) | 0.0030(5) | 0.0008(6) | -0.0021(6) |
| C19 | 0.0431(10) | 0.0156(7) | 0.0263(8) | 0.0037(6) | 0.0004(8) | 0.0046(7) |
| C20 | 0.0221(8) | 0.0220(7) | 0.0157(7) | 0.0006(6) | 0.0004(6) | -0.0007(6) |
| C21 | 0.0194(8) | 0.0250(8) | 0.0260(8) | -0.0002(7) | 0.0001(6) | 0.0014(6) |

**Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å$^2$)**

**for rds943V**

| | x/a | y/b | z/c | U(eq) |
|---|---|---|---|---|
| H4 | 0.5087 | 0.1965 | 0.6317 | 0.022 |
| H5 | 0.5912 | 0.1878 | 0.7397 | 0.028 |
| H6 | 0.6572 | 0.0168 | 0.7866 | 0.031 |
| H7 | 0.6426 | -0.1507 | 0.7283 | 0.027 |
| H9 | 0.4571 | -0.0314 | 0.4365 | 0.02 |
| H10 | 0.5527 | 0.0877 | 0.3532 | 0.021 |
| H11 | 0.5473 | 0.2746 | 0.4393 | 0.022 |
| H12 | 0.5597 | 0.2641 | 0.3073 | 0.022 |
| H14 | 0.6517 | 0.4367 | 0.2540 | 0.023 |
| H15 | 0.6698 | 0.6316 | 0.2497 | 0.023 |
| H17 | 0.4891 | 0.6495 | 0.4318 | 0.025 |
| H18 | 0.4698 | 0.4545 | 0.4349 | 0.023 |
| H19A | 0.5734 | -0.3206 | 0.5737 | 0.042 |
| H19B | 0.4964 | -0.3058 | 0.6442 | 0.042 |
| H19C | 0.7041 | -0.2875 | 0.6308 | 0.042 |
| H21A | 0.7687 | -0.0037 | 0.4188 | 0.035 |
| H21B | 0.7875 | 0.1081 | 0.4600 | 0.035 |
| H21C | 0.8473 | 0.1073 | 0.3870 | 0.035 |

# 4. Enantioselective Synthesis of Amines with Remote Stereogenic Centers through Co-Catalyzed Hydroalkynylation of 2-Azatrienes

Portions of this chapter will be submitted for publication.

## *4.1 Introduction*

Chiral alkyl amines are important scaffolds in medicinal compounds. The aliphatic substituents present in the amine structure play a significant role in determining physical properties of the amine in biological systems[228] leading to their presence amongst pharmaceutical candidates (Figure 9).

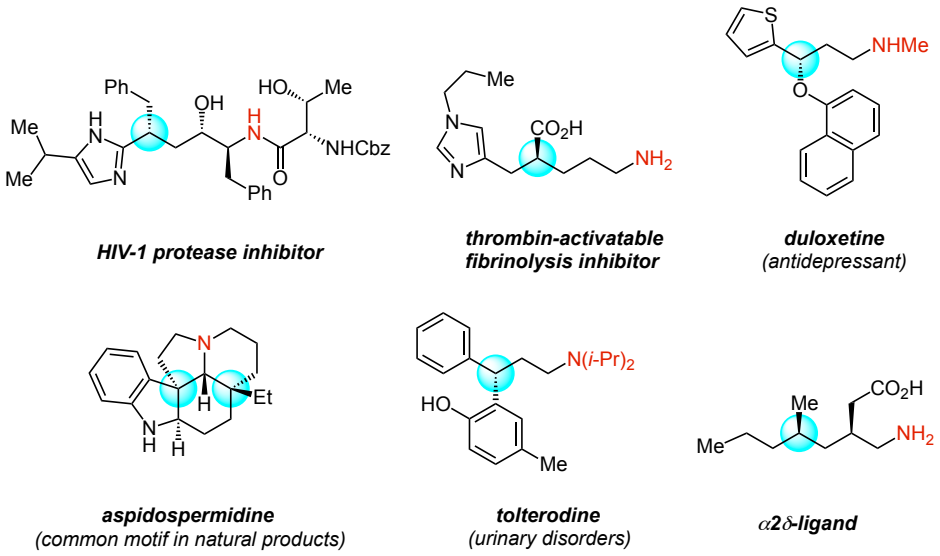


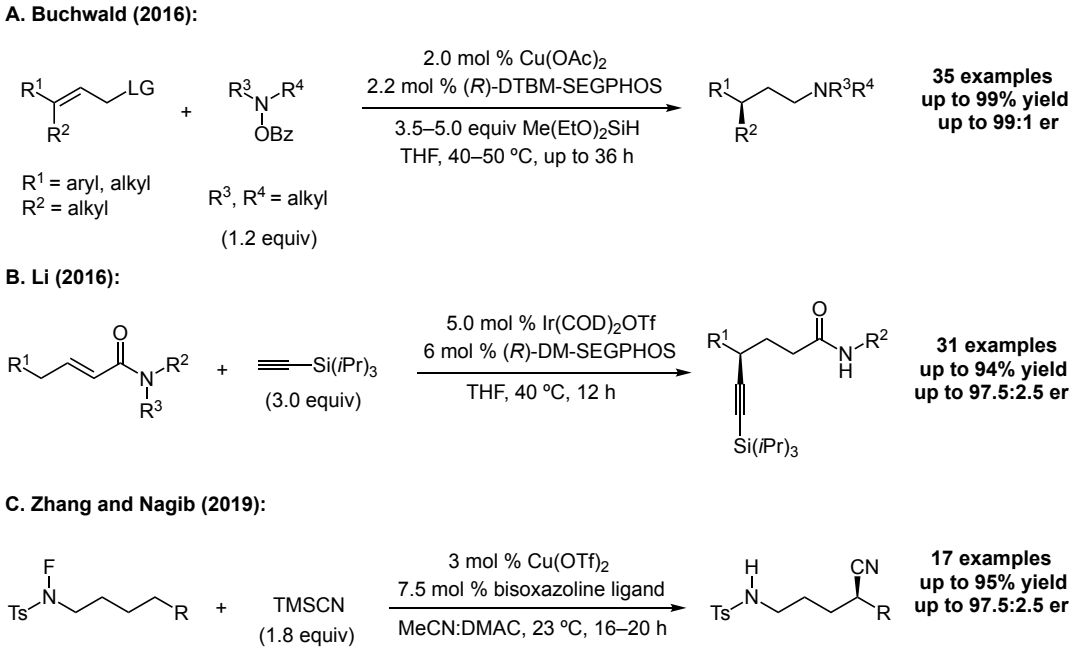

**Figure 9: Chiral Amines with Remote Stereogenic Centers**

Furthermore, the level of saturation or $sp^3$ hybridized carbons they possess allow them to have greater three-dimensionality compared to their unsaturated counterparts.[98] Their ability to adopt multiple conformations allows for increased receptor/ligand

complementarity due to design of out-of-plane substituents, compared to flat aromatic rings, in their molecular structure.[87]

Efforts towards the development of methods for accessing enantioenriched chiral amines have mostly been focused on those bearing stereogenic centers at the α or β-position of the nitrogen atom.[94] The methods for enantioselective synthesis of chiral amines with remote stereogenic centers, however, are less common with existing strategies involving multi-step syntheses. Although the utilization of C–N bond-forming reactions for accessing chiral amines with distal stereogenic centers has been realized, there are only very few examples and they are non-enantioselective.[229] Only recently has Buchwald and coworkers reported a direct approach to amines with remote stereogenic centers (Scheme 38A).[127] These reactions proceed through an enantioselective CuH-catalyzed reductive relay hydroamination reaction. In this work, amines bearing γ- or δ-stereogenic centers with differentiated alkyl substituents could be prepared in high yields in a single step. Excellent enantio-, regio-, and chemoselectivity was observed for a broad range of substrates with high functional group tolerance. The generation of new of C–C bonds for the accessing nitrogen-containing molecules with remote stereogenic centers is another powerful strategy. Such an approach has been explored by Li and coworkers.[230] In their hydroalkynylation effort with α,β-unsaturated amides, the new C–C bond is formed exclusively at the γ-position to deliver the enantioenriched amides (Scheme 38B). Zhang and Nagib have recently demonstrated the construction of

enantioenriched alkyl amines containing δ-stereogenic centers through radical-mediated C–H cyanation (Scheme 38C).[231] The generation of amines with γ-stereogenic centers have also been established using hydroboration[232-234] or reductive amination strategies.[235-236] Although not generating amines directly, other research efforts have focused on the generation of aldehydes and ketones with distal stereogenic centers.[237-239]




**Scheme 38: Formation of Remote Stereogenic Centers**

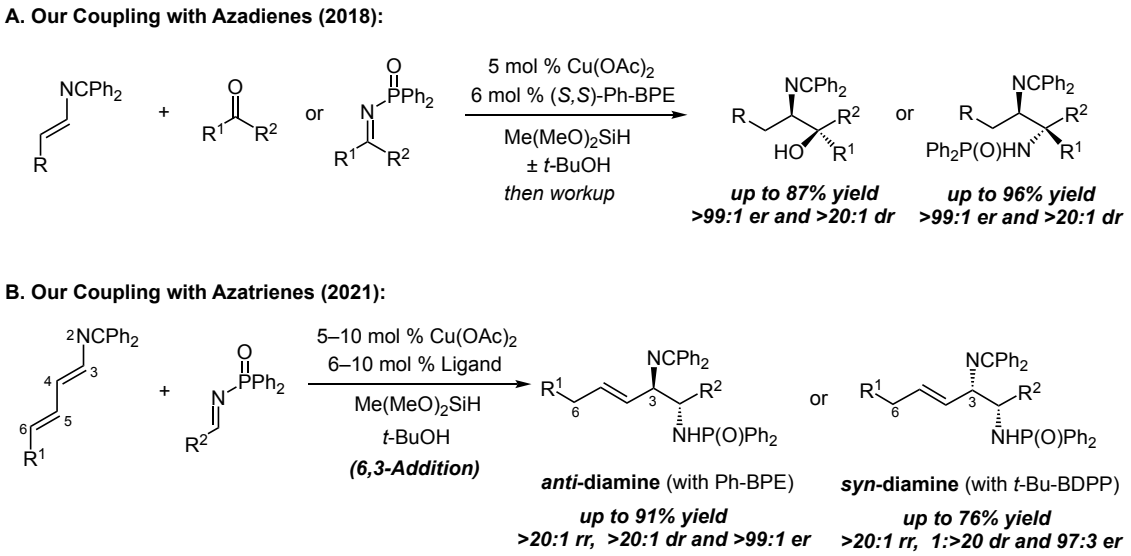
Nevertheless, the development of methods with amines still remains sparse. This is a particularly important problem to solve as chiral amines with remote stereogenic centers (those that are three or more bonds away from the C–N bond) are important motifs in pharmaceutical applications. Hence, we focused our efforts on developing a simple yet efficient method for the construction of this class of amines.

## 4.2 Background

In 2018, we described enantioselective reductive couplings of substituted 2-azadienes with ketones and imines using Cu–H catalyzed reactions.[162-163] In these studies, 2-azadienes are able to undergo an enantioselective migratory insertion into Cu–H allowing the formation of an α-aminoalkyl–Cu nucleophile. This *in situ* generated alkyl Cu species is poised for attack of the electrophilic ketone or imine, furnishing amine products bearing α-stereogenic centers (Scheme 39A). Following this work, we decided to expand our studies in chiral amine synthesis using a novel class of reagents: 2-azatrienes. To this end, our lab has developed a highly chemo-, regio-, diastereo-, and enantioselective reductive coupling of 2-azatrienes with *N*-phosphinoylimines for the synthesis of 1,2-diamines.[240] Crucial to the success of these reactions is the identity of the ligand as Cu–Ph-BPE, which has been essential for our other reductive couplings, promotes the formation of *anti*-diamine. However, the use of *t*-Bu-BDPP, an uncommon ligand in Cu–H catalysis, affords the *syn*-diamine (Scheme 39B).

Nevertheless, the use of 2-azatrienes in Cu–H chemistry presents a new regioselectivity challenge: the alkyl-Cu generated after Cu–H insertion could lead to two different types of regioisomers (6,3- vs 6,5-addition) after coupling. However, in this study, we observed the predominant formation of the 6,3-addition isomer. While the 6,3-addition product is valuable and provides access to allylic amines, establishing a method where 6,5-addition is delivered exclusively bears utility as well: the 6,5-product is an

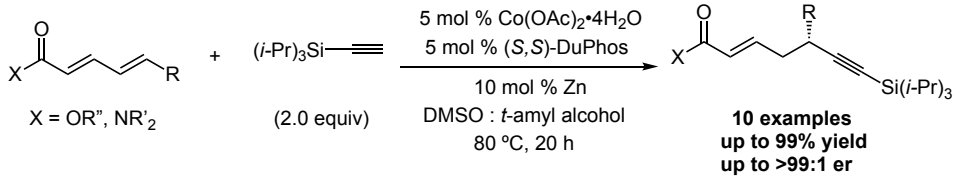
enantioenriched azadiene, a functional handle for downstream synthesis, which can be converted to an alkyl amine bearing a remote stereogenic center through a reduction protocol. Therefore, the development of a novel method for the formation of the azadiene product would be beneficial.




**Scheme 39: Our Previous Work with 2-Azadienes and 2-Azatrienes**

Hayashi and coworkers have disclosed an enantioselective addition of triisopropylsilylacetylene to $\alpha,\beta,\gamma,\delta$-unsaturated esters and amides (Scheme 40).[241] A cobalt–DuPhos catalyst system delivers 1,6-addition products with a stereogenic center at the $\delta$-position in excellent yields, high regio-, and enantioselectivity. It is worthy to note that in this work, there is only one example showing the coupling of an unactivated diene with triisopropylsilylacetylene. Besides this reaction with cobalt as the transition metal catalyst, other hydroalkynylation reaction have been developed using rhodium[242-243], nickel[244-245], and iridium[246-248] catalysts.

**Hayashi (2012):**




**Scheme 40: Enantioselective Hydroalkynylation by Hayashi**

We then envisioned a strategy whereby 2-azatrienes could undergo an enantioselective 5,6-hydroalkynylation to furnish enantioenriched azadienes bearing an alkyne-substituted stereogenic center. Mechanistically, we envisioned that the reaction would proceed in a similar fashion as elucidated by Hayashi (Figure 10). In the presence of zinc as a reducing agent, cobalt(II)acetate, is reduced to cobalt(I) bearing the chiral bis–phosphine ligand to generate the active cobalt catalyst. The acetate ligand on the cobalt could participate in ligand-assisted deprotonation of the alkyne to furnish the alkynyl cobalt or Co–acetylide, which serves as the active nucleophilic species. The azatriene, which can adopt an *s*-cis configuration, binds through $\eta^4$–coordination to the Co–acetylide. Insertion of the Co–acetylide into the azatriene leads to the formation of the stereogenic center and a pendant Co–$\pi$-allyl system, which undergoes protodemetalation (presumably with AcOH generated *in situ)* to furnish the desired product and regenerate the active cobalt species.

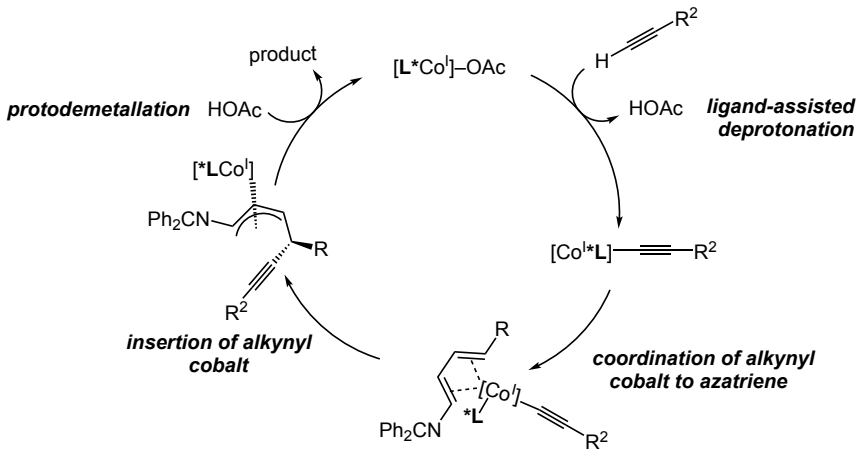



**Figure 10: Proposed Mechanism for Hydroalkynylation of 2-Azatrienes**

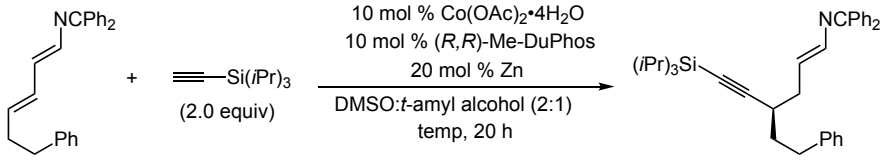
It should be noted that in the mechanism outlined above, which is supported by the regioisomer formed during the hydroalkynylation event, carbometalation of the azatriene by the Co–acetylide occurs first with subsequent protodemetalation to furnish the product. This is in contrast to reactions reported by Suginome's group in their nickel studiess[244-245] and also by Li and coworkers in their rhodium[243] and more recent iridium[246] studies. In these reactions, hydrometallation of the olefin occurs first, followed by C–C reductive elimination to deliver the opposite regioisomer, consistent with a Chalk–Harrod mechanism.

## *4.3 Results and Discussion*

We first examined the coupling of phenethyl-substituted azatriene **4.1** and triisopropylsilylacetylene. We embarked on this reaction development using a cobalt–DuPhos catalyst system similar to Hayashi's conditions (Table 12). Employing a 5 mol% loading of $Co(OAc)_2{\bullet}4H_2O$ and (*R,R*)-Me-DuPhos with 10 mol% zinc powder, we

obtained a reaction that gives exclusively the 5,6-hydroalkynylation product in 45% yield and 99:1 er (entry 2). By increasing the catalyst loading to 10 mol% and 20 mol% zinc, we observed **4.1** in 68% yield with the same level of er. We attempted to reduce the concentration of the reaction to 0.33 M, however we observed formation of **4.2** in only 38% yield (entry 4). The addition of more zinc to enable faster reduction of the Co(II) salt to the active Co(I) species, and hence a more efficient reaction, did not significantly improve the yield (ca. 2% yield increase, entry 5). Changing the duration of the hydroalkynylation reaction to 12 h or 48 h afforded the desired product in 46% yield and 50% yield, respectively (entries 6 and 7). Furthermore, changing the stoichiometry of the alkyne did not have a positive impact on yield (entries 8 and 9). Increasing the temperature of the reaction to 100 °C also did not lead to higher conversion to product (entry 10).

**Table 12: Hydroalkynylation Reaction Optimization with Triisopropylsilylacetylene**[a]




**4.1** **4.2**

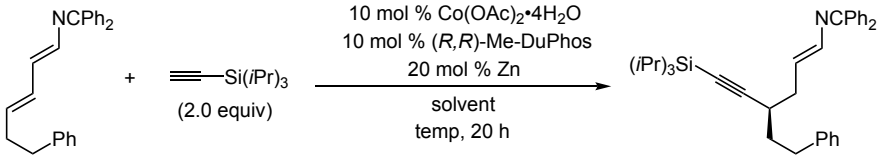
| entry | temperature ( ºC) | yield(%)[b] | unreacted azatriene (%) | er |
|---|---|---|---|---|
| 1[c] | 60 | <2 | 90 | n.a. |
| 2[c] | 80 | 45 | 27 | 99:1 |
| 3 | 80 | 68 | 32 | 99:1 |
| 4[d] | 80 | 38 | 62 | 99:1 |
| 5[e] | 80 | 70 | 30 | 99:1 |
| 6[f] | 80 | 46 | 22 | 99:1 |
| 7[g] | 80 | 50 | 22 | 99:1 |
| 8[h] | 80 | 44 | 32 | 99:1 |
| 9[i] | 80 | 60 | 38 | n.d. |
| 10 | 100 | 42 | 22 | n.d. |

[a]Reaction run under $N_2$ with 0.15 mmol azatriene 0.67 M. [b]Yield of **4.2** determined by $^1$H NMR using dibromomethane as an internal standard. [c]Reaction run with 5 mol % catalyst and 10 mol % Zn. [d]Reaction run at [0.33 M]. [e]Reaction run with 50 mol % Zn. [f]Reaction for 12 h. [g]Reaction for 48 h. [h]Reaction with 1 equiv. of alkyne. [i]Reaction with 3 equiv. of alkyne. n.a = not applicable. n.d. = not determined.

Optimistic about these initial results, we thought that changing the identity of solvent in the reaction might promote coupling. We hoped that polar organic solvents such as NMP and DMP could lead to higher conversions, but no desired product **4.2** was formed under such conditions (Table 13, entries 1 and 2). We were able to determine that a 2:1 ratio of DMSO:*t*-amyl alcohol was optimal, as altering the ratio of these two co-solvents led to reduced yields of product (entries 3–6). The exclusion or replacement of *t*-amyl alcohol with other alcohol solvents was also deleterious to the reaction as coupling

proceeded to give lower yields of product (entries 7–9). In addition, nonpolar organic solvents such as dichloromethane led to no observable product (entry 10).

**Table 13: Evaluation of Solvent Effects on Hydroalkynylation**[a]




**4.1** **4.2**

| entry | solvent | yield(%)[b] | azatriene left (%) | er |
|---|---|---|---|---|
| 1 | NMP | <2 | >95 | n.a. |
| 2 | DMF | <5 | >95 | n.a. |
| 3[c] | DMSO:*t*-amyl alcohol | 58 | 22 | 99:1 |
| 4[d] | DMSO:*t*-amyl alcohol | 34 | 59 | 99:1 |
| 5[e] | DMSO:*t*-amyl alcohol | 52 | 24 | 99:1 |
| 6[f] | DMSO:*t*-amyl alcohol | 68 | 32 | 99:1 |
| 7[f] | DMSO:*t*-BuOH | 52 | 20 | n.d. |
| 8[f] | DMSO:HFIP | 16 | 72 | n.d. |
| 9 | DMSO | <2 | >95 | n.a. |
| 10 | $CH_2Cl_2$ | <2 | >95 | n.a. |

[a]Reaction run under $N_2$ with 0.15 mmol azatriene 0.66 M. [b]Yield determined by $^1$H NMR using dibromomethane as an internal standard. [c]Reaction run with a 1:1 mixture of DMSO:*t*-amyl alcohol at 1.33 M. [d]Reaction run with a 1:20 mixture. [e]Reaction run with a 1:1 mixture. [f]Reaction run with a 2:1 mixture. n.a = not applicable. n.d. = not determined.

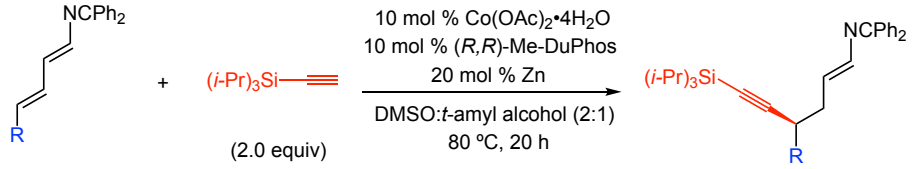
## 4.3.1 Substrate Scope

Upon determination of our optimal reaction conditions, we explored the scope of mono-substituted internal azatrienes to furnish enantioenriched azadienes (Table 14). The desired hydroalkynylation products can be generated in up to 68% yield and 99:1 er. Methyl and *n*-hexyl substituted azatrienes undergo the hydroalkynylation smoothly, furnishing the enantioenriched azadienes **4.12** and **4.13** in 67% and 56% yield with 98:2

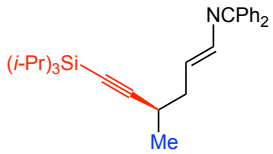
er and 99:1 er, respectively (entries 2 and 3). Carbamate **4.14** and phthalimide-derived **4.15** are obtained in lower yields (43% and 57% yield) but in excellent enantioselectivity, with 99:1 and 97.5:2.5 er, respectively (entries 4 and 5).

Ether-substituted azadienes 4.**16** and **4.17** are delivered in 68% and 56% yield, respectively, with high levels of enantioselectivity. Benzyl-substituted azadiene **4.18** could as be obtained in 55% yield and 95.5:4.5 er. Electron donating and electron withdrawing substituents at the 4-position on the benzyl ring alter the reaction slightly: electron-rich *para*-methoxy-substituted benzyl product **4.19** is delivered in 55% yield and 98:2 er while electron-deficient *para*-fluoro-substituted benzyl derivative **4.20** is obtained in only 45% yield and 94.5:4.5 er. This reaction can only be used for the coupling of the azatrienes to triisopropylsilylacetylene as other alkynes, such as phenylacetylene, trimethylsilylacetylene, and *tert*-butyldimethylsilyl acetylene fail to produce any observable product when employed under the same reaction conditions. This is mostly due to dimerization/polymerization of the alkynes under reaction conditions, as elucidated by Hayashi as well.[241] We also attribute the success of triisopropylsilylacetylene to its unique steric properties. In addition, we attempted to explore its coupling with azatrienes of varying substitution patterns to furnish a diverse range of products. However, these couplings were unsuccessful.

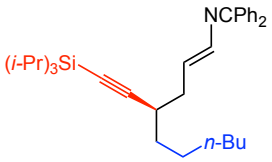
**Table 14: Substrate Scope for Enantioselective Hydroalkynylation**[a]



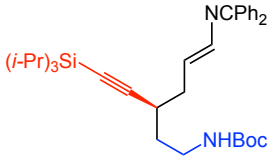

**4.3–4.11** **4.12–20**



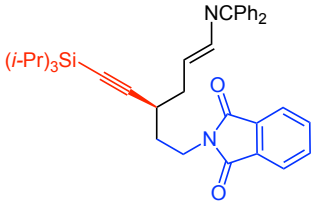

**4.12**
67% yield
**98:2 er**



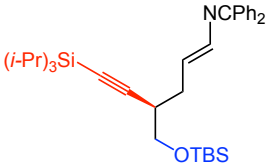

**4.13**
56% yield
**99:1 er**



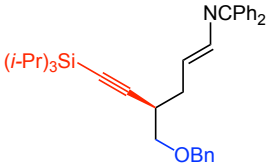

**4.14**
43% yield
**99:1 er**



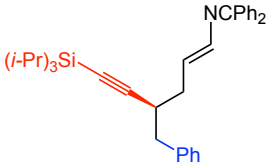

**4.15**
57% yield
**97.5:2.5 er**



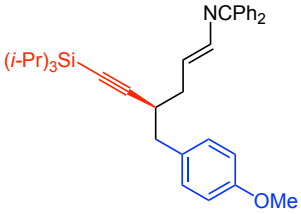

**4.16**
55% yield
**98.5:1.5 er**



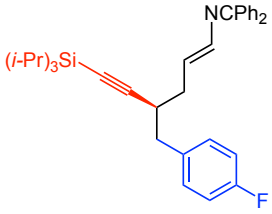

**4.17**
68% yield
**98.5:1.5 er**




**4.18**
55% yield
**94.5:5.5 er**



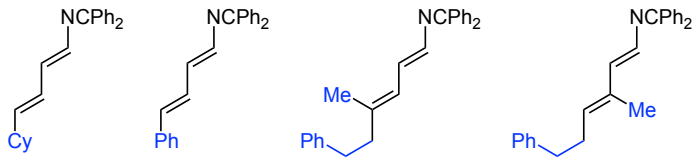

**4.19**
55% yield
**98:2 er**




**4.20**
55% yield
**94.5:5.5 er**

[a]Reaction run under $N_2$ with 0.15 mmol of azatriene [0.67 M]. [b]Enantiomeric ratios (er) determined by HPLC in comparison with an authentic racemic standard.

Azatrienes **4.21** and **4.22** bearing mono-substituted branched substituents at the 6-position fail to deliver an observable amount of product. In addition, 5,6- as well as 6,6-disubstituted azatrienes **4.23** and **4.24** are not tolerated (Figure 11).

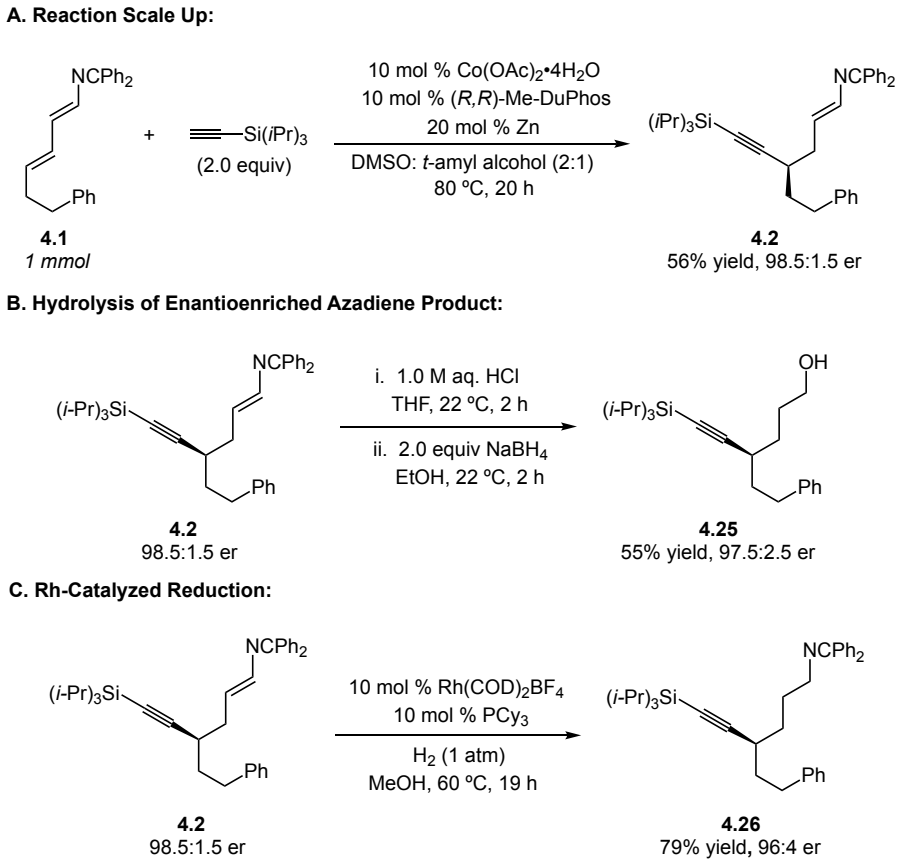



**4.21** **4.22** **4.23** **4.24**

**Figure 11: Incompatible Azatriene Substrates for Hydroalkynylation**

### 4.3.2 Reaction Scale Up and Product Functionalization

The reaction scale can be increased up to 1.0 mmol without significant decrease in yield (61% yield on 0.15 mmol scale vs 56% yield on 1.0 mmol scale) and enantiocontrol during the hydroalkynylation event (Scheme 41A). The direct products derived from the catalytic enantioselective reaction contain an azadiene functional group. These azadienes can be readily hydrolyzed under mild acidic conditions to form the desired aldehyde with a γ-stereogenic center, and then further reduced to form alcohol **4.25** with a δ-stereogenic center in 55% yield over two steps without significant loss of enantiopurity (Scheme 41B). Furthermore, we explored reduction of the C–C double bond of the azadiene to form the alkyl amine product bearing a remote stereogenic center. Under Rh conditions with an atmosphere of hydrogen, the desired protected amine product is obtained in 79% yield and 96:4 er (Scheme 41C).




**Scheme 41: Functionalization of Products**

## *4.4 Conclusions and Outlook*

In conclusion, we have developed a method for the construction of alkyl amines bearing distal stereogenic centers, enabled by the enantioselective 5,6-hydroalkynylation of substituted 2-azatrienes. Prior to this strategy, only chiral amines with α or β-stereogenic centers have been generated using 2-azadienes and 2-azatrienes. With this work, we have been able to demonstrate the coupling of substituted 2-azatrienes using triisopropylsilylacetylene with a Co–DuPhos catalyst for the formation of protected amines with remote stereogenic centers. This reaction adds to our current investigations

into azatrienes but with a different metal catalyst. A substrate scope of sterically and electronically different monosubstituted 2-azatrienes are tolerated, providing the enantioenriched azadienes in good yields and excellent enantioselectivity. Direct hydrolysis of the product delivers the desired aldehyde, which can be subsequently reduced to the alcohol, with the products bearing a remote γ- or δ stereogenic center, respectively. Through sequential catalysis, we have also shown a Rh-catalyzed reduction of the internal C–C double bond of the azadiene to furnish the protected alkyl amines bearing δ-stereogenic centers in high yields and er. Although the alkyne scope is limited to triisopropylsilylacetylene and monosubstituted azatrienes with this system, it is possible that modification of the chiral ligand on cobalt could allow for a broader range of alkyne and azatriene substrates to access diverse chiral amine scaffolds with remote stereogenic centers.

## *4.5 Experimental Details*

General Procedures. All reactions were carried out in oven- (120 °C) or flame-dried glassware under an inert atmosphere of dry $N_2$ unless otherwise noted. 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.

Reagents. Triethylamine (Sigma Aldrich) was distilled from $CaH_2$ prior to use. The following chemicals were used as received:

(+)-1,2-Bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane ((*S,S*)-Ph-BPE) (Strem); (1*R*,1′*R*,2*S*,2′*S*)-2,2′-Di-tert-butyl-2,3,2′,3′-tetrahydro-1H,1′H-(1,1′)biisophosphindolyl ((*R,R,S,S*)-DuanPhos) (Sigma Aldrich); (+)-1,2-Bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene (*S,S*)-Et-DuPhos (Strem); bis[(2-diphenylphosphino)phenyl] ether (DPEPhos) (Strem); (+)-1,2-Bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene (*S,S*)-Me-DuPhos (Strem); (−)-1,2-Bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene (*R,R*)-Me-DuPhos (Strem); (1*R*)-1-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]-2-[(1*R*)-1-(dicyclohexylphosphino)ethyl]ferrocene (Josiphos SL-J007-1) (Strem); (2*R*)-1-[(1*R*)-1-[Bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (Josiphos SL-J009-1) (Strem); (2*R*)-1-[(1*R*)-1-[Bis(1,1-dimethylethyl)phosphino]ethyl]-2-(diphenylphosphino)ferrocene (Josiphos SL-J002-1) (Strem); (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (Alfa Aesar) ((*R*)-BINAP) (Strem); (*S*)-(+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (*S*)-(+)-DTBM-SEGPHOS (Strem); (*tert*-butyldimethylsilyl)acetylene (TCI Chemicals); 1,2-bis(dicyclohexylphosphino)ethane (dcype) (Sigma Aldrich); (1,2-bis(diphenylphosphino)ethane (dppe) (Sigma Aldrich); 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos) (Strem); (*R,R*)-(–)-2,3-bis(tertbutylmethylphosphino)quinoxaline ((*R,R*)-QuinoxP*) (Strem); benzophenone

imine (Chem Impex); bis[(2-diphenylphosphino)phenyl] ether (DPEPhos) (Strem); cobalt (II) acetate tetrahydrate (Alfa Aesar); concentrated hydrochloric acid (VWR); chlorotris(triphenylphosphine)cobalt(I) (Strem); HCl (2.0 M in diethyl ether) (Sigma Aldrich); hydrazine monohydrate (TCI Chemicals); *n*-butyllithium (2.5 M in hexanes) (Sigma Aldrich); *N*-hydroxymethylpthalimide (Beantown Chemicals); phenylacetylene (Alfa Aesar); phosphorus tribromide (Acros); potassium acetate (Mallinckrodt); sodium borohydride (TCI Chemicals); triethyl phosphite (Acros); triisopropylsilylacetylene (Alfa Aesar); trimethylsilylacetylene (Chem Impex); zinc (Alfa Aesar);

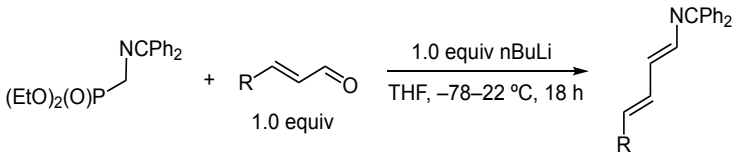
Solvents. Solvents were sparged with dry $N_2$ and purified under a positive pressure of dry $N_2$ by an Innovative Technologies PureSolve solvent purification system: tetrahydrofuran (Sigma-Aldrich), dichloromethane (Sigma-Aldrich), diethyl ether (Sigma-Aldrich), 1,4-dioxane (Sigma-Aldrich), and toluene (Sigma-Aldrich) were passed through two consecutive alumina columns. Methanol (Sigma-Aldrich) and *N,N*-dimethylformamide (Sigma-Aldrich) were used as received. Dimethyl sulfoxide (Sigma-Aldrich), *tert*-amyl alcohol (Sigma-Aldrich), *tert*-butyl alcohol (Alfa Aesar), hexafluoro-2-propanol (Oakwood), and *N*-methyl-2-pyrrolidone (Sigma Aldrich) for reactions were distilled over $CaH_2$ prior to use. HPLC-grade acetonitrile (Sigma-Aldrich), hexanes (Fisher), and ethyl acetate (Fisher) were used for flash column chromatography as received. HPLC-grade hexanes (Sigma-Aldrich) and isopropanol (Sigma-Aldrich) for

HPLC chromatography were used as received. Ethanol (Sigma-Aldrich) was used as received.

Instrumentation. $^{1}$H-NMR spectra were recorded on a Varian INOVA (400 MHz), Varian Unity (500 MHz) or Varian/Agilent VNMRS (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration ($CDCl_3$: δ 7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). $^{13}$C-NMR spectra were recorded on a Varian Unity (400 MHz), Varian/Agilent VNMRS (500 MHz), or Bruker Avance III (700 MHz) spectrometer with complete proton decoupling but with fluorine coupling except where indicated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from chloroform as the internal reference ($CDCl_3$: δ 77.16). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). 19F-NMR spectra were recorded on a Varian/Agilent VNMRS (376 MHz) spectrometer. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) (Hz). 31P-NMR spectra were recorded on a Varian/Agilent VNMRS (500 MHz) spectrometer. NMR yields were determined by internal standard (1,2-dibromomethane). High-resolution

mass spectrometry was performed on an Agilent (1200 Series) LCMS-TOF-DART at the Duke University Mass Spectrometry Facility (HRMS data values reported as an average of four runs). Infrared (IR) spectra were collected on a Nicolet 6700 FT-IR spectrometer, $\upsilon_{max}$ in $cm^{-1}$; bands are characterized as broad (br), strong (s), medium (m), or weak (w). Teledyne Isco, Nextgen 300+ system was used for automated column chromatography. Enantiomer ratios (er) were determined by HPLC (PhenomenexTM Lux® Cellulose I, Cellulose II, Cellulose III, Amylose I, or Chiralpak™ 1A-3 columns) in comparison with authentic racemic materials on a Shimadzu Prominence Modular HPLC.

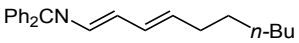
### 4.5.1 Preparation of Azatriene Substrates



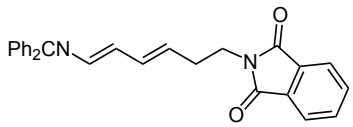

General Method A. A flame dried 100-mL round-bottom flask was charged with diethyl(((diphenylmethylene)amino)methyl)phosphonate (994.0 mg, 3.00 mmol, 1.00 equiv) and THF (9 mL) and then cooled to –78 °C. *n*-BuLi (2.5 M in hexanes, 1.20 mL, 3.00 mmol, 1.00 equiv) was added slowly to the vessel. The mixture was allowed to stir at –78 °C for 15 minutes, after which α,β-unsaturated aldehyde (3.00 mmol, 1.00 equiv) was added to flask. The reaction mixture was then allowed to warm up slowly to room temperature and stirred for 18 h. The reaction was quenched with deionized water (15.0 mL) and diluted with diethyl ether (10.0 mL). The organic layer was separated, and the aqueous layer was then washed with two portions of diethyl ether (15.0 mL x 3). The

combined organic extracts were washed with brine (15.0 mL), dried over $Na_2SO_4$, filtered, and concentrated. The residue was then purified by flash column or automated column chromatography.

The following 2-azatrienes were prepared as previously described: **4.1**, **4.3**, **4.5**, and **4.8**.

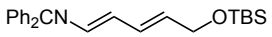



*N*-((1*E*,3*E*)-deca-1,3-dien-1-yl)-1,1-diphenylmethanimine (**4.4**). Title compound **4.4** was prepared according to general method A on 1.50 mmol scale. The material was purified by silica gel column chromatography (100% hexanes to 98:2 hexanes:ethyl acetate) to obtain **4.4** as a yellow oil (432.0 mg, 1.36 mmol, 90.8% yield). **IR** (thin film) 3059 (w), 3019 (w), 2955 (m), 2924 (s), 2854 (m), 1639 (w), 1537 (w) $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ 7.60 (2H, d, $J$ = 6.9 Hz), 7.42–7.36 (3H, m), 7.31–7.26 (3H, m), 7.14–7.13 (2H, m), 6.80 (1H, d, $J$ = 12.8 Hz), 6.62 (1H, dd, $J$ = 12.8, 11.0 Hz), 6.00–5.95 (1H, m), 5.77 (1H, dt, $J$ = 14.7, 6.9 Hz), 2.01 (2H, q, $J$ = 7.9, 7.3 Hz), 1.29 (2H, q, $J$ = 7.4 Hz), 1.23–1.18 (6H, m), 0.82–0.78 (3H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.3, 139.7, 138.4, 137.3, 136.4, 133.1, 130.1, 128.9, 128.7, 128.7, 128.6, 128.5, 128.1, 33.1, 31.7, 29.2, 28.9, 22.6, 14.1. **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{23}H_{27}N$: 318.2216, found: 318.2223.



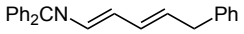

2-((3*E*,5*E*)-6-((diphenylmethylene)amino)hexa-3,5-dien-1-yl)isoindoline-1,3-dione (**4.6**). Title compound **4.6** was prepared according to general method A on 2.25 mmol scale.

The material was purified by automated column chromatography (100% hexanes to 85:15 hexanes:ethyl acetate) to obtain **4.6** as a yellow oil (270 mg, 0.66 mmol, 29.5% yield). **IR** (thin film) 3022 (w), 1772 (w), 1711 (s), 1537 (w) $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) 7.86–7.84 (2H, m), 7.73–7.72 (2H, m), 7.69 (d, *J* = 7.3 Hz, 1H), 7.48–7.47 (3H, m), 7.42–7.34 (3H, m), 7.20–7.18 (2H, m), 6.85 (d, *J* = 12.8 Hz, 1H), 6.68 (t, *J* = 11.4 Hz, 1H), 6.12 (dd, *J* = 15.1, 11.1 Hz, 1H), 5.81 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.78 (t, *J* = 7.2 Hz, 2H), 2.51 (q, *J* = 7.2 Hz, 2H); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$168.24, 166.11, 139.46, 136.21, 133.88, 132.09, 132.05, 131.47, 131.28, 130.26, 130.07, 128.80, 128.77, 128.49, 128.29, 128.14, 123.24, 37.48, 32.16. **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{27}H_{22}N_2O_2$: 407.1754, found: 407.1763.

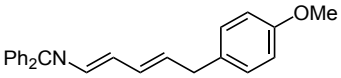



*N*-((1*E*,3*E*)-5-((*tert*-butyldimethylsilyl)oxy)penta-1,3-dien-1-yl)-1,1-diphenylmethanimine (**4.7**). Title compound **4.7** was prepared according to general method A on 1.50 mmol scale. The material was purified by silica gel column chromatography (100% hexanes to 97:3 hexanes:ethyl acetate) to obtain **4.7** as a yellow oil (199.0 mg, 0.527 mmol, 35.1% yield). **IR** (thin film) 3059 (w), 2953 (m), 2928 (m), 2856 (m), 2186 (w), 2031 (m), 1660 (s), 1278 (s) $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ 7.62 (2H, d, *J* = 6.9 Hz), 7.44–7.40 (3H, m), 7.34–7.26 (3H, m), 7.16 (2H, dd, *J* = 7.5, 2.0 Hz) 6.87 (1H, d, *J* = 12.8 Hz), 6.74 – 6.59 (1H, m), 6.20–6.15 (1H, m), 5.84 (1H, dt, *J* = 15.2, 5.2 Hz, 1H), 4.17 (2H, d, *J* = 4.5 Hz), 0.84 (9H, s), 0.00 (6H, s); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.6, 139.6, 138.9, 137.6, 136.4, 134.6, 132.9,

132.7, 132.4, 130.5, 130.2, 130.1, 128.9, 128.8, 128.7, 128.5, 128.3, 128.1, 128.1, 62.8, 36.7, 26.0, 18.4, -5.2; **HRMS** (ESI$^+$) [M+H]$^+$ calc'd for $C_{24}H_{31}NOSi$: 378.2248, found: 378.2254.

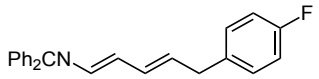



1,1-diphenyl-*N*-((1*E*,3*E*)-5-phenylpenta-1,3-dien-1-yl)methanimine (**4.9**). Title compound **4.9** was prepared according to general method A on 1.50 mmol scale. The material was purified by silica gel column chromatography (100% hexanes to 97:3 hexanes:ethyl acetate) to obtain **4.9** as a yellow oil (199.0 mg, 0.527 mmol, 35.1% yield). **IR** (thin film) 3056 (w), 3024 (w), 2511 (w), 1601 (w), 1536 (w), 1493 (w) cm$^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 6.9 Hz), 7.55–7.47 (3H, m), 7.43–7.35 (3H, m), 7.33–7.27 (2H, m), 7.24 (2H, dd, *J* = 7.6, 1.9 Hz), 7.21–7.17 (2H, m), 6.93 (1H, d, *J* = 12.8 Hz), 6.75 (1H, dd, *J* = 12.8, 10.9 Hz), 6.18–6.10 (1H, m), 6.02 (1H, dt, *J* = 14.7, 6.9 Hz), 3.47 (2H, d, *J* = 6.8 Hz**); $^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.83, 140.02, 139.62, 139.23, 136.37, 134.80, 132.50, 130.22, 130.10, 129.92, 128.93, 128.88, 128.81, 128.75, 128.67, 128.53, 128.49, 128.31, 128.22, 128.16, 126.43, 126.17, 39.34; **HRMS** (ESI$^+$) [M+H]$^+$ calc'd for $C_{24}H_{21}N$: 324.1747, found: 324.1756.



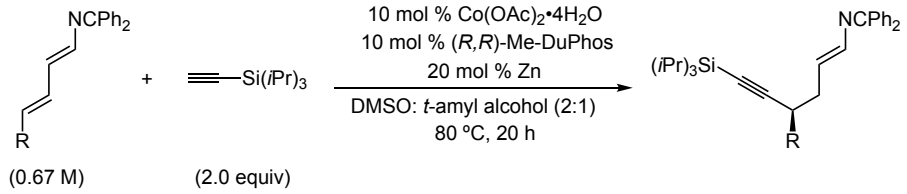

*N*-((1*E*,3*E*)-5-(4-methoxyphenyl)penta-1,3-dien-1-yl)-1,1-diphenylmethanimine (**4.10**). Title compound **4.10** was prepared according to general method A on 1.70 mmol scale. The material was purified by automated column chromatography (100% hexanes to 98:2 hexanes:ethyl acetate) to obtain **4.10** as a yellow oil (221.0 mg, 0.625 mmol, 36.7% yield). **IR** (thin film) 3058 (w), 3021 (w), 2833 (w), 1660 (w), 1637 (w), 1609 (m), 1511 (s) cm$^{-1}$; **$^1$H**

**NMR** (500 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 6.9 Hz), 7.52–7.48 (3H, m), 7.42–7.35 (3H, m), 7.23 (2H, dd, *J* = 7.6, 1.8 Hz), 7.10 (2H, d, *J* = 8.5 Hz), 6.91 (1H, d, *J* = 12.8 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 6.74 (1H, dd, *J* = 12.7, 10.9 Hz) 6.13–6.08 (1H, m), 6.02–5.96(1H, m), 3.81 (3H, s), 3.40 (2H, d, *J* = 6.8 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.6, 157.9, 139.5, 139.0, 136.2, 135.2, 132.4, 131.9, 130.0, 129.4, 128.7, 128.6, 128.6, 128.4, 128.0, 113.8, 55.1, 38.3; **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{25}H_{23}NO$: 354.1852, found: 354.1861.



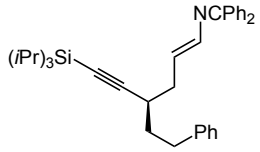

*N*-((1*E*,3*E*)-5-(4-fluorophenyl)penta-1,3-dien-1-yl)-1,1-diphenylmethanimine (**4.11**). Title compound **4.11** was prepared according to general method A on 2.25 mmol scale. The material was purified by automated column chromatography (100% hexanes to 98:2 hexanes:ethyl acetate) to obtain **4.11** as a yellow oil (370 mg, 1.08 mmol, 48.2% yield). **IR** (thin film) 3058 (w), 3022 (w), 1660 (w), 1638 (w), 1599 (m), 1537 (w), 1508 (s) $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 7.0 Hz), 7.53–7.48 (3H, m), 7.42–7.35 (3H, m), 7.23 (2H, dd, *J* = 7.5, 1.9 Hz), 7.14 (2H, dd, *J* = 8.5, 5.5 Hz), 6.99 (2H, t, *J* = 8.7 Hz), 6.92 (1H, d, *J* = 12.8 Hz), 6.74 (1H, dd, *J* = 12.7, 11.0 Hz), 6.13–6.08 (1H, m), 6.00–5.94 (1H, m), 3.42 (1H, d, *J* = 6.8 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 166.0, 161.5 (d, *J* = 244.0 Hz), 139.6, 139.4, 136.3, 135.6, 134.5, 132.3, 130.3, 130.1, 130.0, 129.9, 128.9, 128.9, 128.8 (2C, d, *J* = 5.9 Hz), 128.8, 128.5, 128.3, 128.2, 128.2, 115.2 (2C, d, *J* = 21.1 Hz), 38.4. **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{24}H_{20}FN$: 342.1653, found: 342.1656.

## 4.5.2 Hydroalkynylation of Azatrienes



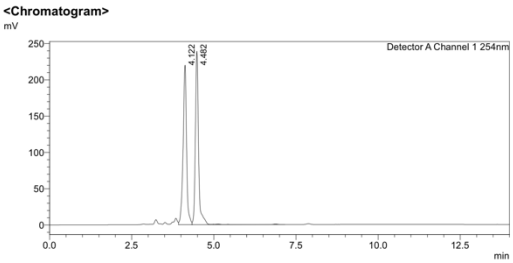

General Method B. In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial equipped with magnetic stir bar was charged with cobalt(II)acetate tetrahydrate (1.9 mg, 7.5 μmol, 0.0500 equiv), (*R*,*R*)-Me-DuPhos (2.3 mg, 7.5 μmol, 0.0500 equiv), zinc (1.0 mg, 10.0 μmol, 0.100 equiv), DMSO (150 μL), and *tert*-amyl alcohol (75 μL). The mixture was allowed to stir at ambient temperature for 15 minutes. To the vial was then added azatriene (0.150 mmol, 1.00 equiv) and triisopropylsilylacetylene (67.2 μL, 0.300 mmol, 2.00 equiv) whereupon the reaction vials were capped, taken out of the glovebox, and stirred at 80 °C for 20 h. The reaction mixture was then cooled to room temperature quenched with water (1 mL) and ethyl acetate (3 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 mL). The combined organic extracts were dried over $Na_2SO4$, filtered, and concentrated under reduced pressure. The residue was then purified by automated reverse phase column chromatography with silica gel (100% acetonitrile).

**Note**: Isolated yields reported are an average of 2 runs. Authentic racemic standards were prepared using a 1:1 mixture of both enantiomers of Me-DuPhos.




(*S*,*E*)-*N*-(4-phenethyl-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.2**). Title compound **4.2** was prepared according to general method X. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.2** as a yellow oil (47.4 mg, 0.092 mmol, 60.8% yield). **IR** (thin film) 3061 (w), 3025 (m), 2941 (s), 2890 (m), 2863 (s), 2164 (m), 1603 (w), 1554 (w) 1495 (w) $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ 7.58 (2H, d, *J* = 8.3 Hz), 7.37–7.35 (3H, m), 7.32–7.24 (3H, m), 7.21–7.18 (2H, m), 7.12–7.09 (5H, m), 6.68 (1H, d, *J* = 13.0 Hz), 6.17 (1H, dt, *J* = 12.9, 7.7 Hz), 2.80 (1H, ddd, *J* = 14.3, 9.8, 5.0 Hz), 2.63 (1H, ddd, *J* = 13.5, 9.9, 7.1 Hz), 2.40 (1H, dtd, *J* = 9.5, 6.7, 4.5 Hz), 2.29 – 2.12 (2H, m), 1.73–1.59 (2H, m), 1.03–1.01 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.4, 142.2, 139.7, 139.5, 136.4, 130.9, 130.1, 128.8, 128.6, 128.6, 128.4, 128.4, 128.1, 125.8, 111.3, 82.2, 36.6, 36.5, 33.6, 32.6, 18.7, 11.3; **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{36}H_{45}NSi$: 520.3394, found: 520.3404. $[\alpha]_D^{23}$ = +4.32 (*c* = 1.0, $CHCl_3$) for a sample of 99:1 er.

**HPLC:** Column: Cellulose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 254 nm. Er = 99:1.




<Peak Table>
Detector A Channel 1 254nm

| Peak# | Ret. Time | Area | Area% |
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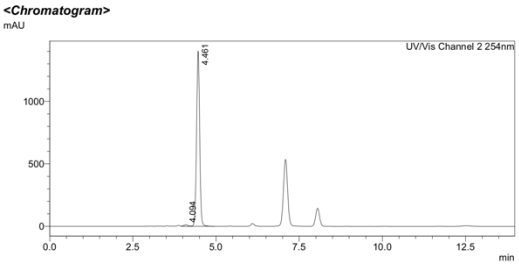
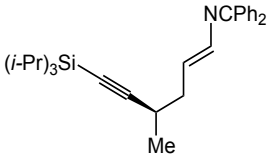
| 2 | 4.482 | 1628158 | 50.360 |
| Total | | 3233018 | 100.000 |



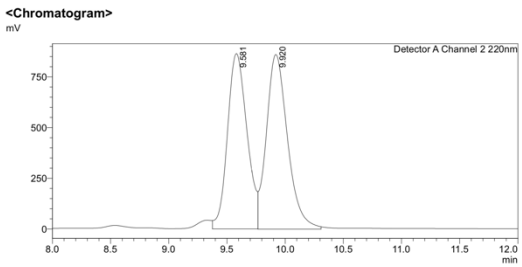

<Peak Table>
UV/Vis Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 4.094 | 108904 | 1.172 |
| 2 | 4.461 | 9187041 | 98.828 |
| Total | | 9295945 | 100.000 |



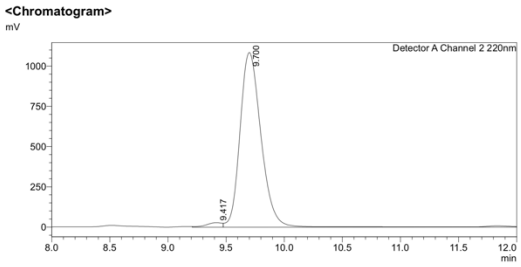

(*S*,*E*)-*N*-(4-methyl-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.12**). Title compound **4.12** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.12** as a yellow oil (43.0 mg, 0.100 mmol, 66.7% yield). **IR** (thin film) 3060 (w), 3025 (w), 2942 (s), 2891 (m), 2864 (s), 2162 (w), 1599 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.54 (2H, d, $J$ = 7.0 Hz), 7.35–7.31 (3H, m), 7.25–7.19 (3H, m), 7.08–7.06 (2H, m), 6.65 (1H, d, $J$ = 12.9 Hz), 6.13 (1H, dt, $J$ = 12.9, 7.7 Hz), 2.46–2.39 (1H, m), 2.20–2.14 (1H, m), 2.11–2.05 (1H, m), 1.05 (3H, $J$ = 6.9 Hz), 0.92 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.3, 139.7, 139.7, 138.3, 136.4, 130.5, 130.1, 128.8, 128.8, 128.6, 128.5, 128.4, 128.1, 127.6, 108.7, 82.6, 73.2, 72.4, 33.7, 33.0, 18.7, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{29}H_{39}NSi$: 430.2925, found: 430.2926. **$[\alpha]_D^{23}$** = –20.56 ($c$ = 1.0, $CHCl_3$) for a sample of 98:2 er.

**HPLC:** Column: Cellulose-2 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 0.35 mL/min. Detection wavelength: 254 nm. Er = 98:2.



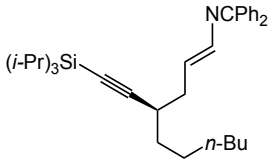

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 9.581 | 10150704 | 48.319 |
| 2 | 9.920 | 10857123 | 51.681 |
| Total | | 21007827 | 100.000 |




<Peak Table>
Detector A Channel 2 220nm

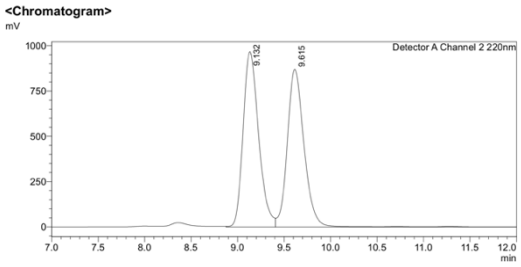
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 9.417 | 265017 | 1.860 |
| 2 | 9.700 | 13983243 | 98.140 |
| Total | | 14248260 | 100.000 |




(*S*,*E*)-1,1-diphenyl-*N*-(4-((triisopropylsilyl)ethynyl)dec-1-en-1-yl)methanimine (**4.13**). Title compound **4.13** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.13** as a yellow oil (42.0 mg, 0.0840 mmol, 56.0% yield). **IR** (thin film) 3060 (w), 3024 (w), 2929 (s), 2863 (s), 2164 (m), 1555 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.59 (2H, d, $J$ = 7.1 Hz), 7.40–7.36 (3H, m), 7.31–7.24 (3H, m), 7.12 (2H, dd, $J$ = 7.5, 1.7 Hz), 6.69 (1H, d, $J$ = 12.9 Hz), 6.19 (1H, dt, $J$ = 13.0, 7.7 Hz), 2.40–2.35 (1H, m) 2.18 (2H, qt, $J$ = 14.0, 7.2 Hz),1.42–1.40 (2H, m), 1.34–1.28 (2H, m), 1.24–1.19 (6H, m), 0.98–0.98 (21H, m), 0.80 (3H, t, $J$ = 6.9 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.2, 139.7, 139.3, 136.5, 131.3, 130.1, 128.8, 128.8, 128.6, 128.4, 128.1, 112.0, 81.3, 36.5, 34.5, 33.0, 31.8, 29.1, 27.1, 22.6, 18.7, 14.1,

11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{34}H_{49}NSi$: 500.3707, found: 500.3717. **[α]D²³** = –17.46 ($c$ = 1.0, $CHCl_3$) for a sample of 99:1 er.

**HPLC:** Column: Cellulose-2 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 0.35 mL/min. Detection wavelength: 254 nm. Er= 99:1.




<Peak Table>
Detector A Channel 1 254nm

| Peak# | Ret. Time | Area | Area% |
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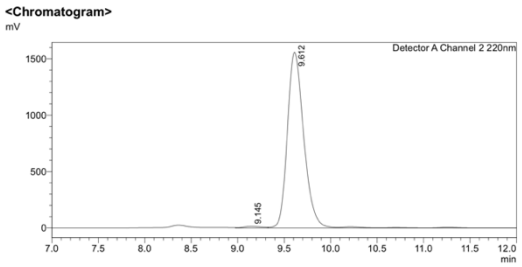
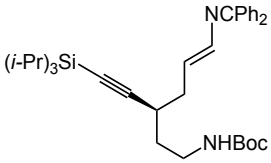
| 1 | 9.131 | 6714903 | 50.580 |
| 2 | 9.613 | 6560870 | 49.420 |
| Total | | 13275773 | 100.000 |




<Peak Table>
Detector A Channel 2 220nm

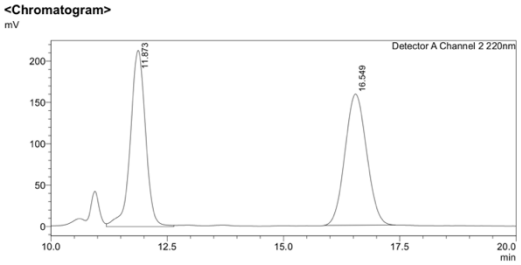
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 9.145 | 192236 | 0.981 |
| 2 | 9.612 | 19400972 | 99.019 |
| Total | | 19593208 | 100.000 |




*tert*-butyl (*R*,*E*)-(6-((diphenylmethylene)amino)-3-((triisopropylsilyl)ethynyl)hex-5-en-1-yl)carbamate (**4.14**). Title compound **4.14** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.14** as a yellow oil (35.9 mg, 0.0642 mmol, 42.8% yield). **IR** (thin film) 3353 (br), 3059 (w), 2941 9s), 2864 (s), 2165 (m), 1714 (s), 1506 (m) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.54 (2H, d, $J$ = 7.1 Hz), 7.36–7.32 (3H, m), 7.27–7.20 (3H, m), 7.08–7.06 (2H, m), 6.65 (1H, d, $J$ = 12.9 Hz), 6.11 (1H, dt, $J$ = 13.0, 7.7 Hz), 4.72 (1H, s), 3.17 (2H, m), 2.44–2.38 (1H, m), 2.18–2.14 (2H, m), 1.45–1.39 (2H, m) 1.31 (9H, m), 0.93 (21H, m);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.4, 142.2, 139.7, 139.5, 136.4, 130.9, 130.2, 128.8, 128.7, 128.6, 128.4, 128.4, 128.1, 125.8, 111.3, 82.2, 36.6, 36.5, 33.7, 32.6, 18.8, 11.3; **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{35}H_{50}N_2O_2Si$: 559.3714, found: 559.3719. $[\alpha]_D^{23}$ = –5.12 ($c$ = 1.0, $CHCl_3$) for a sample of 98.5:1.5 er.

**HPLC:** Column: Amylose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 220 nm. Er = 98.5:1.5.




<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
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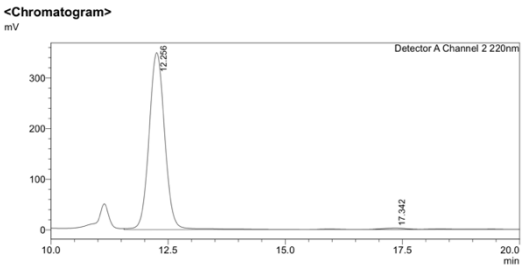
| 1 | 11.873 | 4833078 | 48.438 |
| 2 | 16.549 | 5144726 | 51.562 |
| Total | | 9977805 | 100.000 |




<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
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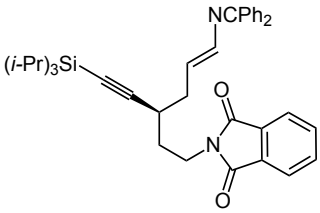
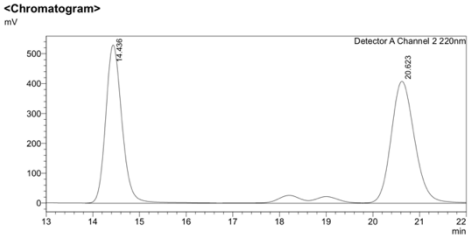
| 1 | 12.256 | 8292846 | 98.783 |
| 2 | 17.342 | 102173 | 1.217 |
| Total | | 8395019 | 100.000 |




(*R*,*E*)-2-(6-((diphenylmethylene)amino)-3-((triisopropylsilyl)ethynyl)hex-5-en-1-yl)isoindoline-1,3-dione (**4.15**). Title compound **4.15** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.15** as a yellow oil (50.6 mg, 0.0859 mmol,

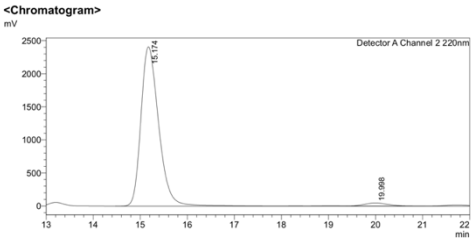
57.3% yield). **IR** (thin film) 2942 (m), 2864 (m), 2164 (w), 1773 (w) 1715 (s), 1554 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.59 (2H, d, $J$ = 7.1 Hz), 7.40–7.36 (3H, m), 7.31–7.24 (3H, m), 7.12 (3H, dd, $J$ = 7.5, 1.7 Hz), 6.69 (1H, d, $J$ = 12.9 Hz), 6.19 (1H, dt, $J$ = 13.0, 7.7 Hz), 2.40–2.35 (1H, m) 2.18 (2H, qt, $J$ = 14.0, 7.2 Hz),1.42–1.40 (2H, m), 1.34–1.28 (2H, m), 1.24–1.19 (7H, m), 0.98–0.98 (21H, m), 0.80 (3H, t, $J$ = 6.9 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 168.2, 165.6, 139.7, 139.7, 136.4, 133.8, 132.2, 130.2, 130.1, 128.8, 128.8, 128.7, 128.4, 128.1, 123.2, 110.0, 82.8, 36.5, 33.2, 31.1, 18.7, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{38}H_{44}N_2O_2Si$: 589.3245, found: 589.3244. **$[\alpha]_D^{23}$** = –24.64 ($c$ = 1.0, $CHCl_3$) for a sample of 97.5:2.5 er.

**HPLC:** Column: Amylose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 220 nm. Er = 97.5:2.5.



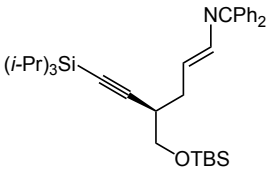

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 14.436 | 14583390 | 50.420 |
| 2 | 20.623 | 14340406 | 49.580 |
| Total | | 28923796 | 100.000 |




<Peak Table>
Detector A Channel 2 220nm

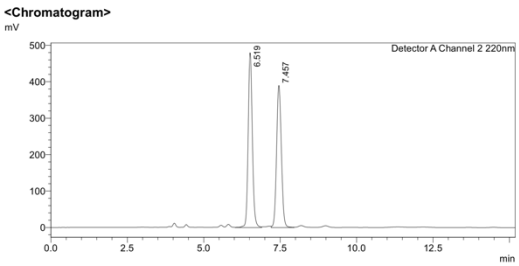
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 15.174 | 64093747 | 97.516 |
| 2 | 19.998 | 1632416 | 2.484 |
| Total | | 65726163 | 100.000 |




(*S*,*E*)-*N*-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.16**). Title compound **4.16** was prepared according to

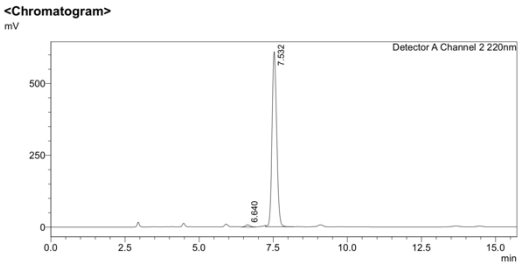
general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.16** as a yellow oil (47.1 mg, 0.0841 mmol, 56.0% yield). **IR** (thin film) 2941 (s), 2891 (m), 2863 (s), 2163 (w), 1663 (w), 1599 (w), 1556 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.64 (2H, d, *J* = 7.0 Hz), 7.46–7.42 (3H, m), 7.37–7.30 (3H, m), 7.17 (2H, dd, *J* = 7.4, 1.8 Hz) 6.78 (1H, d, *J* = 12.9 Hz), 6.27 (1H, dt, *J* = 12.9, 7.8 Hz), 3.65 (1H, dd, *J* = 9.6, 5.3 Hz), 3.52 (1H, dd, *J* = 9.5, 7.6 Hz), 2.64–2.59 (1H, m), 2.43–2.38 (1H, m), 2.26–2.20 (1H, m), 1.02 (21H, s), 0.83( 9H, s), 0.00 (6H, d, *J* = 2.6 Hz); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.3, 139.7, 139.4, 136.5, 131.1, 130.1, 128.8, 128.8, 128.6, 128.4, 128.1, 111.2, 81.6, 61.0, 37.7, 36.6, 29.5, 26.0, 18.7, 18.4, 11.3, -5.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{36}H_{55}NOSi_2$: 574.3895, found: 574.3905. **$[\alpha]_D^{23}$** = –31.24 (*c* = 1.0, $CHCl_3$) for a sample of 98.5:1.5 er.

**HPLC:** Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 220 nm. Er = 98.5:1.5.



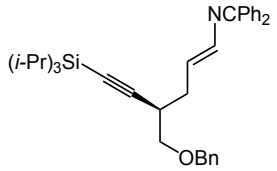

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 6.519 | 4521554 | 51.610 |
| 2 | 7.457 | 4239483 | 48.390 |
| Total | | 8761038 | 100.000 |



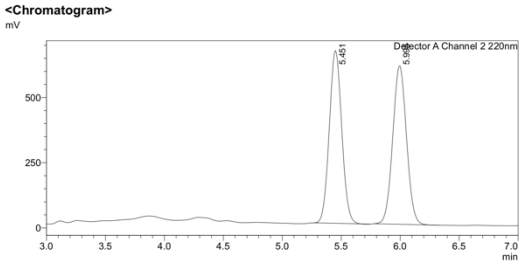

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 6.640 | 87813 | 1.306 |
| 2 | 7.532 | 6638298 | 98.694 |
| Total | | 6726111 | 100.000 |



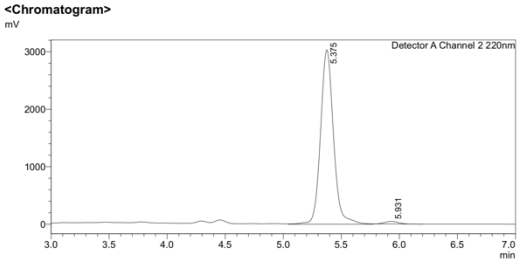

(*S*,*E*)-*N*-(4-((benzyloxy)methyl)-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.17**). Title compound **4.17** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.17** as a yellow oil (54.6 mg, 0.102 mmol, 67.9% yield). **IR** (thin film) 3061 (w), 3029 (w), 2941 (s), 2891 (m), 2864 (s), 2169 (w), 1554 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.54 (2H, d, *J* = 7.1 Hz), 7.32–7.30 (3H, m), 7.25–7.14 (7H, m), 7.07–7.05 (2H, m), 6.69 (1H, d, *J* = 12.9 Hz), 6.17 (1H, dt, *J* = 13.0, 7.7 Hz), 4.38 (2H, d, *J* = 2.3 Hz), 3.46 (1H, dd, *J* = 9.2, 5.6 Hz), 3.35 (1H, t, *J* = 7.9 Hz), 2.69 (1H, ddd, *J* = 13.1, 7.5, 5.6 Hz), 2.36–2.31 (2H, m), 2.21–2.15 (1H, m), 0.93–0.90 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.3, 139.7, 139.7, 138.3, 136.4, 130.5, 130.1, 128.8, 128.8, 128.6, 128.5, 128.4, 128.1, 127.6, 108.7, 82.6, 73.2, 72.4, 33.7, 33.01, 18.7, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{36}H_{45}NOSi$: 536.3343, found: 536.3345. **$[\alpha]_D^{23}$** = –18.71 (*c* = 1.0, $CHCl_3$) for a sample of 98.5:1.5 er.

**HPLC:** Column: Cellulose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:*I*PrOH, 1.0 mL/min. Detection wavelength: 220nm. Er = 98.5:1.5.



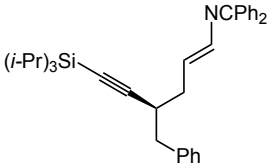

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 5.451 | 4861996 | 49.605 |
| 2 | 5.995 | 4939398 | 50.395 |
| Total | | 9801394 | 100.000 |



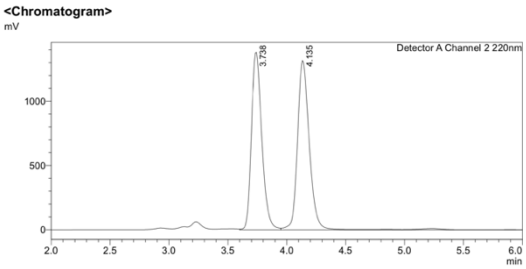

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 5.375 | 23596960 | 98.518 |
| 2 | 5.931 | 355080 | 1.482 |
| Total | | 23952040 | 100.000 |



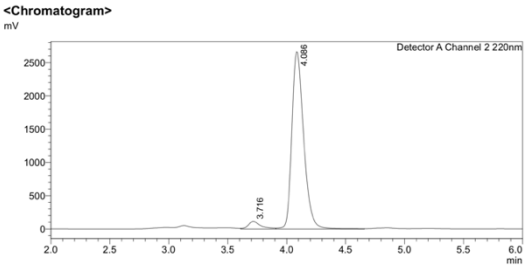

((*R*,*E*)-*N*-(4-benzyl-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.18**). Title compound **4.18** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.18** as a yellow oil (41.6 mg, 0.0821 mmol, 54.8% yield). **IR** (thin film) 3027 (w), 2941 (m), 2863 (m), 2167 (w), 1662 (w), 1600 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.59 (2H, d, $J$ = 7.0 Hz), 7.39–7.36 (3H, m), 7.30–7.24 (3H, m), 7.16–7.09 (7H, m), 6.71 (1H, d, $J$ = 12.9 Hz), 6.26–6.21 (1H, dt, $J$ = 13.0, 7.7 Hz), 2.74–2.63 (3H, m), 2.22–2.19 (2H, m), 0.94 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.4, 139.7, 139.4, 136.5, 130.8, 130.2, 129.4, 128.8, 128.8, 128.7, 128.5, 128.1, 128.1, 126.2, 110.9, 82.6, 40.6, 35.9, 34.9, 18.7, 11.3; **HRMS** ($ESI^+$) $[M+H]^+$ calc'd for $C_{35}H_{43}NSi$: 506.3238, found: 506.3246. **$[\alpha]_D^{23}$** = –11.19 ($c$ = 1.0, $CHCl_3$) for a sample of 95.5:4.5 er.

**HPLC:** Column: Cellulose-2 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 220 nm. Er = 95.5:4.5



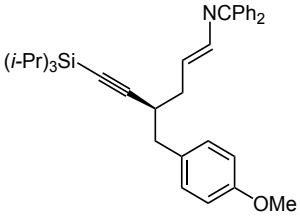

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 3.738 | 8445804 | 47.544 |
| 2 | 4.135 | 9318224 | 52.456 |
| Total | | 17764028 | 100.000 |




<Peak Table>
Detector A Channel 2 220nm

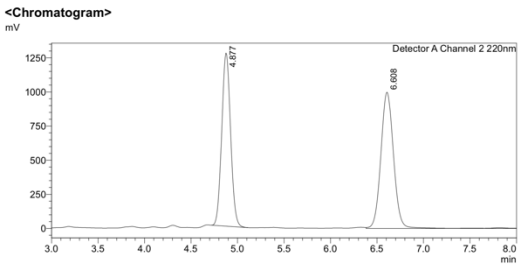
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 3.716 | 825672 | 4.244 |
| 2 | 4.086 | 18630838 | 95.756 |
| Total | | 19456510 | 100.000 |




(*R*,*E*)-*N*-(4-(4-methoxybenzyl)-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.19**). Title compound **4.19** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.19** as a yellow oil (44.3 mg, 0.0827 mmol, 55.1% yield). **IR** (thin film) 2941 (s), 2863 (s), 2163 9w), 1662 (w), 1612 (m), 1584 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.64 (2H, d, *J* = 8.5 Hz), 7.44–7.42 (3H, m), 7.35–7.29 (3H, m), 7.18–7.17 (2H, m), 7.10 (2H, d, *J* = 8.5 Hz), 6.77–6.74 (2H, m), 6.28 (1H, dt, *J* = 13.0, 7.7 Hz), 3.74 (3H, m), 2.73–2.63 (3H, m), 2.25–2.22 (2H, m), 1.00–0.98 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.4, 158.1, 139.7, 136.5, 131.5, 131.0, 130.3, 130.2, 128.8, 128.8, 128.6,

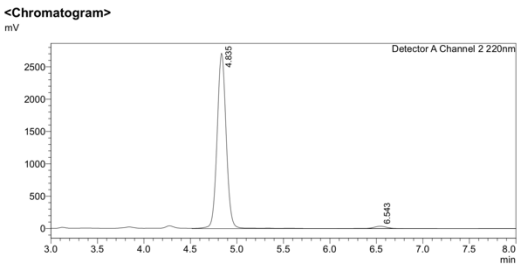
128.5, 128.1, 113.5, 111.1, 82.5, 55.3, 39.7, 35.7, 35.1, 18.7, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{36}H_{45}NOSi$: 536.3343, found: 536.3337. $[\alpha]_D^{23}$ = –11.35 (*c* = 1.0, $CHCl_3$) for a sample of 99:1 er.

**HPLC:** Column: Cellulose-1 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99:1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 220 nm. Er = 99:1.



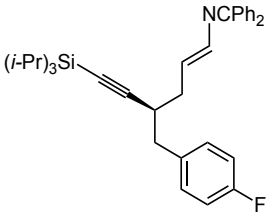

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 4.877 | 8411859 | 46.482 |
| 2 | 6.608 | 9685322 | 53.518 |
| Total | | 18097181 | 100.000 |




<Peak Table>
Detector A Channel 2 220nm

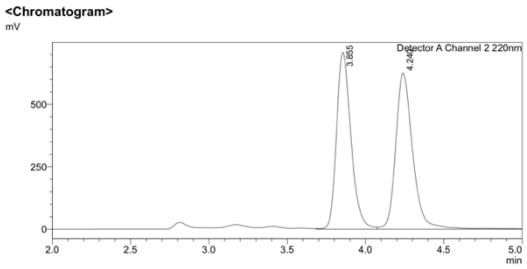
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 4.835 | 18636476 | 98.114 |
| 2 | 6.543 | 358265 | 1.886 |
| Total | | 18994740 | 100.000 |




(*R*,*E*)-*N*-(4-(4-fluorobenzyl)-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.20**). Title compound **4.20** was prepared according to general method B. The material was purified by reverse phase automated column chromatography (100% acetonitrile) to obtain **4.20** as a yellow oil (35.5 mg, 0.0674 mmol, 44.9% yield). **IR** (thin film) 2941 (s), 2890 (m), 2864 (s), 2166 (w), 1662 (w), 1600 (w), 1554

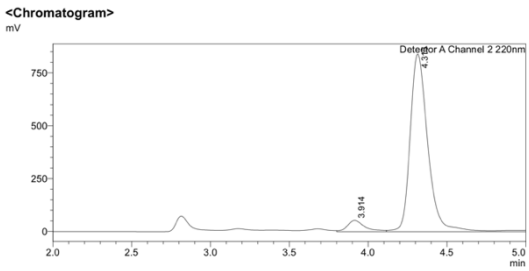
(w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.55 (2H, d, $J$ = 8.3 Hz), 7.35–7.34 (3H, m), 7.26–7.20 (3H, m), 7.08 (2H, dd, $J$ = 7.3, 1.9 Hz), 7.04 (2H, dd, $J$ = 8.4, 5.6 Hz), 6.79 (2H, t, $J$ = 8.7 Hz), 6.66 (1H, d, $J$ = 12.9 Hz), 6.17 (1H, dt, $J$ = 13.0, 7.7 Hz), 2.60 (3H, m), 2.16 (2H, t, $J$ = 6.9 Hz), 0.89–0.88 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 165.6, 161.6 (d, $J$ = 243.9 Hz), 139.8, 139.6, 136.5, 135.0, 130.7 (2C, d, $J$ = 7.7) Hz, 130.6, 130.2, 128.7 (2C, d, $J$ = 6.7 Hz), 128.7, 128.5, 128.1, 114.8 (2C, d, $J$ = 21.1 Hz), 110.5, 82.9, 39.7, 35.9, 35.0, 18.6, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{35}H_{42}FNSi$: 524.3143, found: 524.3149. **$[\alpha]_D^{23}$** = –7.16 ($c$ = 1.0, $CHCl_3$) for a sample of 94.5:5.5 er.

**HPLC:** Column: Cellulose-2 (3 µm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 220 nm. Er = 94.5:5.5.




<Peak Table>
Detector A Channel 2 220nm

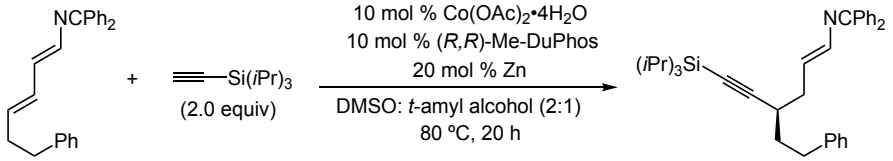
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 3.855 | 4549788 | 47.922 |
| 2 | 4.240 | 4944444 | 52.078 |
| Total | | 9494233 | 100.000 |



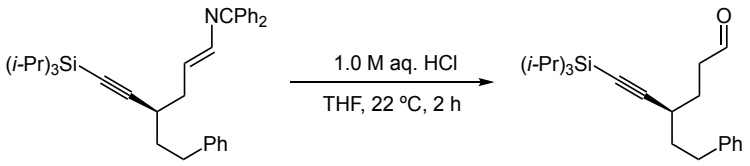

<Peak Table>
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 3.914 | 409048 | 5.387 |
| 2 | 4.315 | 7183501 | 94.613 |
| Total | | 7592549 | 100.000 |

## 4.5.3 Reaction Scale Up and Product Functionalization

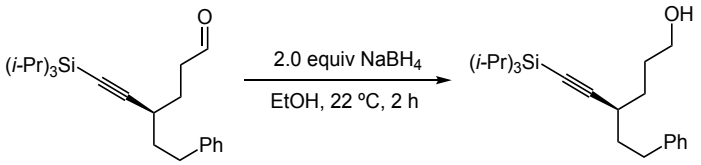


(*S*,*E*)-*N*-(4-phenethyl-6-(triisopropylsilyl)hex-1-en-5-yn-1-yl)-1,1-diphenylmethanimine (**4.2**). In an $N_2$-filled glovebox, an oven-dried (120 °C) microwave vial equipped with magnetic stir bar was charged with cobalt(II)acetate tetrahydrate (24.9 mg, 0.100 mmol, 0.100 equiv), (*R*,*R*)-Me-DuPhos (30.6 mmol, 0.100 mmol, 0.100 equiv), zinc (13.1 mg, 0.200 mmol, 0.200 equiv), DMSO (1.00 mL), and *t*-amyl alcohol (500 μL). The mixture was allowed to stir at ambient temperature for 15 minutes. To the vial was then added azatriene 4.1 (337 mg, 1.00 mmol, 1.00 equiv) and triisopropylsilylacetylene (449 μL, 2.00 mmol, 2.00 equiv) whereupon the reaction vial was capped, taken out of the glovebox, and stirred at 80 °C for 20 h. The reaction mixture was then cooled to room temperature quenched with water (15 mL) and ethyl acetate (10 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated, and then the residue purified by reverse-phase automated column chromatography to afford the desired product as a yellow oil (291 mg, 0.561 mmol, 56.1% yield).




**(***S*)-4-phenethyl-6-(triisopropylsilyl)hex-5-ynal. A 2-dram vial, equipped with stir bar, was charged with azadiene **4.2** (52.0 mg, 0.100 mmol, 1.00 equiv), THF (0.700 mL), and 1.0 M aq HCl (0.700 mL). The mixture was allowed to stir for 2 h at 22 °C. The mixture was diluted with diethyl ether (3.00 mL) and the aqueous and organic layers were

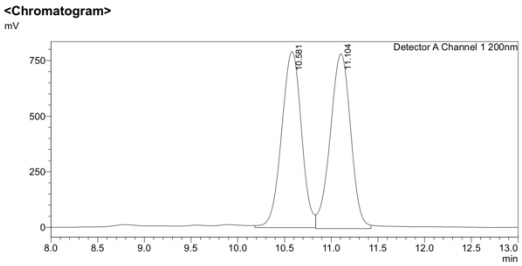
separated. The aqueous later was then washed with diethyl ether (5.00 mL x 3). The combined organic extracts were then dried over $Na_2SO_4$, filtered, and then concentrated *in vacuo*. The residue was then purified by reverse phase automated chromatography (100% acetonitrile) to afford the title compound as a faint yellow oil (19.3 mg, 0.541 mmol, 54.1% yield). **IR** (thin film) 3027 (w), 2941 (s), 2863 (s), 2163 (m), 1711 (s), 1603 (w), 1496 (w) $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 9.69 (1H, s), 7.18–7.13 (2H, m), 7.08–7.05 (3H, m), 2.80–2.75 (1H, m), 2.66–2.48 (3H, m), 2.36–2.30 (1H, m),1.77–1.71 (1H, m), 1.70–1.55 (3H, m), 0.97 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 202.1, 141.9, 141.9, 128.5, 128.4, 125.9, 42.0, 37.3, 37.2, 33.7, 31.8, 31.7, 29.9, 27.4, 18.7, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{23}H_{36}OSi$: 357.2608, found: 357.2611 $[\alpha]_D^{23}$ = +23.84 (*c* = 1.0, $CHCl_3$) for a sample of 97.5:2.5 er.




(*S*)-4-phenethyl-6-(triisopropylsilyl)hex-5-yn-1-ol (**4.25**). A 2-dram vial was charged with crude aldehyde, $NaBH_4$ (7.56 mg, 0.200 mmol, 2.00 equiv), ethanol (600 μL). The reaction mixture was then allowed to stir at room temperature for 2 hours after which it was quenched with 10% aqueous NaOH (1.00 mL) and further stirred at room temperature for 10 minutes. The mixture was dissolved in water (2.00 mL) and dichloromethane (5.00 mL). The aqueous and organic layers were separated. The aqueous later was then washed with dichloromethane (5.00 mL x 3). The combined organic extracts were then

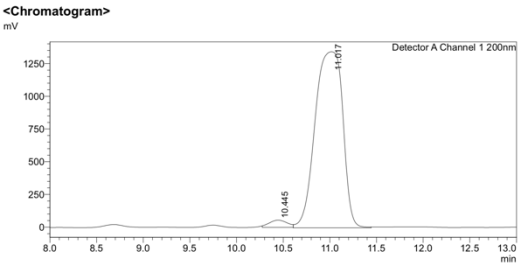
dried over $Na_2SO_4$, filtered, and then concentrated *in vacuo*. The residue was then purified by reverse phase automated chromatography (100% acetonitrile) to afford the title compound as a colorless oil (19.7 mg, 0.549 mmol, 54.9% yield after two steps). **IR** (thin film) 3333 (br), 3026 (w), 2940 (s), 2890 (m), 2863 (s), 2161 (m), 1607 (w), 1496 (w) $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ 7.15– 7.11 (2H, m), 7.07–7.03 (3H, m), 3.52 (2H, t, $J$ = 6.4 Hz), 2.75 (1H, ddd, $J$ = 14.2, 8.3, 6.6 Hz), 2.60 (1H, dt, $J$ = 13.6, 8.1 Hz), 2.27 (1H, tt, $J$ = 8.8, 5.4 Hz, 1H), 1.69–1.51 (4H, m), 1.47–1.35 (2H, m), 1.20 (1H, s), 0.96–0.93 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 142.2, 128.5, 128.4, 125.8, 111.8, 82.1, 62.8, 37.4, 33.7, 32.2, 31.5, 30.6, 18.7, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{23}H_{38}OSi$: 359.2765, found: 359.2760. **$[\alpha]_D^{23}$** = +31.64 ($c$ = 1.0, $CHCl_3$) for a sample of 97.5:2.5 er.

**HPLC:** Column: amylose-1 (3 μm, 4.6 mm X 250 mm). Mobile phase: 99.9:0.1 hexanes:*i*-PrOH, 1.0 mL/min. Detection wavelength: 200 nm. Er = 97.5:2.5



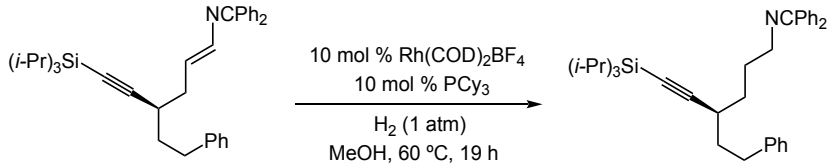

<Peak Table>
Detector A Channel 1 200nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.581 | 11710983 | 49.519 |
| 2 | 11.104 | 11938546 | 50.481 |
| Total | | 23649529 | 100.000 |



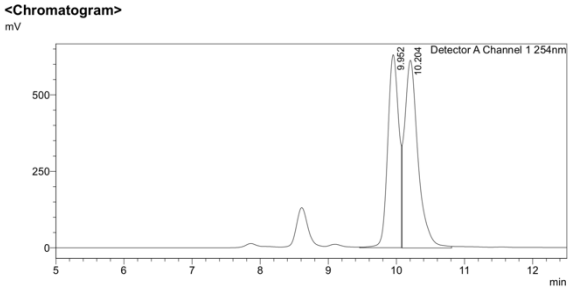

<Peak Table>
Detector A Channel 1 200nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.445 | 745243 | 2.609 |
| 2 | 11.017 | 27821719 | 97.391 |
| Total | | 28566962 | 100.000 |



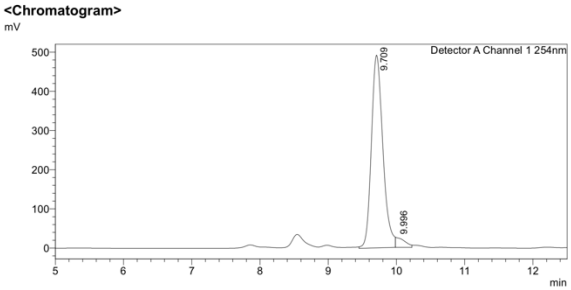

(*R*)-*N*-(4-phenethyl-6-(triisopropylsilyl)hex-5-yn-1-yl)-1,1-diphenylmethanimine (**4.26**). In an $N_2$-filled glovebox, a 2-dram vial equipped with a stirbar was charged with $Rh(COD)_2BF_4$ (2.0 mg, 0.005 mmol, 0.050 equiv), tricyclohexylphosphine (1.4 mg, 0.005 mmol, 0.050 equiv), and methanol (200 mL). The reaction mixture was allowed to stir at ambient temperature for 30 minutes after which azadiene **3a** (26.0 mg, 0.050 mmol, 1.00 equiv) and methanol (200 mL) was added to the vial. The vial was taken out of the glovebox. The vial was evacuated and backfilled with hydrogen gas (from hydrogen balloon). The vial was then allowed to stir at 60 °C under an atmosphere of hydrogen for 19 h. The reaction vessel was then cooled to room temperature, and the crude material was passed through a short pad of silica gel, and eluted with EtOAc (8 mL), and then concentrated *in vacuo.* The residue was then purified by reverse phase automated chromatography (100% acetonitrile) to afford the title compound as a yellow oil (20.7 mg, 0.0396 mmol, 79.2% yield). **IR** (thin film) 3061 (w), 3026 (w), 2941 (s), 2863 (s), 2163 (m), 1623 (w), 1578 (w) $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ 7.50 (2H, d, $J$ = 7.0 Hz), 7.36–7.32 (3H, m), 7.27–7.21, (3H, m), 7.19–7.16 (2H, m), 7.11–7.08 (3H, m), 7.05 (2H, dd, $J$ = 7.8, 1.7 Hz), 3.29 (2H, t, dt, $J$ = 6.8 Hz), 2.82–2.76 (1H, m), 2.66–2.60 (1H, m), 2.32–2.26 (1H, m), 1.86–1.79 (1H, m), 1.72–1.62 (3H, m), 1.47–1.41 (2H, m), 1.00 (21H, m); **$^{13}$C NMR** (126 MHz, $CDCl_3$) $\delta$ 167.8, 142.4, 140.0, 137.0, 129.8, 128.8, 128.5, 128.5, 128.3, 128.3, 128.0,

127.8, 125.7, 112.1, 81.6, 53.6, 37.3, 33.7, 33.3, 32.3, 29.1, 18.7, 11.3; **HRMS** (ESI$^+$) $[M+H]^+$ calc'd for $C_{36}H_{47}NSi$: 522.3551, found: 522.3563. **[α]D$^{23}$** = +10.2 (*c* = 1.0, $CHCl_3$) for a sample of 96:4 er.




<Peak Table>
Detector A Channel 1 254nm

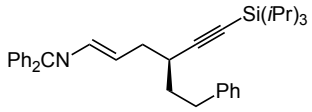
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 9.952 | 7163735 | 46.176 |
| 2 | 10.204 | 8350391 | 53.824 |
| Total | | 15514126 | 100.000 |




<Peak Table>
Detector A Channel 1 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 9.709 | 5748626 | 96.026 |
| 2 | 9.996 | 237880 | 3.974 |
| Total | | 5986506 | 100.000 |

## 4.5.4 X-ray crystallographic data for 4.2




≡

**Crystal data and structure refinement for 4.2.**

| | | |
|---|---|---|
| **Empirical formula** | $C_{36}H_{45}NSi$ | |
| **Formula weight** | 519.85 | |
| **Crystal color, shape, size** | colorless block, 0.345 x 0.256 x 0.074 $mm^3$ | |
| **Temperature** | 150 K | |
| **Wavelength** | 0.71073 Å | |
| **Crystal system, space group** | Monoclinic, P 1 21 1 | |
| **Unit cell dimensions** | a = 9.7211(8) Å | α= 90°. |
| | b = 9.2365(9) Å | β= 93.834(3)°. |
| | c = 18.1128(16) Å | γ = 90°. |
| **Volume** | 1622.7(3) $Å^3$ | |
| **Z** | 2 | |
| **Density (calculated)** | 1.064 $Mg/m^3$ | |
| **Absorption coefficient** | 0.095 $mm^{-1}$ | |
| **F(000)** | 564 | |

| | |
|---|---|
| **Data collection** | |
| **Diffractometer** | Bruker Kappa ApexII, Bruker |
| **Theta range for data collection** | 2.100 to 26.375°. |
| **Index ranges** | -10<=h<=12, -11<=k<=11, -22<=l<=22 |
| **Reflections collected** | 47417 |
| **Independent reflections** | 3526 [R(int) = 0.064] |
| **Observed Reflections** | 2951 |
| **Completeness to theta = 26.375°** | 99.7 % |

| | |
|---|---|
| **Solution and Refinement** | |
| **Absorption correction** | Numerical |
| **Max. and min. transmission** | 0.99 and 0.98 |
| **Solution** | Intrinsic phasing methods |
| **Refinement method** | Full-matrix least-squares on $F^2$ |
| **Weighting scheme** | $w = [\sigma^2 Fo^2 + AP^2 + BP]^{-1}$, with |
| | $P = (Fo^2 + 2\,Fc^2)/3$, A = 0.032, B = 0.335 |
| **Data / restraints / parameters** | 3516 / 4 / 479 |

| | |
|---|---|
| **Goodness-of-fit on $F^2$** | 1.0239 |
| **Final R indices [I>2sigma(I)]** | R1 = 0.0370, wR2 = 0.0699 |
| **R indices (all data)** | R1 = 0.0512, wR2 = 0.0769 |
| **Absolute structure parameter** | 0.0(3) |
| **Largest diff. peak and hole** | 0.31 and -0.27 e.$Å^{-3}$ |

**Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for 4.2. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Si1 | 4776(1) | 4995(2) | 8233(1) | 27 |
| N1 | 1080(2) | 7743(2) | 6180(1) | 23 |
| C1 | 2949(3) | 4523(3) | 8013(1) | 28 |
| C2 | 1743(2) | 4239(3) | 7906(1) | 24 |
| C3 | 263(2) | 3898(3) | 7789(1) | 25 |
| C4 | -298(3) | 4344(3) | 7006(2) | 26 |
| C5 | -11(2) | 5892(3) | 6834(2) | 25 |
| C6 | 774(2) | 6287(3) | 6296(1) | 23 |
| C7 | 5021(3) | 6996(4) | 8042(2) | 44 |
| C8 | 4123(4) | 7573(4) | 7381(2) | 60 |
| C9 | 6529(4) | 7390(5) | 7951(3) | 68 |
| C10 | 5862(3) | 3823(4) | 7654(2) | 44 |
| C11 | 5626(4) | 2213(4) | 7804(3) | 63 |
| C12 | 5651(4) | 4153(5) | 6825(2) | 61 |
| C13 | 5150(3) | 4540(4) | 9242(2) | 39 |
| C14 | 6675(4) | 4582(6) | 9495(3) | 74 |
| C15 | 4269(5) | 5437(6) | 9740(2) | 78 |
| C16 | 2(3) | 2285(3) | 7935(1) | 27 |
| C17 | 464(3) | 1841(3) | 8723(2) | 36 |
| C18 | 261(3) | 254(3) | 8876(1) | 34 |
| C19 | -809(3) | -196(4) | 9293(2) | 42 |
| C20 | -998(4) | -1645(4) | 9448(2) | 56 |
| C21 | -134(5) | -2662(4) | 9188(2) | 59 |
| C22 | 922(4) | -2245(4) | 8770(2) | 59 |
| C23 | 1122(3) | -780(4) | 8611(2) | 45 |
| C24 | 1762(2) | 8116(3) | 5621(1) | 21 |
| C25 | 2118(2) | 9679(3) | 5557(1) | 19 |
| C26 | 2312(2) | 10302(3) | 4875(1) | 22 |
| C27 | 2557(2) | 11772(3) | 4811(1) | 26 |
| C28 | 2637(2) | 12638(3) | 5436(2) | 28 |
| C29 | 2474(2) | 12029(3) | 6123(2) | 26 |
| C30 | 2207(2) | 10562(3) | 6186(1) | 23 |
| C31 | 2188(2) | 7112(3) | 5031(1) | 20 |
| C32 | 1213(2) | 6411(3) | 4565(1) | 25 |
| C33 | 1601(3) | 5474(3) | 4018(2) | 29 |

| | | | | |
|---|---|---|---|---|
| C34 | 2984(3) | 5224(3) | 3937(1) | 29 |
| C35 | 3972(3) | 5902(3) | 4397(2) | 32 |
| C36 | 3583(3) | 6854(3) | 4939(2) | 27 |

**Bond lengths [Å] and angles [°] for 4.2.**

| | | | |
|---|---|---|---|
| Si1-C1 | 1.846(3) | Si1-C7 | 1.898(4) |
| Si1-C10 | 1.880(3) | Si1-C13 | 1.887(3) |
| N1-C6 | 1.396(3) | N1-C24 | 1.293(3) |
| C1-C2 | 1.205(3) | C2-C3 | 1.475(3) |
| C3-C4 | 1.540(4) | C3-C16 | 1.538(4) |
| C3-H31 | 1.06(3) | C4-C5 | 1.494(4) |
| C4-H41 | 0.97(3) | C4-H42 | 0.99(3) |
| C5-C6 | 1.328(3) | C5-H51 | 0.96(3) |
| C6-H61 | 0.98(3) | C7-C8 | 1.530(4) |
| C7-C9 | 1.530(5) | C7-H71 | 1.15(3) |
| C8-H81 | 0.97(4) | C8-H82 | 1.00(4) |
| C8-H83 | 1.11(3) | C9-H91 | 1.00(4) |
| C9-H92 | 1.10(4) | C9-H93 | 1.05(3) |
| C10-C11 | 1.532(5) | C10-C12 | 1.532(5) |
| C10-H101 | 1.03(3) | C11-H111 | 0.97(4) |
| C11-H112 | 1.07(4) | C11-H113 | 0.93(4) |
| C12-H121 | 0.99(4) | C12-H122 | 1.01(4) |
| C12-H123 | 1.00(4) | C13-C14 | 1.523(5) |
| C13-C15 | 1.528(5) | C13-H131 | 1.03(3) |
| C14-H141 | 1.02(4) | C14-H142 | 1.07(3) |
| C14-H143 | 0.92(4) | C15-H151 | 1.00(4) |
| C15-H152 | 1.03(5) | C15-H153 | 0.96(4) |
| C16-C17 | 1.523(4) | C16-H161 | 0.99(3) |
| C16-H162 | 0.96(3) | C17-C18 | 1.507(4) |
| C17-H171 | 0.98(3) | C17-H172 | 1.00(3) |
| C18-C19 | 1.389(4) | C18-C23 | 1.377(4) |
| C19-C20 | 1.382(5) | C19-H191 | 1.01(3) |
| C20-C21 | 1.365(6) | C20-H201 | 0.96(4) |
| C21-C22 | 1.371(6) | C21-H211 | 0.99(4) |
| C22-C23 | 1.400(5) | C22-H221 | 0.83(4) |
| C23-H231 | 0.99(3) | C24-C25 | 1.491(3) |
| C24-C31 | 1.495(3) | C25-C26 | 1.387(3) |
| C25-C30 | 1.399(3) | C26-C27 | 1.385(3) |
| C26-H261 | 0.92(3) | C27-C28 | 1.384(4) |
| C27-H271 | 1.03(3) | C28-C29 | 1.384(4) |
| C28-H281 | 0.97(3) | C29-C30 | 1.386(4) |
| C29-H291 | 1.00(3) | C30-H301 | 0.98(2) |
| C31-C32 | 1.386(3) | C31-C36 | 1.398(3) |

| | | | |
|---|---|---|---|
| C32-C33 | 1.387(4) | C32-H321 | 0.95(2) |
| C33-C34 | 1.382(4) | C33-H331 | 0.92(3) |
| C34-C35 | 1.379(4) | C34-H341 | 1.00(3) |
| C35-C36 | 1.388(4) | C35-H351 | 0.95(3) |
| C36-H361 | 0.94(3) | | |

| | | | |
|---|---|---|---|
| C1-Si1-C7 | 108.74(13) | C1-Si1-C10 | 108.17(14) |
| C7-Si1-C10 | 112.14(16) | C1-Si1-C13 | 106.05(13) |
| C7-Si1-C13 | 112.03(15) | C10-Si1-C13 | 109.45(16) |
| C6-N1-C24 | 120.0(2) | Si1-C1-C2 | 176.6(2) |
| C1-C2-C3 | 179.0(3) | C2-C3-C4 | 111.0(2) |
| C2-C3-C16 | 110.6(2) | C4-C3-C16 | 111.4(2) |
| C2-C3-H31 | 105.2(13) | C4-C3-H31 | 108.1(13) |
| C16-C3-H31 | 110.3(13) | C3-C4-C5 | 112.9(2) |
| C3-C4-H41 | 107.2(15) | C5-C4-H41 | 110.8(16) |
| C3-C4-H42 | 109.9(15) | C5-C4-H42 | 110.0(16) |
| H41-C4-H42 | 106(2) | C4-C5-C6 | 122.8(3) |
| C4-C5-H51 | 119.3(16) | C6-C5-H51 | 117.3(16) |
| N1-C6-C5 | 120.9(2) | N1-C6-H61 | 120.3(15) |
| C5-C6-H61 | 118.7(15) | Si1-C7-C8 | 114.2(2) |
| Si1-C7-C9 | 112.6(2) | C8-C7-C9 | 109.5(3) |
| Si1-C7-H71 | 105.1(16) | C8-C7-H71 | 109.9(15) |
| C9-C7-H71 | 105.0(15) | C7-C8-H81 | 108(2) |
| C7-C8-H82 | 114(2) | H81-C8-H82 | 110(3) |
| C7-C8-H83 | 111.7(19) | H81-C8-H83 | 105(3) |
| H82-C8-H83 | 107(3) | C7-C9-H91 | 112(2) |
| C7-C9-H92 | 113.1(19) | H91-C9-H92 | 98(3) |
| C7-C9-H93 | 109(2) | H91-C9-H93 | 120(3) |
| H92-C9-H93 | 104(3) | Si1-C10-C11 | 111.3(2) |
| Si1-C10-C12 | 112.9(3) | C11-C10-C12 | 110.8(3) |
| Si1-C10-H101 | 103.8(17) | C11-C10-H101 | 111.8(18) |
| C12-C10-H101 | 106.0(16) | C10-C11-H111 | 107(2) |
| C10-C11-H112 | 106(2) | H111-C11-H112 | 114(3) |
| C10-C11-H113 | 112(3) | H111-C11-H113 | 119(3) |
| H112-C11-H113 | 98(3) | C10-C12-H121 | 114(2) |
| C10-C12-H122 | 111(2) | H121-C12-H122 | 108(3) |
| C10-C12-H123 | 115.3(20) | H121-C12-H123 | 107(3) |
| H122-C12-H123 | 100(3) | Si1-C13-C14 | 114.0(2) |

| | | | |
|---|---|---|---|
| Si1-C13-C15 | 111.8(2) | C14-C13-C15 | 112.4(3) |
| Si1-C13-H131 | 103.7(17) | C14-C13-H131 | 106.6(17) |
| C15-C13-H131 | 107.6(17) | C13-C14-H141 | 109(2) |
| C13-C14-H142 | 105(2) | H141-C14-H142 | 106(3) |
| C13-C14-H143 | 115(3) | H141-C14-H143 | 117(4) |
| H142-C14-H143 | 103(4) | C13-C15-H151 | 110(3) |
| C13-C15-H152 | 103(3) | H151-C15-H152 | 108(4) |
| C13-C15-H153 | 112(3) | H151-C15-H153 | 102(3) |
| H152-C15-H153 | 121(4) | C3-C16-C17 | 112.4(2) |
| C3-C16-H161 | 110.1(17) | C17-C16-H161 | 109.4(15) |
| C3-C16-H162 | 111.7(16) | C17-C16-H162 | 107.4(16) |
| H161-C16-H162 | 106(2) | C16-C17-C18 | 113.6(2) |
| C16-C17-H171 | 108.5(17) | C18-C17-H171 | 112.7(18) |
| C16-C17-H172 | 108.6(16) | C18-C17-H172 | 109.7(18) |
| H171-C17-H172 | 103(2) | C17-C18-C19 | 120.2(3) |
| C17-C18-C23 | 121.3(3) | C19-C18-C23 | 118.5(3) |
| C18-C19-C20 | 120.9(4) | C18-C19-H191 | 118.4(17) |
| C20-C19-H191 | 120.3(18) | C19-C20-C21 | 120.3(4) |
| C19-C20-H201 | 118(2) | C21-C20-H201 | 122(2) |
| C20-C21-C22 | 119.8(3) | C20-C21-H211 | 118(2) |
| C22-C21-H211 | 122(2) | C21-C22-C23 | 120.3(4) |
| C21-C22-H221 | 126(3) | C23-C22-H221 | 114(3) |
| C22-C23-C18 | 120.2(3) | C22-C23-H231 | 122.0(19) |
| C18-C23-H231 | 117.8(19) | N1-C24-C25 | 117.0(2) |
| N1-C24-C31 | 125.1(2) | C25-C24-C31 | 117.9(2) |
| C24-C25-C26 | 121.2(2) | C24-C25-C30 | 120.2(2) |
| C26-C25-C30 | 118.6(2) | C25-C26-C27 | 121.0(2) |
| C25-C26-H261 | 123.3(16) | C27-C26-H261 | 115.7(16) |
| C26-C27-C28 | 119.9(2) | C26-C27-H271 | 122.2(15) |
| C28-C27-H271 | 117.8(15) | C27-C28-C29 | 119.8(2) |
| C27-C28-H281 | 118.4(16) | C29-C28-H281 | 121.8(16) |
| C28-C29-C30 | 120.4(3) | C28-C29-H291 | 119.8(15) |
| C30-C29-H291 | 119.8(15) | C25-C30-C29 | 120.3(2) |
| C25-C30-H301 | 119.0(16) | C29-C30-H301 | 120.7(16) |
| C24-C31-C32 | 121.0(2) | C24-C31-C36 | 120.5(2) |
| C32-C31-C36 | 118.5(2) | C31-C32-C33 | 121.3(2) |
| C31-C32-H321 | 120.1(15) | C33-C32-H321 | 118.5(15) |
| C32-C33-C34 | 119.5(2) | C32-C33-H331 | 118.7(16) |
| C34-C33-H331 | 121.8(16) | C33-C34-C35 | 120.2(2) |
| C33-C34-H341 | 120.9(15) | C35-C34-H341 | 118.8(15) |

| | | | |
|---|---|---|---|
| C34-C35-C36 | 120.2(2) | C34-C35-H351 | 119.2(17) |
| C36-C35-H351 | 120.6(17) | C31-C36-C35 | 120.3(2) |
| C31-C36-H361 | 120.2(16) | C35-C36-H361 | 119.6(15) |

Symmetry transformations used to generate equivalent atoms:

**Anisotropic displacement parameters (Å$^2$x 10$^3$) for 4.2. The anisotropic displacement factor exponent takes the form: -2π$^2$[ h$^2$ a*$^2$U$^{11}$ + ... + 2 h k a* b* U$^{12}$]**

| $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|
| Si120(1) | 32(1) | 28(1) | 0(1) | 0(1) | -3(1) |
| N121(1) | 23(1) | 26(1) | 4(1) | 3(1) | 1(1) |
| C126(1) | 29(1) | 28(1) | 2(1) | 2(1) | -1(1) |
| C227(1) | 21(1) | 25(1) | 4(1) | 4(1) | 0(1) |
| C322(1) | 25(1) | 27(1) | 4(1) | 3(1) | -4(1) |
| C418(1) | 32(1) | 30(1) | 4(1) | 2(1) | -4(1) |
| C521(1) | 29(1) | 27(1) | 3(1) | 2(1) | 1(1) |
| C620(1) | 22(1) | 27(1) | 3(1) | 3(1) | 1(1) |
| C741(2) | 38(2) | 52(2) | 9(2) | -8(1) | -12(2) |
| C846(2) | 52(2) | 79(3) | 32(2) | -12(2) | -13(2) |
| C954(2) | 61(3) | 83(3) | 27(2) | -26(2) | -31(2) |
| C1025(2) | 59(2) | 50(2) | -11(2) | 9(1) | -7(1) |
| C1151(2) | 51(2) | 88(3) | -22(2) | 17(2) | 5(2) |
| C1250(2) | 92(3) | 42(2) | -19(2) | 13(2) | -22(2) |
| C1340(2) | 42(2) | 35(2) | 7(1) | -2(1) | -6(1) |
| C1455(2) | 108(4) | 55(2) | 26(3) | -27(2) | -21(2) |
| C1599(3) | 105(4) | 32(2) | -7(2) | 10(2) | 13(3) |
| C1626(1) | 28(1) | 27(1) | 4(1) | 2(1) | -6(1) |
| C1751(2) | 29(2) | 27(2) | 3(1) | 3(1) | -6(1) |
| C1844(2) | 31(2) | 24(1) | 6(1) | -6(1) | -6(1) |
| C1953(2) | 41(2) | 33(2) | 3(2) | 1(1) | -13(2) |
| C2077(3) | 54(2) | 37(2) | 11(2) | -4(2) | -34(2) |
| C2188(3) | 35(2) | 49(2) | 14(2) | -27(2) | -21(2) |
| C2269(3) | 37(2) | 66(2) | -5(2) | -21(2) | 14(2) |
| C2350(2) | 38(2) | 46(2) | 1(2) | -5(2) | -1(2) |
| C2413(1) | 24(1) | 24(1) | 4(1) | -3(1) | 2(1) |
| C2514(1) | 19(1) | 25(1) | 1(1) | 2(1) | 1(1) |
| C2621(1) | 22(1) | 25(1) | 0(1) | 2(1) | 0(1) |
| C2724(1) | 26(1) | 28(1) | 4(1) | 5(1) | -3(1) |
| C2821(1) | 20(1) | 43(2) | 2(1) | 2(1) | -1(1) |
| C2920(1) | 25(1) | 32(1) | -5(1) | 2(1) | 1(1) |
| C3016(1) | 28(1) | 25(1) | 2(1) | 2(1) | 3(1) |
| C3119(1) | 17(1) | 23(1) | 6(1) | 4(1) | -1(1) |
| C3218(1) | 26(1) | 30(1) | 3(1) | 2(1) | -1(1) |
| C3333(1) | 23(1) | 29(1) | 1(1) | 0(1) | -5(1) |

| | | | | | |
|---|---|---|---|---|---|
| C3436(1) | 20(1) | 33(1) | -2(1) | 15(1) | -3(1) |
| C3525(1) | 27(1) | 44(2) | 0(1) | 13(1) | 1(1) |
| C3619(1) | 26(1) | 37(2) | -1(1) | 2(1) | -4(1) |

**Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for 4.2.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H31 | -230(20) | 4550(30) | 8177(14) | 30 |
| H41 | -1280(30) | 4160(30) | 6973(13) | 32 |
| H42 | 90(30) | 3700(30) | 6633(15) | 32 |
| H51 | -290(30) | 6630(30) | 7163(14) | 31 |
| H61 | 1180(30) | 5530(30) | 5999(14) | 28 |
| H71 | 4740(30) | 7580(40) | 8576(17) | 53 |
| H81 | 4280(40) | 8610(40) | 7340(20) | 72 |
| H82 | 3120(40) | 7370(40) | 7403(19) | 72 |
| H83 | 4440(30) | 7130(40) | 6851(17) | 72 |
| H91 | 6710(40) | 8450(50) | 8030(20) | 82 |
| H92 | 7230(40) | 6990(50) | 8410(20) | 82 |
| H93 | 6860(40) | 6860(40) | 7480(20) | 82 |
| H101 | 6860(30) | 4140(40) | 7811(16) | 53 |
| H111 | 6280(40) | 1670(40) | 7520(20) | 76 |
| H112 | 5780(40) | 2070(40) | 8390(20) | 76 |
| H113 | 4700(40) | 1970(40) | 7760(20) | 76 |
| H121 | 6150(40) | 3490(40) | 6510(20) | 73 |
| H122 | 5950(40) | 5180(50) | 6713(19) | 73 |
| H123 | 4670(40) | 4190(40) | 6623(19) | 73 |
| H131 | 4840(30) | 3480(40) | 9278(16) | 47 |
| H141 | 6800(40) | 4210(50) | 10030(20) | 89 |
| H142 | 6940(40) | 5700(40) | 9520(20) | 89 |
| H143 | 7260(40) | 4220(50) | 9160(20) | 89 |
| H151 | 4340(40) | 5020(50) | 10250(20) | 95 |
| H152 | 4760(50) | 6430(50) | 9750(20) | 95 |
| H153 | 3300(50) | 5350(50) | 9600(20) | 95 |
| H161 | -990(30) | 2060(30) | 7838(14) | 33 |
| H162 | 480(30) | 1680(30) | 7607(15) | 33 |
| H171 | 10(30) | 2470(30) | 9066(16) | 43 |
| H172 | 1460(30) | 2100(30) | 8818(15) | 43 |
| H191 | -1510(30) | 550(30) | 9432(16) | 51 |
| H201 | -1740(40) | -1910(40) | 9748(19) | 68 |
| H211 | -330(30) | -3700(40) | 9285(19) | 70 |
| H221 | 1490(40) | -2800(50) | 8590(20) | 70 |
| H231 | 1870(30) | -450(30) | 8308(17) | 54 |

| | | | | |
|---|---|---|---|---|
| H261 | 2270(20) | 9790(30) | 4438(14) | 27 |
| H271 | 2640(20) | 12260(30) | 4308(14) | 31 |
| H281 | 2830(30) | 13660(30) | 5378(14) | 34 |
| H291 | 2560(20) | 12650(30) | 6578(14) | 31 |
| H301 | 2080(20) | 10130(30) | 6668(14) | 27 |
| H321 | 250(30) | 6540(30) | 4630(13) | 30 |
| H331 | 920(30) | 5050(30) | 3708(14) | 34 |
| H341 | 3290(30) | 4510(30) | 3566(15) | 35 |
| H351 | 4910(30) | 5690(30) | 4348(14) | 38 |
| H361 | 4270(30) | 7320(30) | 5246(14) | 32 |

**Torsion angles [°] for 4.2.**

| | | | |
|---|---|---|---|
| C1-Si1-C7-C8 | -34.9(3) | C1-Si1-C7-C9 | -160.6(3) |
| C10-Si1-C7-C8 | 84.7(3) | C10-Si1-C7-C9 | -41.0(3) |
| C13-Si1-C7-C8 | -151.7(2) | C13-Si1-C7-C9 | 82.5(3) |
| C1-Si1-C10-C11 | -58.9(3) | C1-Si1-C10-C12 | 66.5(3) |
| C7-Si1-C10-C11 | -178.8(2) | C7-Si1-C10-C12 | -53.4(3) |
| C13-Si1-C10-C11 | 56.3(3) | C13-Si1-C10-C12 | -178.4(2) |
| C1-Si1-C13-C14 | 169.0(3) | C1-Si1-C13-C15 | -62.2(3) |
| C7-Si1-C13-C14 | -72.6(3) | C7-Si1-C13-C15 | 56.3(3) |
| C10-Si1-C13-C14 | 52.5(3) | C10-Si1-C13-C15 | -178.7(3) |
| C24-N1-C6-C5 | -175.1(2) | C6-N1-C24-C25 | -176.65(19) |
| C6-N1-C24-C31 | 4.9(3) | C2-C3-C4-C5 | -53.9(3) |
| C16-C3-C4-C5 | -177.7(2) | C2-C3-C16-C17 | 59.8(3) |
| C4-C3-C16-C17 | -176.3(2) | C3-C4-C5-C6 | 117.1(3) |
| C4-C5-C6-N1 | -176.4(2) | C3-C16-C17-C18 | -178.2(2) |
| C16-C17-C18-C19 | -104.9(3) | C16-C17-C18-C23 | 75.2(3) |
| C17-C18-C19-C20 | -179.1(3) | C23-C18-C19-C20 | 0.8(4) |
| C17-C18-C23-C22 | 179.2(3) | C19-C18-C23-C22 | -0.8(4) |
| C18-C19-C20-C21 | -0.3(5) | C19-C20-C21-C22 | -0.3(6) |
| C20-C21-C22-C23 | 0.3(6) | C21-C22-C23-C18 | 0.2(5) |
| N1-C24-C25-C26 | -153.1(2) | N1-C24-C25-C30 | 24.3(3) |
| C31-C24-C25-C26 | 25.5(3) | C31-C24-C25-C30 | -157.15(19) |
| N1-C24-C31-C32 | 63.8(3) | N1-C24-C31-C36 | -115.9(3) |
| C25-C24-C31-C32 | -114.7(3) | C25-C24-C31-C36 | 65.6(3) |
| C24-C25-C26-C27 | 175.90(19) | C30-C25-C26-C27 | -1.5(3) |
| C24-C25-C30-C29 | -176.97(18) | C26-C25-C30-C29 | 0.5(3) |
| C25-C26-C27-C28 | 1.2(3) | C26-C27-C28-C29 | 0.1(3) |
| C27-C28-C29-C30 | -1.1(3) | C28-C29-C30-C25 | 0.9(3) |
| C24-C31-C32-C33 | -179.7(2) | C36-C31-C32-C33 | -0.1(4) |
| C24-C31-C36-C35 | 178.9(2) | C32-C31-C36-C35 | -0.7(4) |
| C31-C32-C33-C34 | 0.5(4) | C32-C33-C34-C35 | -0.1(4) |
| C33-C34-C35-C36 | -0.8(4) | C34-C35-C36-C31 | 1.2(4) |

Symmetry transformations used to generate equivalent atoms:

# 5. Conclusion

## *5.1 Palladium-Catalyzed Synthesis of α-Trifluoromethyl Benzylic Amines via Fluoroarylation of gem-Difluoro-2-azadienes*

In this work, we reported a palladium-catalyzed method for the synthesis of α-trifluoromethyl benzylic amines through the vicinal fluoroarylation of *gem*-difluoro-2-azadienes. We identified an α-trifluoromethyl azaallyl–silver species, which has been characterized via NMR spectroscopy, as the likely nucleophilic partner in the cross-coupling. XPhos is proposed to play a dual role in the transformation. First, the phosphine serves as a phase transfer catalyst that promotes the addition of AgF to the difluoroazadiene, generating the nucleophilic α-trifluoromethyl azaallyl–silver intermediate. Second, XPhos forms the active Pd catalyst, which couples the aryl iodide substrates to the *in situ* formed azaallyl–silver species.

We also explored a broad substrate scope of aryl iodides with varying electronic and steric parameters, which furnished the product in appreciable yield. Critical to the success of several challenging cross-couplings, such as sterically hindered or electron-poor aryl iodides, was modification of the azadiene's activating group from a benzophenone imine to a benzylidene.

Furthermore, we were able to perform a simple hydrolysis on the imine products to liberate the primary benzylic ammonium salts, and then functionalized the products to deliver a concise route to a HDAC6 inhibitor. This method provided a novel approach for the synthesis of α-$CF_3$ benzylic amines using an umpolung strategy.

## *5.2 Enantio- and Diastereoselective Synthesis of α-Trifluoromethyl Homoallylic Amines by Catalytic Hydroalkylation of Dienes*

In this work, which bridged two research programs in our laboratory, one on enantioselective imine/enamine umpolung and one on enantioselective diene hydrofunctionalization, we described a Pd-catalyzed enantio- and diastereoselective approach for the construction of α-trifluoromethyl homoallylic amines. Isatin-derived azadienolates underwent regioselective γ-addition to terminal 1,3-dienes in the presence of a bulky Pd–DTBM-SEGPHOS ligand to furnish the *anti*-diastereomer of the imine products in up to 86% yield, 10:1 dr, and 97.5:2.5 er.

The substrate scope of the reaction was considerable, tolerating aryl, heteroaryl, as well as aliphatic 1,3-dienes with high levels of enantio- and diastereoselectivity. Mechanistic studies elucidated that the γ-alkylation product is formed kinetically in the reaction as opposed to α-product formation then subsequent aza-Cope rearrangement as observed in the previous literature. The imines obtained from the hydroalkylation reactions could then be hydrolyzed under mild conditions to liberate the primary α-$CF_3$ homoallylic amines without significant loss in enantio- or diastereopurity.

In this olefin hydrofunctionalization approach, the relative and absolute configuration of vicinal stereogenic centers could be controlled in a single catalytic step. Additionally, this project was the first example of an enantioselective diene

hydroalkylation using an umpolung carbon nucleophile. This work holds the potential to open up new chemical space for discovery of new medicines.

## *5.3 Enantioselective Synthesis of Amines with Remote Stereogenic Centers through Co-Catalyzed Hydroalkynylation of 2-Azatrienes*

In this work, we described a novel enantioselective 5,6-hydroalkynylation of substituted 2-azatrienes. This work adds to our current investigations into the reactivity of 2-azatrienes for the development of different chiral amine scaffolds. We were able to show the coupling of triisopropylsilylacetylene to different 2-azatrienes in the presence of a Co-DuPhos catalyst to form the enantioenriched azadiene products in up to 68% yield and 99:1 er as a single regioisomer.

The substrate scope of the reaction is broad, tolerating aliphatic substrates, ethers, secondary and tertiary imides. Products arising exclusively from 5,6-addition are observed in all cases as the alkyne is delivered to the distal carbon on the azatriene. Furthermore, the enantioenriched azadienes obtained from the coupling can be hydrolyzed under mildly acidic conditions to liberate the aldehyde or alcohol (upon further reduction) bearing γ- or δ-stereogenic center, respectively. Rh–catalyzed hydrogenation can also be performed on the azadiene product to deliver the corresponding alkyl amine, containing a δ-stereogenic center. This is one of the few methods where amine products bearing a remote stereogenic center is accessed.

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# Biography

Chibueze Onyeagusi obtained his Ph.D. in chemistry from Duke University in May 2022. While at Duke, Chibueze worked on the synthesis of chiral amines in the research group of Dr. Steven J. Malcolmson. He also received the Burroughs-Wellcome Fellowship in 2019 and the Duke Conference Travel Award in 2019 and 2021. Outside of the lab, Chibueze was Vice-President and Media Coordinator of the Graduate Chemistry Council in the Department of Chemistry at Duke University. Prior to his time at Duke, Chibueze completed his B.S. in chemistry at Southeastern Louisiana University in 2016.

Chibueze co-authored and published a number of articles during his undergraduate and graduate studies, including "Strategies for the Catalytic Enantioselective Synthesis of α-Trifluoromethyl Amines" and "Palladium-Catalyzed Synthesis of α-Trifluoromethyl Benzylic Amines via Fluoroarylation of gem-Difluoro-2-azadienes Enabled by Phosphine-Catalyzed Formation of an Azaallyl–Silver Intermediate" both in *ACS Catalysis*, "Enantio- and Diastereoselective Synthesis of α-Trifluoromethyl Homoallylic Amines by Catalytic Hydroalkylation of Dienes" in *Organic Letters*, and "Nano-Dispersed Platinum(0) in Organically Modified Silicate Matrices as Sustainable Catalysts for a Regioselective Hydrosilylation of Alkenes and Alkynes" in *New Journal of Chemistry*.