

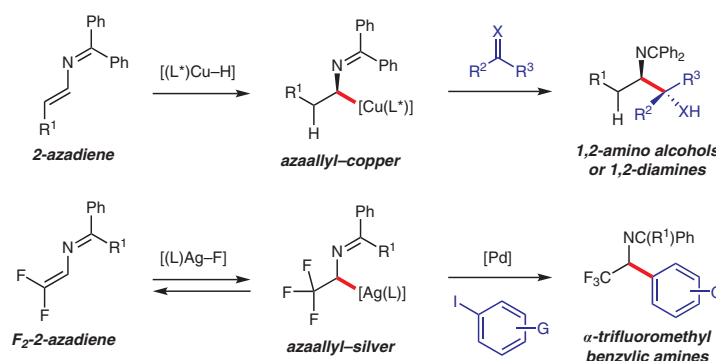
# 2-Azadienes as Enamine Umpolung Synthons for the Preparation of Chiral Amines

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Received: 02.02.2019

Accepted after revision: 05.03.2019

Published online: 26.03.2019

DOI: 10.1055/s-0037-1611770; Art ID: st-2019-p0065-sp

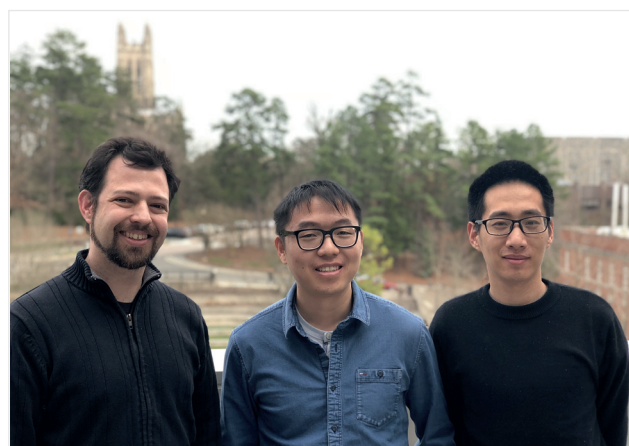
**Abstract** The development of new strategies for the preparation of chiral amines is an important objective in organic synthesis. In this *Synfacts*, we summarize our approach for catalytically accessing nucleophilic aminoalkyl metal species from 2-azadienes, and its application in generating a number of important but elusive chiral amine scaffolds. Reductive couplings with ketones and imines afford 1,2-amino tertiary alcohols and 1,2-diamines, respectively, whereas fluoroarylations of *gem*-difluoro-2-azadienes deliver  $\alpha$ -trifluoromethylated benzylic amines.

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**Key words** diamines, amino alcohols, 2-azadienes, reductive coupling, cross-coupling, fluoroarylation

## 1 Introduction

The synthesis of nitrogen-containing molecules has long been recognized as significant due to the widespread presence of this heteroatom in natural products, agrochemicals, pharmaceuticals, and catalysts (Figure 1).<sup>1</sup> In particular, methods that access N-substituted stereogenic carbon centers are highly compelling. Among these, C–C bond-forming strategies have attracted great attention due to the ability to assemble numerous challenging motifs quickly in a complexity-building manner.



**Steven Malcolmson** (left) was born in Boston, Massachusetts, and received his bachelor's degree in chemistry from Boston University (2004). After graduate work with Amir Hoveyda at Boston College (Ph.D. 2010) developing new Mo catalysts and methods for olefin metathesis as part of a collaborative project with Richard Schrock at MIT, Steven moved to Harvard Medical School to study natural product biosynthesis with Christopher Walsh as an NIH postdoctoral fellow. He began his independent career as an assistant professor at Duke University in 2013, with research interests that include developing new enantioselective transition-metal-catalyzed reactions and investigating their reaction mechanisms.

**Kangnan Li** (center) was born in Chongqing, P. R. of China, and received his undergraduate degree in chemical physics from the University of Science of Technology of China (2013), working with LiuZhu Gong. He joined the Malcolmson group at Duke University in 2013, where he developed new stereoselective methods for umpolung synthesis of chiral amines, receiving his Ph.D. in 2018.

**Xinxin Shao** (right) was born in Zhejiang, P. R. of China, and received his bachelor's degree from Northwest University (Xi'an) in 2010 and his Ph.D. from Shanghai Institute of Organic Chemistry (2015) under the supervision of Long Lu and Qilong Shen. After one year as an SIOC postdoctoral fellow with Dean Toste at the University of California, Berkeley, he joined the Malcolmson laboratory at Duke University as a postdoctoral researcher in early 2017. His research interests include developing new catalytic enantioselective transformations of 2-azadienes that deliver several classes of chiral amines.

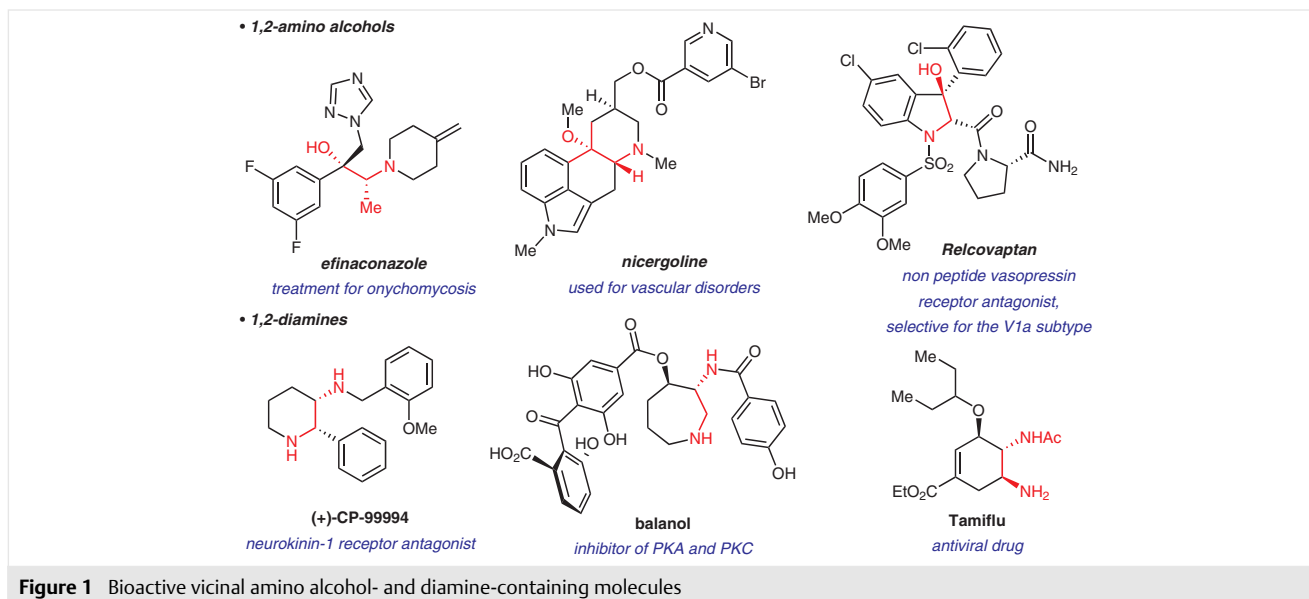


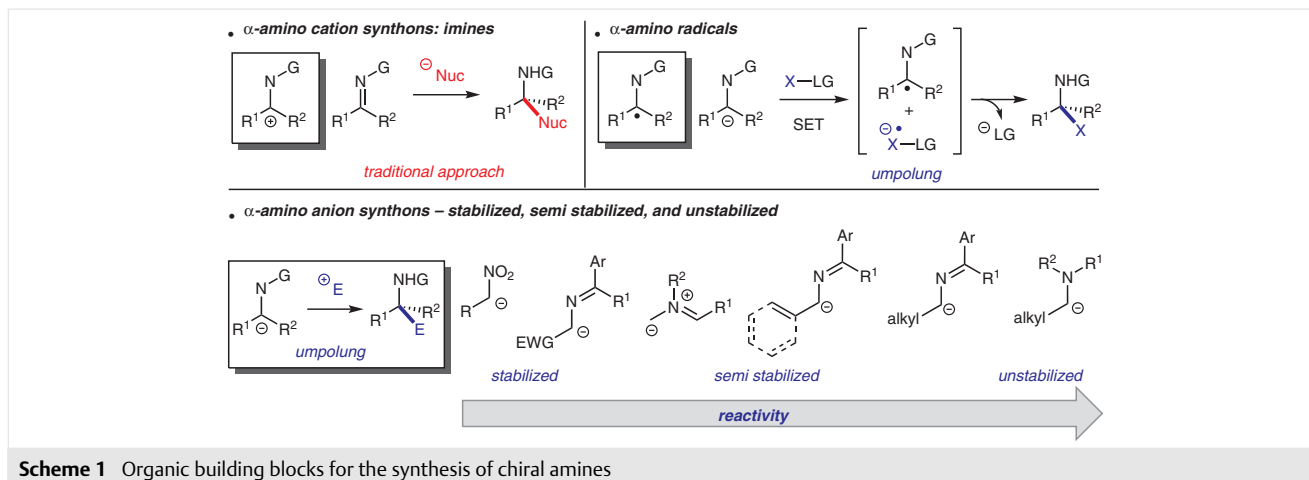
Figure 1 Bioactive vicinal amino alcohol- and diamine-containing molecules

Nucleophile addition to electrophilic imines is a long-standing approach for preparing N-substituted stereogenic centers through C–C bond formation (Scheme 1).<sup>2</sup> Such a normal-polarity tactic inherently limits the chemical space generated within the products if conventional nucleophiles are employed. In contrast, the reverse-polarity strategy<sup>3</sup> of utilizing  $\alpha$ -amino anion synthons to engage in reaction with C-based electrophiles opens up new avenues to highly sought-after chemical scaffolds, including vicinal amino alcohols and diamines, among others.

## 2 Background: Umpolung Strategies for Preparing Chiral Amines

### 2.1 Introduction

Reverse-polarity strategies permit the streamlined stereoselective synthesis of a number of chiral amine motifs, potentially facilitating access to new chemical space in the process. Generation of  $\alpha$ -amino radical anions through single-electron reduction of imines under photoredox catalysis is one approach that has been used to prepare several amine derivatives.<sup>4</sup> For example, the dimerization of these intermediates in pinacol-type reactions to give vicinal diamines has been explored.<sup>5</sup> In addition, theyTorker have also been employed in enantioselective cross-couplings to generate 1,2-diamines. Ooi and co-workers have developed



Scheme 1 Organic building blocks for the synthesis of chiral amines

a photoredox/Brønsted acid-catalyzed coupling of aldimines and *N*-arylaminoethanes,<sup>6</sup> and Huang and co-workers have similarly reported an enantioselective photoredox/Lewis acid-catalyzed synthesis of vicinal amino alcohols.<sup>7</sup>

In addition, the formation of  $\alpha$ -amino radicals from  $\alpha$ -amino anions through single-electron transfer, for example from super-electron-donor<sup>8</sup> 2-azaallyl anions, provides a strategy toward these umpolung synthons (Scheme 1). Recent research has utilized the  $\alpha$ -amino radicals generated in these processes directly in coupling reactions with vinyl bromides, aryl or alkyl halides, or cyanopyridines.<sup>9</sup>

$\alpha$ -Amino anions offer a different reverse-polarity tactic for the synthesis of chiral amines. Within the context of these building blocks, an enduring approach has involved nitronate nucleophiles (Scheme 1);<sup>10</sup> however, to secure the desired chiral amine, subsequent reduction of the nitro group must be carried out after C–C bond formation with these nucleophiles, thereby reducing step and redox economy.<sup>11</sup> Some previous strategies have focused on the use of other stabilized  $\alpha$ -amino anion nucleophiles, such as those derived from Schiff bases of amino acids,<sup>12</sup> alkylnitriles,<sup>13</sup> or isocyanoacetates,<sup>14</sup> to prepare substituted amino acids. Both stabilized and semi-stabilized 2-azomethine ylides provide chemists with alternative reagents for designing syntheses of nitrogen-containing heterocycles<sup>15</sup> through [3+2]-dipolar cycloadditions.<sup>16</sup>

In general, the preparation of more-reactive semi-stabilized or nonstabilized  $\alpha$ -amino anions has customarily required a strong base or decarboxylation.<sup>17</sup> Controlling enantioselectivity in catalytic reactions of semi-stabilized nucleophiles has recently emerged as a viable strategy toward enantioenriched amines.<sup>18</sup> Directed lithiation approaches for nonstabilized anions have employed stoichiometric sparteine or its analogues to control enantioselectivity.<sup>19</sup> Instead, if a comparatively more stable but still highly reactive  $\alpha$ -aminoalkyl metal species could be formed in the re-

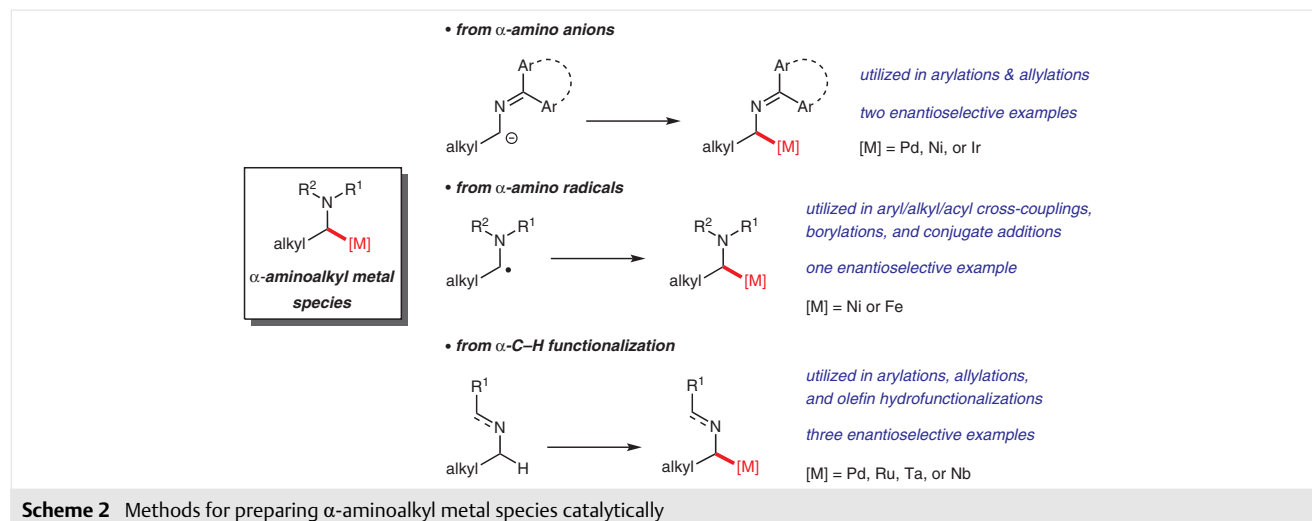
action, this would present new opportunities for controlling enantio- and diastereoselectivity en route to numerous chiral amine scaffolds.

## 2.2 $\alpha$ -Aminoalkyl Metal Species

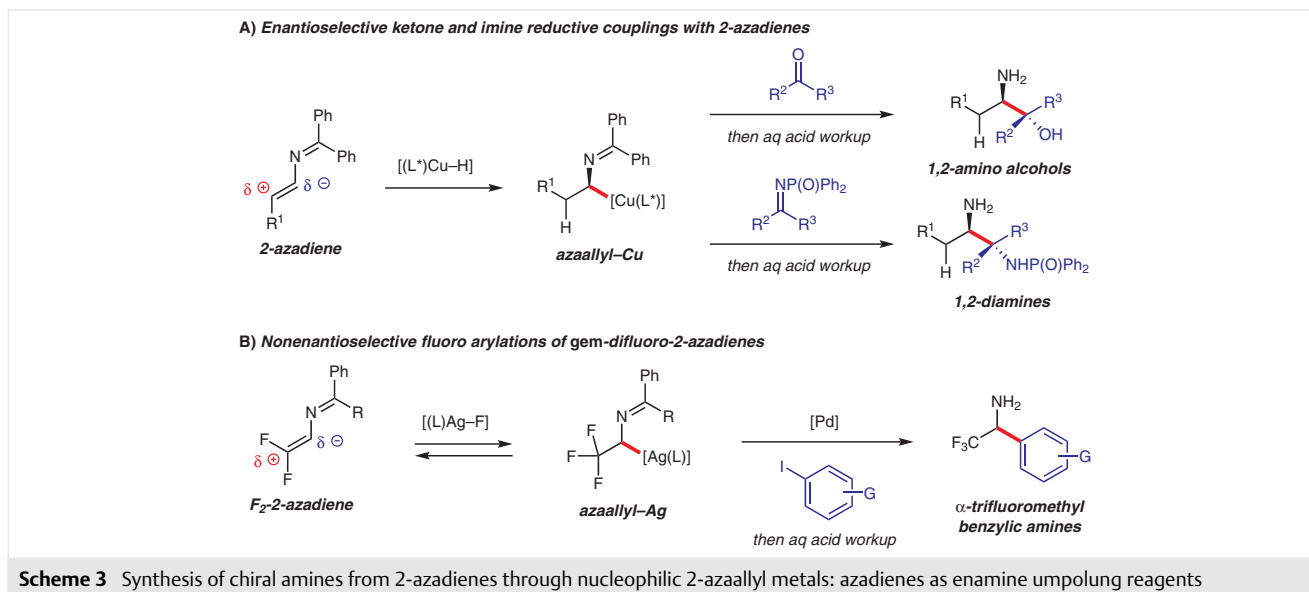
Catalytic formation of  $\alpha$ -aminoalkyl metal species is a powerful means for preparing chiral amines (Scheme 2).<sup>20</sup> The generation of semi-stabilized 2-azaallyl anions by  $\alpha$ -deprotonation or  $\alpha$ -decarboxylation of imines, followed by trapping with transition metals to form 2-azaallyl metal species, has been utilized in couplings with aryl<sup>21</sup> or allyl electrophiles.<sup>22</sup> Carboxylic acids and redox-active esters have also been employed to generate  $\alpha$ -amino radicals, which undergo catalytic recombination with transition metals in a number of applications.<sup>23</sup> Furthermore, C–H functionalization protocols provide a straightforward direct approach toward accessing  $\alpha$ -amino metal species, and they have been utilized in aryl cross-couplings,<sup>24</sup> electrophilic allylations,<sup>25</sup> and olefin alkylations.<sup>26</sup>

Although these transformations provide elegant and unique avenues to several classes of chiral amines, as well as insight into the reactivity of several  $\alpha$ -aminoalkyl metal species, for the most part they have not been enantioselective. Additionally, the chemical space accessible by these reactions has been somewhat limited, largely focused on  $\alpha$ -arylation. Several valuable classes of chiral amines, including sterically congested vicinal diamines and amino tertiary alcohols, remain difficult to prepare, especially through enantio- and diastereoselective C–C bond formation.

To address some of these challenges in chiral amine synthesis, our group has designed a new strategy to access substituted 2-azaallyl metals (Scheme 3). We utilize 2-azadienes as enamine umpolung reagents in which the olefin portion of the azadiene engages in an addition reaction with an [M]–X species. In this step, X is placed at the electrophilic position  $\beta$  to the nitrogen atom, and the nitrogen



**Scheme 2** Methods for preparing  $\alpha$ -aminoalkyl metal species catalytically

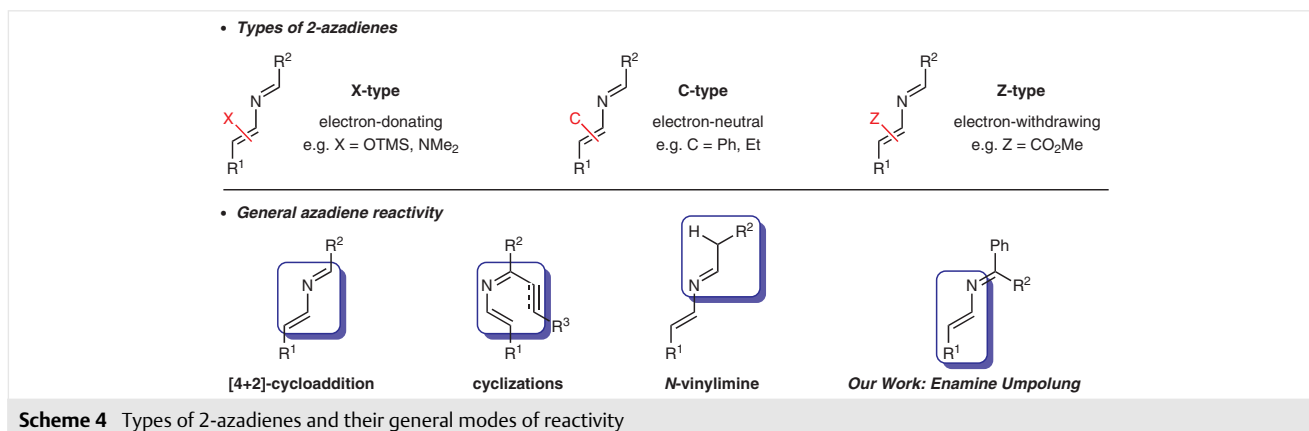


$\alpha$ -position is trapped with [M], affording a nucleophilic resonance-stabilized 2-azaallyl metal. In this *Synfacts*, we describe our group's work in catalytic Cu-H addition to 2-azadienes to furnish nucleophilic azaallyl-Cu species. These complexes engage in stereoselective couplings with ketones or imines to deliver 1,2-amino alcohols and diamines, respectively (Scheme 3A). We also highlight our recent work in phosphine-catalyzed additions of Ag-F to *gem*-difluoroazadienes to generate  $\alpha$ -trifluoromethyl-azaallyl-Ag, an active nucleophile in Pd-catalyzed aryl cross-couplings that afford  $\alpha$ -trifluoromethylated benzylic amines (Scheme 3B).

### 3 Background: 2-Azadienes

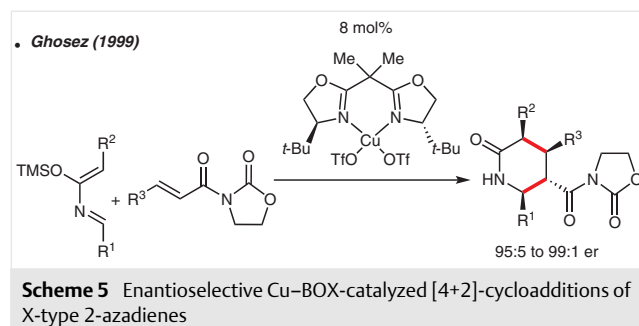
#### 3.1 Reactions of 2-Azadienes

As defined by Barluenga,<sup>27</sup> 2-azadienes can be classified into three categories based upon the electronic character of the diene substituents: electron-donating (X-type), electron-neutral (C-type), or electron-withdrawing (Z-type). Most research concerning 2-azadienes has focused on the use of X-type reagents as carbodiene analogues in [4+2]-cycloadditions (Scheme 4).<sup>28</sup> Additionally, Z-type 2-azadienes have been reported as partners in inverse-electron-demand [4+2]-cycloadditions.<sup>29</sup> C-type 2-azadienes with electron-neutral substituents are usually less reactive. The reactivity of C-type 2-azadienes falls into four categories (Scheme 4): (1) as a heterodiene in [4+2]-cycloadditions;<sup>30</sup> (2) in cyclization reactions to produce heterocycles;<sup>31</sup> (3) as an *N*-



vinylimine that undergoes reaction at the  $\alpha$ -position of the imine;<sup>32</sup> and (4), in our own work, as enamine umpolung reagents.<sup>33,34</sup>

Diels–Alder reactions with X-type 2-azadienes are well-established. Jnoff and Ghosez demonstrated an enantioselective [4+2]-cycloaddition with *N*-acyloxazolidinone dienophiles promoted by a Cu–BOX catalyst (Scheme 5).<sup>35</sup> This constitutes a rare example of an enantioselective transformation involving azadienes.



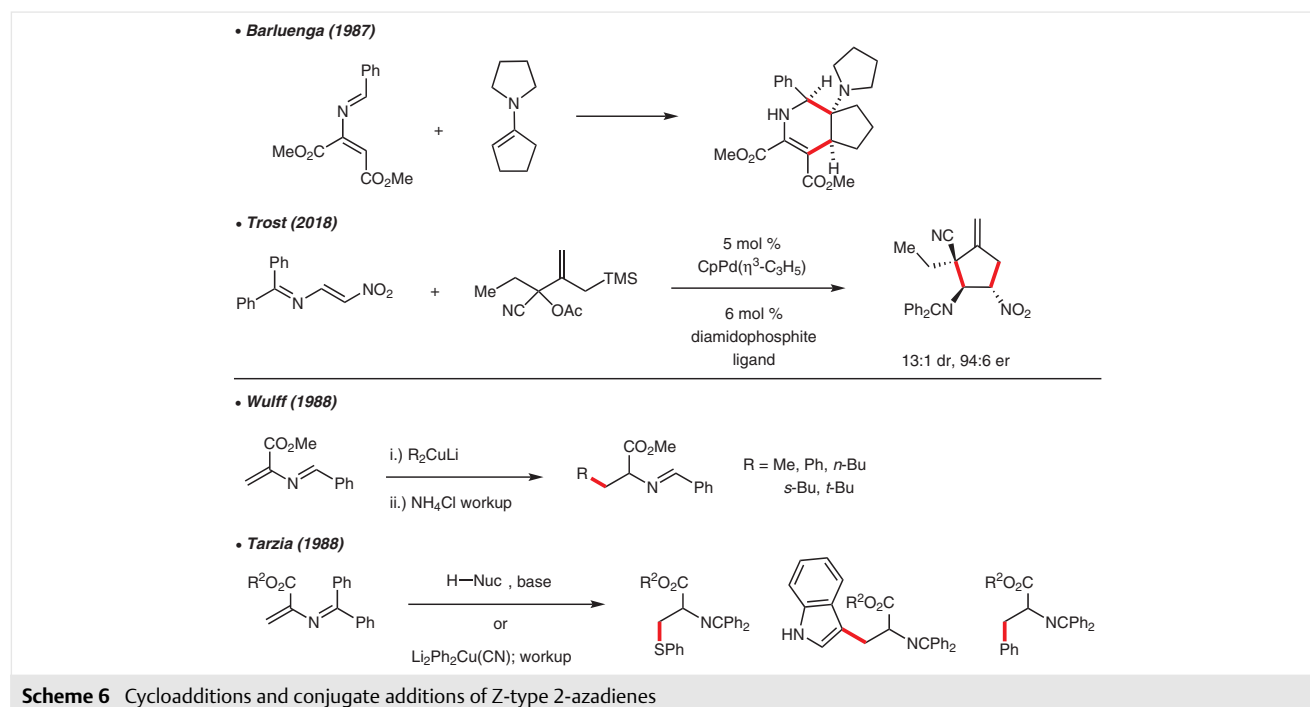
Inverse-electron-demand Diels–Alder reactions of Z-type azadienes, such as the [4+2]-cycloaddition developed by Barluenga and co-workers (Scheme 6), are also known.<sup>29b</sup> Recently, Trost and co-workers have also used a Z-type 2-azadiene as the two-atom component in an enantioselective [3+2]-cycloaddition.<sup>36</sup>

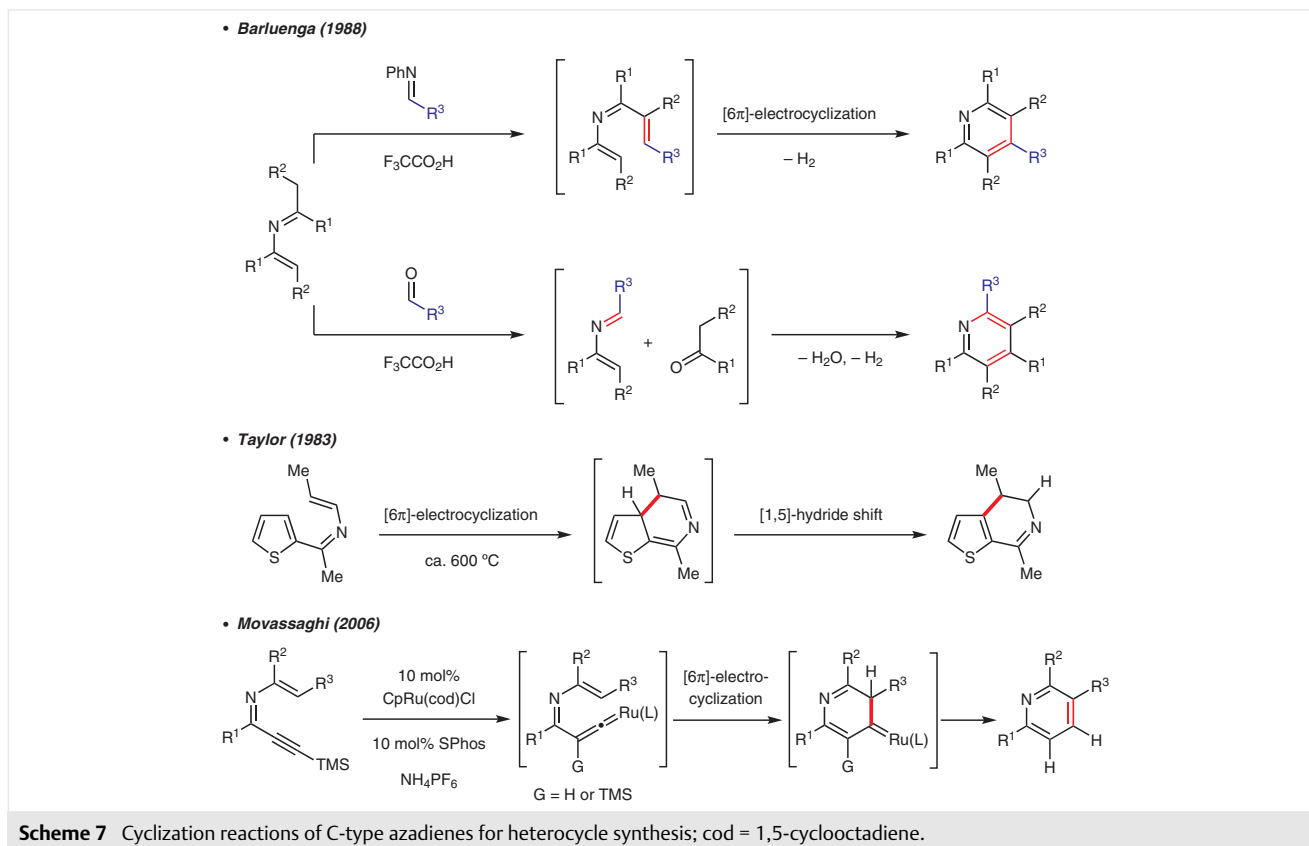
Conjugate addition reactions with electron-deficient azadienes have also been widely explored (Scheme 6).<sup>37</sup> Wulff and co-workers developed cuprate and other nucleo-

philic additions to Z-type 2-azadienes.<sup>38</sup> The Tarzia group has also disclosed the addition of several classes of nucleophiles to azadienes to prepare  $\alpha$ -amino acids.<sup>39</sup>

Most previous research involving C-type 2-azadienes has largely focused on employing these reagents as heterodienes in cycloadditions; due to the lower reactivity of C-type azadienes, electron-deficient dienophiles have often been employed for these reactions (e.g., aldehydes,<sup>40</sup> dialkyl azodicarboxylates,<sup>41</sup> isocyanates,<sup>41</sup> or maleimides).<sup>42</sup> Lewis acids have also been utilized as catalysts to activate 2-azadienes for cycloaddition through coordination to the nitrogen, which temporarily converts the C-type reagent into a Z-type reagent.<sup>30d</sup> Additionally, these azadienes participate in dipolar cycloadditions<sup>43</sup> and in alkyllithium additions.<sup>44</sup>

Cyclization reactions involving C-type 2-azadienes have also been reported (Scheme 7). Barluenga et al. demonstrated a regiodivergent synthesis of highly substituted pyridines from azadienes, the regioselectivity of which depends on the identity of the reaction partner.<sup>31a</sup> Aldimines lead to symmetrical pyridines through condensation, [6 $\pi$ ]-electrocyclization, and spontaneous oxidation. Conversely, aldehydes deliver unsymmetrical isomers by exchange of the azadiene's 'imine' with the aldehyde, followed by condensation and spontaneous oxidation. Taylor and co-workers have also disclosed a thermal [6 $\pi$ ]-electrocyclization of 2-azadienes that occurs with subsequent [1,5]-hydride shift to prepare dihydroisoquinoline derivatives.<sup>31b</sup> The Movasaghi group has developed a Ru–phosphine-catalyzed cycloisomerization of azadienyne to prepare substituted pyridines.<sup>45</sup> The reactions proceed by electrocyclization of a





Ru-vinylidene and subsequent aromatization through rearrangement and protodemetalation of the resulting Ru-carbene.<sup>46</sup>

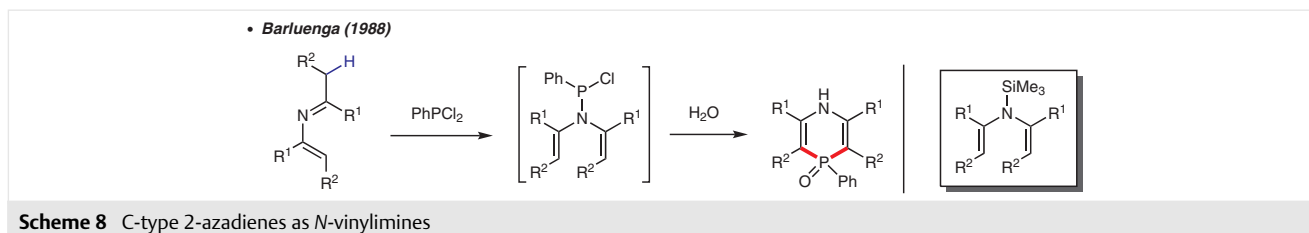
The use of azadienes as *N*-vinylimines, taking advantage of the acidity of the imine  $\alpha$ -proton, has also been explored. Following a report by Barluenga and co-workers that detailed an *N*-silylation with TMSOTf, leading to a bis(enamine) species,<sup>32b</sup> the same group later described a similar reaction with  $\text{PhPCl}_2$  (Scheme 8). Ultimately, upon hydrolysis, this intermediate delivered 1,4-dihydro-1,4- $\lambda^5$ -azaphosphinines.<sup>32a</sup>

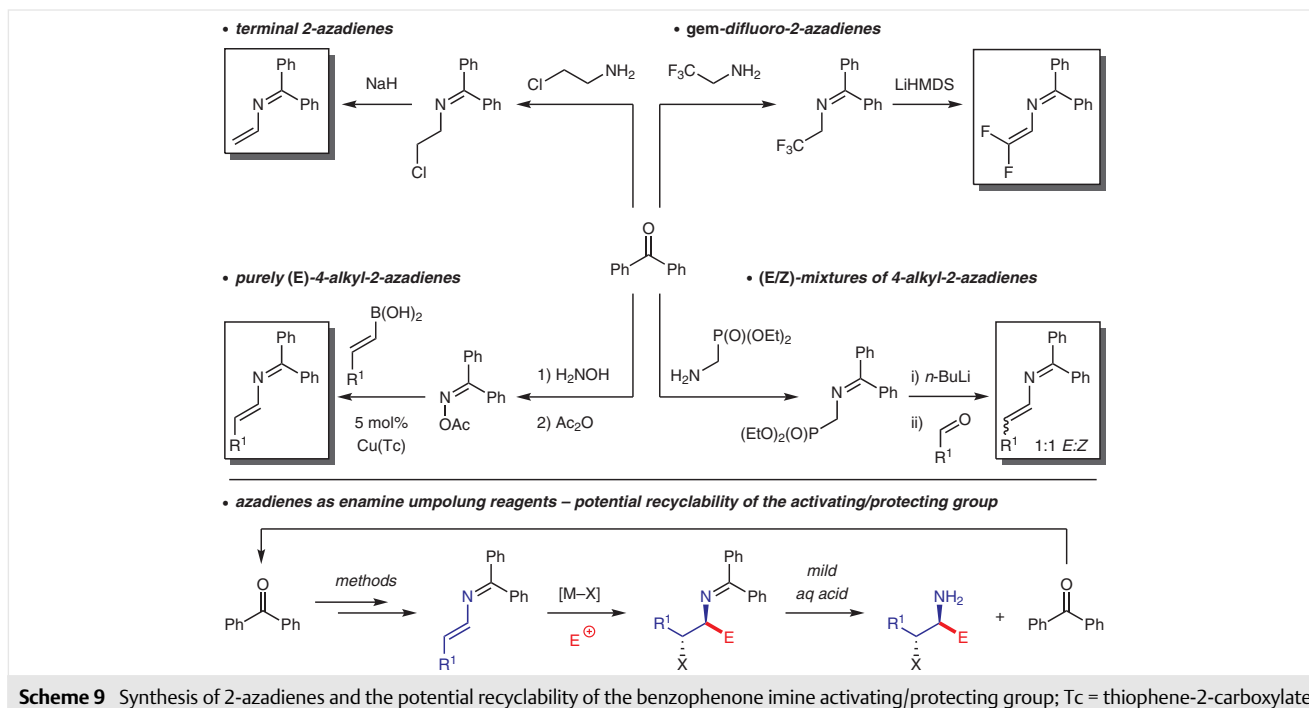
Although reactions of enamines, including enantioselective transformations, are certainly known,<sup>47</sup> the concept of utilizing the C=C double bond of 2-azadienes for enamine umpolung reactivity had never been explored. Such a strategy to prepare functionalized amines through C–C bond formation would complement conventional methods for ac-

cessing chiral amines.<sup>48</sup> Furthermore, enantioselective reactions with 2-azadienes are rare, previously achieved only in cycloadditions (Scheme 5).<sup>35,36,49</sup> Such an approach for the construction of challenging amine scaffolds in enantio-enriched form therefore has great appeal.

### 3.2 Preparation of 2-Azadienes

The aza-Wittig reaction provides a conventional approach for synthesizing 2-azadienes.<sup>50</sup> Other common methods include Hofmann elimination,<sup>39,51</sup> alcohol elimination with diethylaminosulfur trifluoride or thionyl chloride,<sup>52,53</sup> isomerization of *N*-allyl imines into conjugation with base,<sup>48,54</sup> addition of *N*-(trimethylsilyl)imines to electron-deficient acetylenes,<sup>55</sup> self-condensation of imines under acid conditions,<sup>40</sup> and rearrangement from aziridines.<sup>56</sup>





We have adopted several methods to prepare different types of 2-azadienes (Scheme 9). All begin with condensation of an amine with benzophenone (or an alternative carbonyl compound). Terminal azadienes are obtained by elimination of HCl after condensation with  $\beta$ -chloroethylamine.<sup>57</sup> Similarly, condensation of trifluoroethylamine and elimination of HF delivers *gem*-difluoroazadienes. Azadienes bearing alkyl substituents at the 4-position are prepared in two different ways. The first utilizes Cu-catalyzed cross-coupling of an *O*-acyloxime and an alkenylboronic acid to deliver the (*E*)-stereoisomer of the azadiene exclusively.<sup>58</sup> The other relies upon a Horner–Wadsworth–Emmons olefination of aldehydes,<sup>59</sup> which affords a separable 1:1 mixture of *cis*- and *trans*-azadiene stereoisomers.<sup>33</sup>

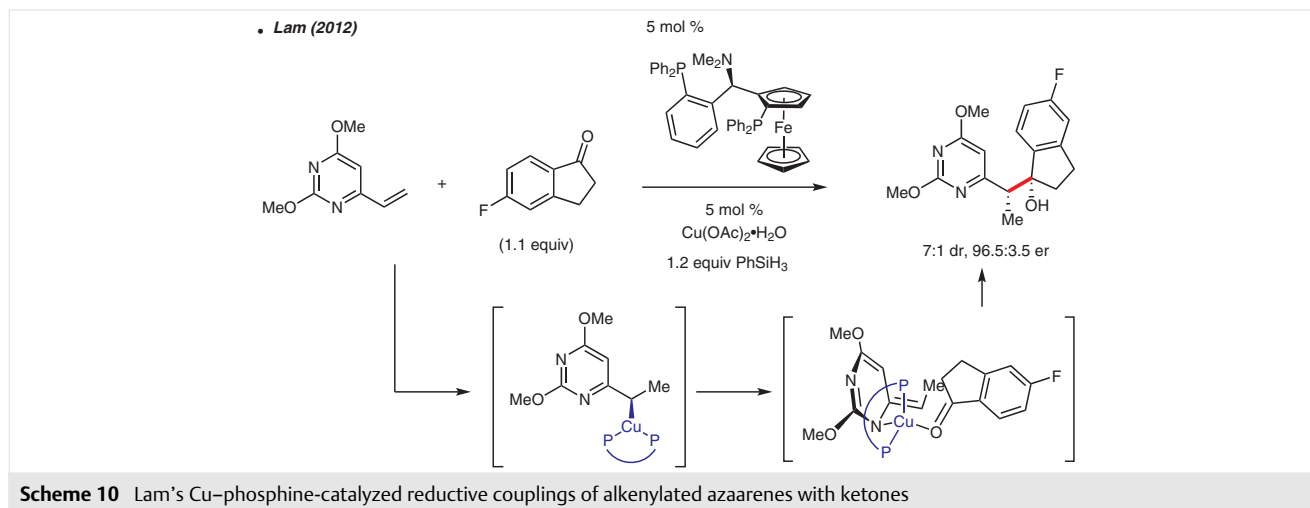
Other aspects of these azadiene-synthesis strategies, coupled with the employment of these reagents as enamine umpolung synthons in generating chiral amines, are noteworthy. As shown in Scheme 9, the benzophenone condensation serves two purposes: (1) in forming an azadiene, it activates the olefin for reaction and accomplishes the enamine umpolung, and (2) after functionalization of the azadiene's olefin group, a benzophenone-protected form of the chiral amine is obtained. The imine protecting group is robust, capable of being carried through several subsequent transformations, but is also readily hydrolyzed under mildly acidic conditions to reveal the free amine. In the hydroly-

sis event, benzophenone is regenerated and easily separated from the amine, potentially facilitating its recycling and providing an overall high degree of atom economy in this process.

## 4 Reductive Couplings of 2-Azadienes

### 4.1 Cu–Phosphine-Catalyzed Reductive Couplings Overview

Reductive couplings of olefin derivatives with various electrophiles has emerged as a powerful strategy for preparing some unprecedented motifs, with simple alkenes serving as alkyl pronucleophiles.<sup>60</sup> Recent advances utilizing Cu-based catalysts that generate Cu–H species<sup>61</sup> have permitted a number of useful couplings between unsaturated hydrocarbons and several classes of electrophiles. Within this class of transformations involving Cu–H species, Lam and co-workers utilized alkenylated azaarenes as '1-azadiene' sources for reductive couplings with ketones (Scheme 10).<sup>62</sup> These authors proposed a Zimmerman–Traxler-type transition state to rationalize the stereoselectivity of the reaction. This report, among others,<sup>63</sup> inspired our design involving the use of 2-azadienes in reductive couplings.



## 4.2 1,2-Amino Tertiary Alcohols through Azadiene–Ketone Coupling

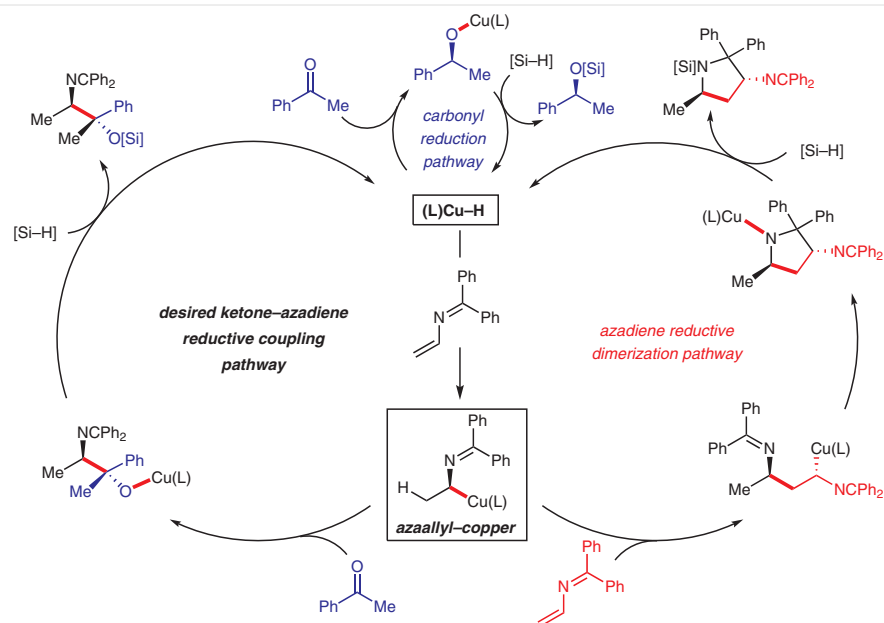
We first set out to develop a process for the chemo-, diastereo-, and enantioselective Cu-catalyzed reductive coupling of 2-azadienes with ketones<sup>62,63f,64</sup> to afford 1,2-amino tertiary alcohols. The synthesis of vicinal amino alcohols is established,<sup>65</sup> however, the catalytic enantioselective synthesis of 1,2-amino *tertiary* alcohols still remains challenging. Previous research efforts include the addition of nitronates to activated ketones<sup>66</sup> (or retro-Henry reactions)<sup>67</sup> and the vinylogous Mannich reaction of siloxyfurans with aldimines.<sup>68</sup> Meggers and co-workers reported the photochemical generation of  $\alpha$ -amino radicals for enantioselective addition to ketones.<sup>69</sup> Intramolecular enantioselective cross-pinacol-type reactions between aldehydes/ketones and imines that utilize photocatalysis have also been developed.<sup>6,70</sup> However, the most general method for preparing 1,2-amino tertiary alcohols involves diastereoselective addition of Grignard reagents to  $\alpha$ -amino ketones derived from  $\alpha$ -amino acids.<sup>71</sup> We aimed to utilize the  $\alpha$ -aminoalkyl metal species formed by 2-azadiene insertion into Cu–H for the synthesis of these challenging amino alcohols.

The success of this strategy, however, demands not only a high degree of diastereo- and enantioselectivity by the chiral catalyst, but also chemoselectivity (Scheme 11). Furthermore, chemoselectivity must occur at two critical stages of the reaction. First, (L)Cu–H insertion into the 2-azadiene to form an azaallyl–Cu species must occur in preference to its addition to the ketone, which would result in carbonyl reduction.<sup>72</sup> Secondly, the azaallyl–Cu intermediate must then react with the ketone and not with another equivalent of 2-azadiene, which would ultimately lead to an aminopyrrolidine product through cyclization and catalyst release.

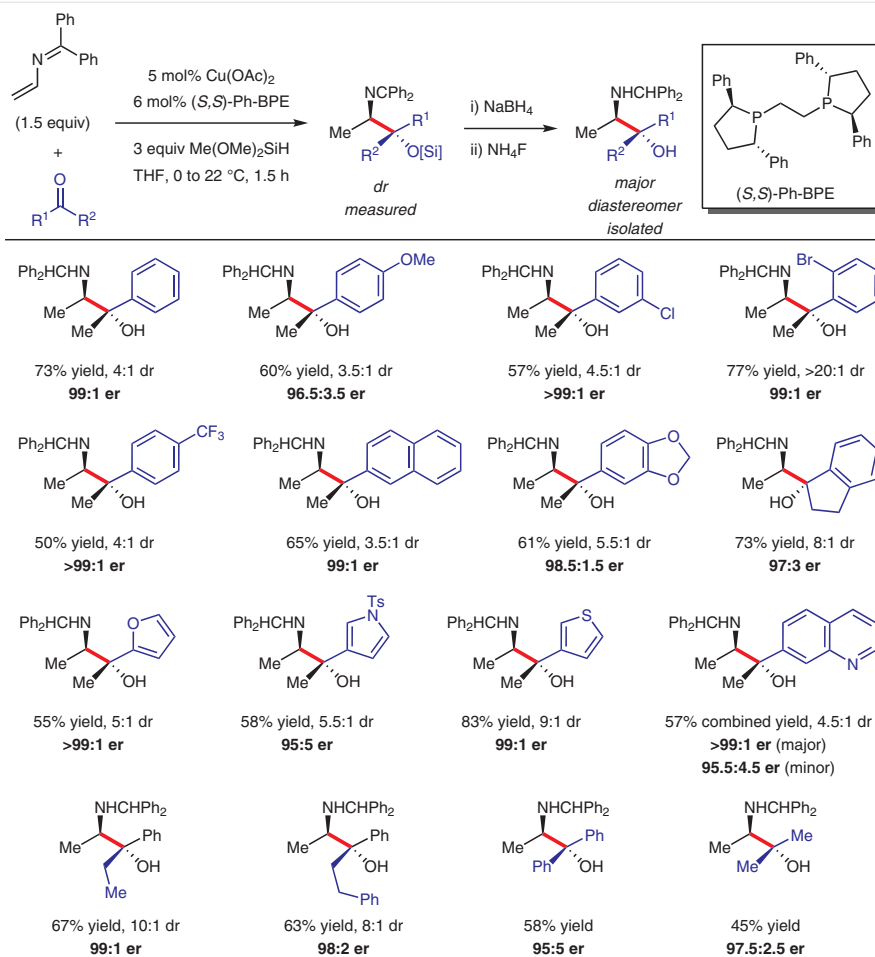
Whereas several chiral bis(phosphines) afford exclusive ketone reduction, in some cases accompanied by formation of an aminopyrrolidine through the reductive dimerization

pathway, 1,1'-ethane-1,2-diylbis(2,5-diphenylphosphine) (Ph-BPE) proved to be exquisitely selective for the desired reductive coupling to give 1,2-amino tertiary alcohols. Under the optimized reaction conditions, reductive dimerization of the azadiene is completely suppressed, but the quantity of ketone reduction versus reductive coupling is heavily substrate dependent. Several aryl/alkyl ketones undergo efficient reductive coupling with the terminal 2-azadiene to deliver vicinal amino tertiary alcohols with high levels of enantioselectivity (Scheme 12).<sup>33</sup> Both electron-donating (4-methoxy) and electron-withdrawing (4-trifluoromethyl) groups on the aryl ring are tolerated. Yields are higher with electron-rich ketones as they favor azadiene coupling over ketone reduction. Highly electron-deficient ketones, such as  $\alpha$ -trifluoromethyl ketones or  $\alpha$ -keto esters afford reduction product exclusively. Aryl halides are tolerated under the mild reaction conditions. As illustrated by the *ortho*-bromoaryl example, the presence of a substituent in the *ortho*-position delivers a single diastereomer of the amino alcohol; with other ketones, diastereoselectivity is modest (3–5:1 dr). Lower diastereoselectivity also affects the yield, as only the major diastereomer of the amino alcohol is isolated. The cyclic ketone indanone reacts efficiently to afford the corresponding amino alcohol. Several heteroaromatic rings on the ketone are also tolerated in the reaction, including furyl, thienyl, pyrrolyl, or quinolyl. Beyond methyl ketones, longer aliphatic chains lead to improved diastereoselectivity. Diaryl ketones such as benzophenone also couple with the highly reactive azaallyl–Cu–phosphine species. With dialkyl ketones, the unwanted reduction pathway is prevalent, and several substrates fail to deliver an amino alcohol product (e.g., cyclopentanone or cyclohexyl methyl ketone). After some optimization, azadiene coupling with acetone gave the corresponding amino alcohol in 45% yield (97.5:2.5 er).

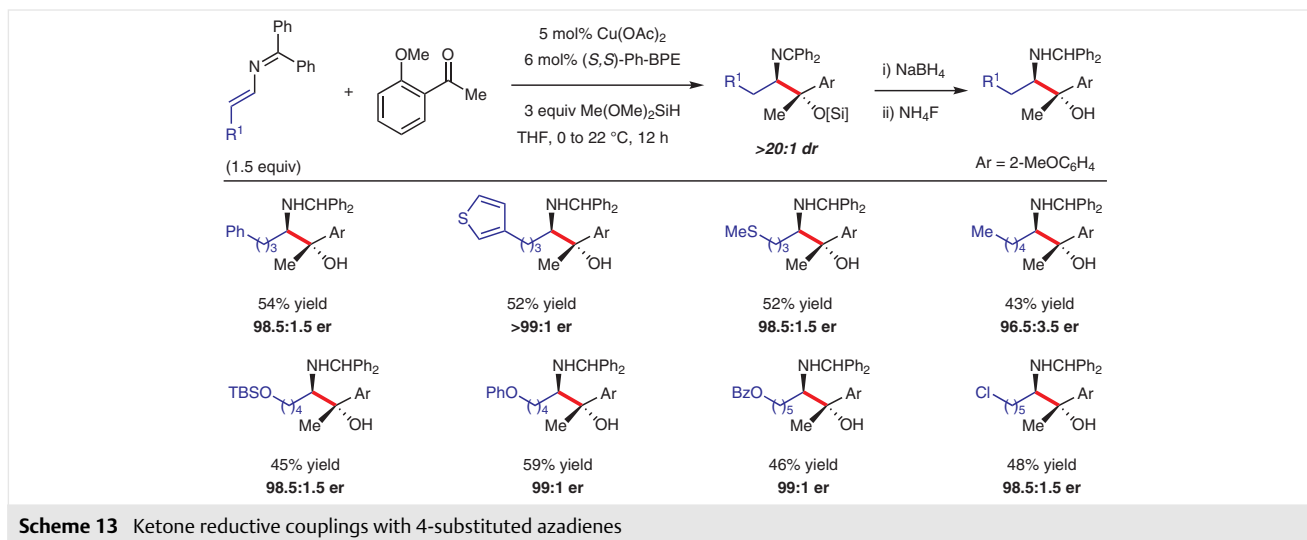




**Scheme 11** Cu-H at the intersection of the desired ketone-azadiene reductive coupling and other reductive processes



**Scheme 12** 1,2-Amino tertiary alcohols through terminal azadiene couplings with ketones



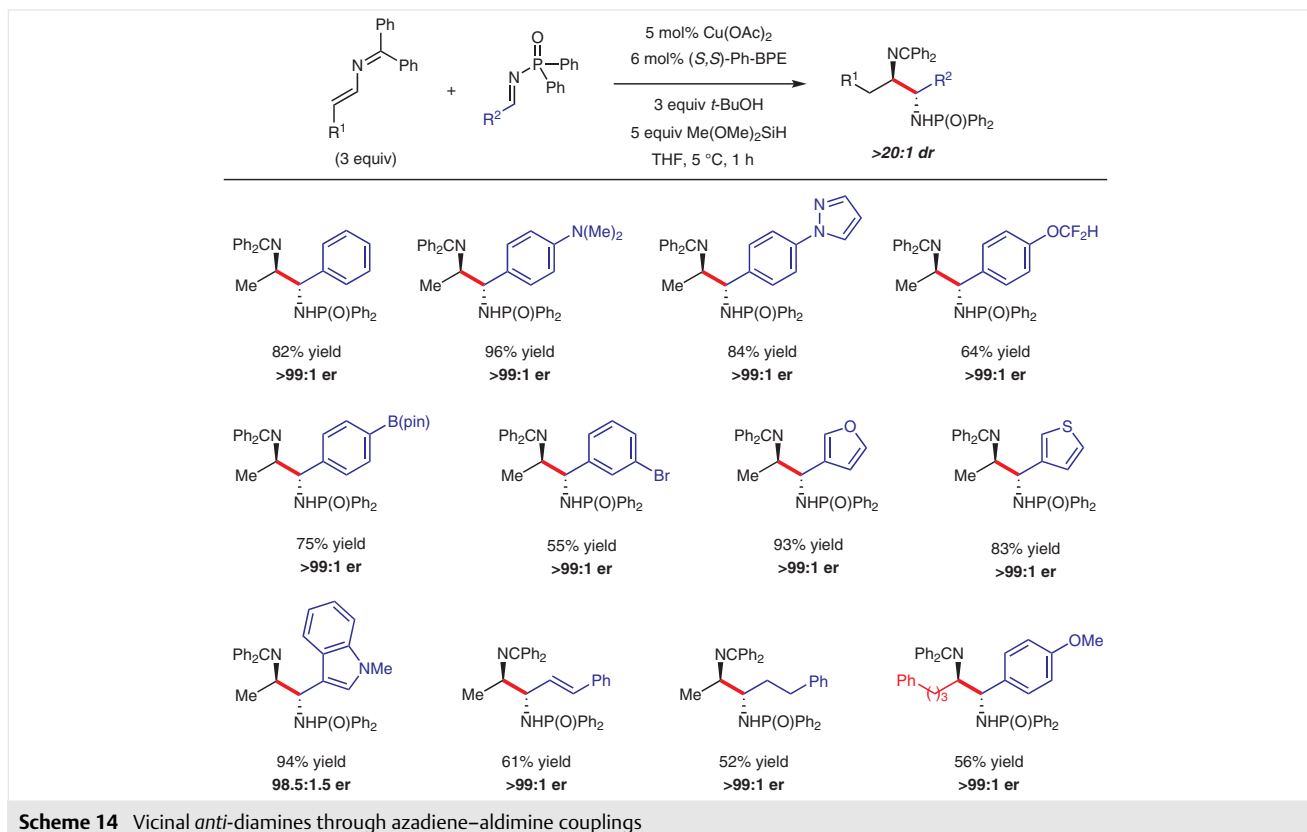
The transformations with the terminal azadiene shown in Scheme 12 deliver  $\alpha$ -methyl amines. To prepare chiral amines with additional  $\alpha$ -alkyl groups, we investigated reactions with a number of 4-substituted 2-azadienes. With the additional olefin substituent, Cu–H migratory insertion was significantly hampered,<sup>73</sup> resulting in a large proportion of ketone reduction in most cases. From the terminal azadiene studies, we knew that ketones bearing an *ortho*-group on the aromatic ring can lead to higher chemoselectivity for the reductive coupling process. Therefore, to mitigate the undesirable side reaction, we employed 2'-methoxyacetophenone as the electrophile (Scheme 13). (Note that 2'-bromoacetophenone delivers similar results, perhaps suggesting that a range of *ortho*-groups might lead to the same effect.) Several linear alkyl groups on the azadiene permit reductive coupling with these more sterically encumbered ketones; however,  $\alpha$ - or  $\beta$ -branched groups at the azadiene 4-position lead to exclusive ketone reduction. A diverse range of functionality is tolerated, including sulfur-containing groups, ethers, esters, and even an alkyl chloride, delivering the corresponding amino alcohols in 45–52% yield and with >95:5 er. Illustrating the catalyst's insensitivity to the stereochemistry of the azadiene, in several instances both (*E*)- and (*Z*)-isomers delivers nearly identical results, including the stereochemistry of the major enantiomer of the product. However, this phenomenon was not universal: for the thioether-containing azadiene, only the (*Z*)-stereoisomer was reactive. Further experiments to explain these differences in reactivity are ongoing.

### 4.3 1,2-Diamines through Azadiene–Ketone Reductive Coupling

Chiral vicinal diamines have long been known as useful scaffolds in drugs or as ligands for metals during enantioselective catalysis.<sup>74</sup> Much effort has been devoted to preparing enantioenriched 1,2-diamines, for example by classical resolution<sup>75</sup> or by multistep enantioselective routes such as nitro–Mannich and Strecker reactions.<sup>76</sup> Alkene diamination reactions additionally represent a straightforward and valuable route for the construction of this type of skeleton through the introduction of two amino groups directly onto readily available alkenes.<sup>77</sup> However, catalytic enantioselective olefin diamination remains challenging due to poisoning of metal catalysts, so examples are limited. In 2007, Shi and co-workers reported a Pd–phosphoramidite-catalyzed diamination of dienes and trienes with a diaziridinone reagent, which served as both the diamine source and oxidant in highly regio- and enantioselective reactions.<sup>78</sup> In 2017, Liu and co-workers described the enantioselective radical diamination of alkenes triggered by the intermolecular addition of dialkylaminyll or azidyl radicals to the olefin through Cu/chiral phosphoric acid dual catalysis.<sup>79</sup>

However, a number of 1,2-diamine structures, such as those with tetrasubstituted carbon centers are still difficult to obtain by current methods. Therefore, the tactic of accessing  $\alpha$ -aminoalkyl metal species through Cu–H insertion into 2-azadienes is an attractive and complementary strategy for the preparation of vicinal diamines through additions to imines. In particular, by employing ketimine electrophiles, it might be possible to construct 1,2-diamines with N-containing fully-substituted stereogenic centers.

We first examined terminal azadiene couplings with aldimines to deliver *anti*-1,2-diamines (Scheme 14).<sup>34</sup> In every case, products were formed in >98:2 er as single diastereomers. As observed in other Cu–phosphine-catalyzed ole-

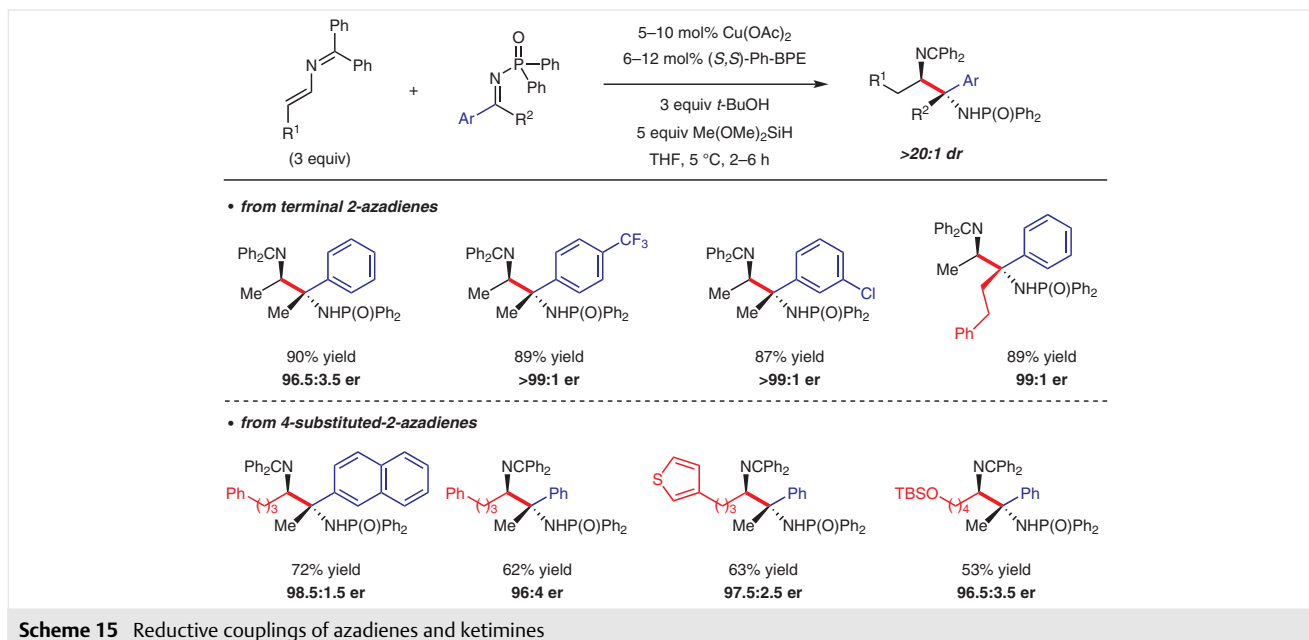


fin–imine reductive couplings,<sup>63e,80</sup> Ph-BPE proved to be the optimal ligand. Two other factors were critical: first, the presence of a diphenylphosphinoyl activating group for the electrophilic imine was essential for promoting reductive coupling versus imine reduction and, secondly, a *tert*-butanol additive increased both the reaction rate and the chemoselectivity for the coupling process. Under the optimized conditions, a variety of substituted aromatic aldimines were tolerated. As with ketones, electron-donating groups (e.g., 4-dimethylamino) delivered higher yields of the desired product as reduction of the imine was less competitive.<sup>81</sup> This side reaction was again more significant when electron-withdrawing groups (e.g., 4-difluoromethoxy) were present. Other substituents on the aromatic ring, such as boronic esters, halides, or heterocycles, were tolerated. Heteroaromatic aldimines also proved to be excellent substrates.

Unsaturated aldimines participate in this reaction. In the case of the relatively unhindered cinnamyl aldimine, a 61% yield of the desired product was obtained along with 15% of the over-reduced saturated diamine. Aliphatic aldimines are also competent reaction partners; however, their instability presents a challenge to achieving high yields and their generation *in situ* under basic conditions from a sulfinyl adduct is not a viable strategy.

In a similar manner to couplings with ketones, the reactions of substituted 2-azadienes show slow Cu–H insertion, leading to higher quantities of the imine-reduction product; however, electron-rich aldimines (e.g., 4-methoxyphenyl) afforded reasonable yields of product. Both an extended reaction time (6 h) and five equivalents of the azadiene were necessary to achieve satisfactory conversions.

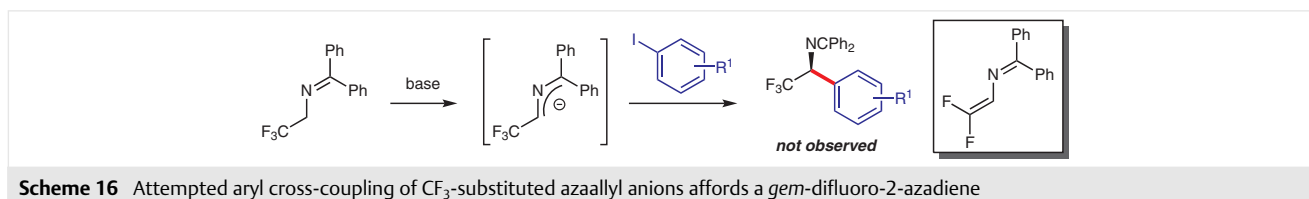
In an attempt to prepare diamines in which one stereogenic center is fully substituted, we also examined the reductive coupling reactions of terminal and substituted azadienes with various ketimines (Scheme 15). Notably, and in sharp contrast to similar reactions with ketones, a single diastereomer of the diamine was generated in each case, probably as a result of the large size of the diphenylphosphinoyl group on the nitrogen compared with that of the oxygen lone pair of electrons. This substitution pattern might also explain the perfect diastereoselectivity observed in aldimine couplings (Scheme 14). The addition of terminal azadienes to ketimines takes place with a high degree of chemoselectivity, and various aryl and alkyl substituents within the electrophile permit efficient and highly enantioselective reductive coupling. Substituted azadienes also participate in ketimine couplings, but are less reactive, requiring a higher catalyst loading (10 mol% Cu) and a prolonged reaction time (6 h). Chemoselectivity is imperfect in these more-challenging transformations, but favors reductive coupling.



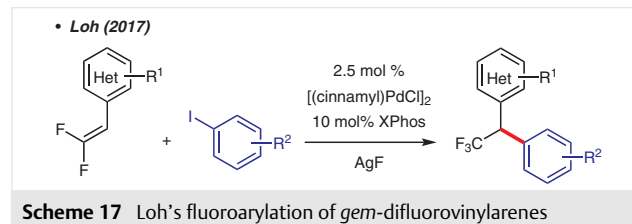
## 5 Fluoroarylations of *gem*-Difluoro-2-azadienes

$\alpha$ -(Trifluoromethyl)amines are important building blocks for the synthesis of pharmaceutical drugs. Not only does the incorporation of fluorine impart important pharmacological properties within the molecule, but the  $\text{CF}_3$  group also acts as a proteolysis-resistant surrogate for an amide.<sup>82</sup> The majority of C–C bond-forming strategies to prepare this motif involve nucleophilic additions to  $\text{CF}_3$ -substituted imines<sup>83</sup> or the converse trifluoromethyl addition to imines.<sup>84</sup> More recently,  $\text{CF}_3$ -substituted azaallyl anions have been employed in several catalytic enantioselective conjugate additions.<sup>18</sup> Additionally, electrophilic fluorinations of *gem*-difluorostyrenes permit the synthesis of  $\alpha$ - $\text{CF}_3$  amines through a Ritter-type reaction.<sup>85</sup>

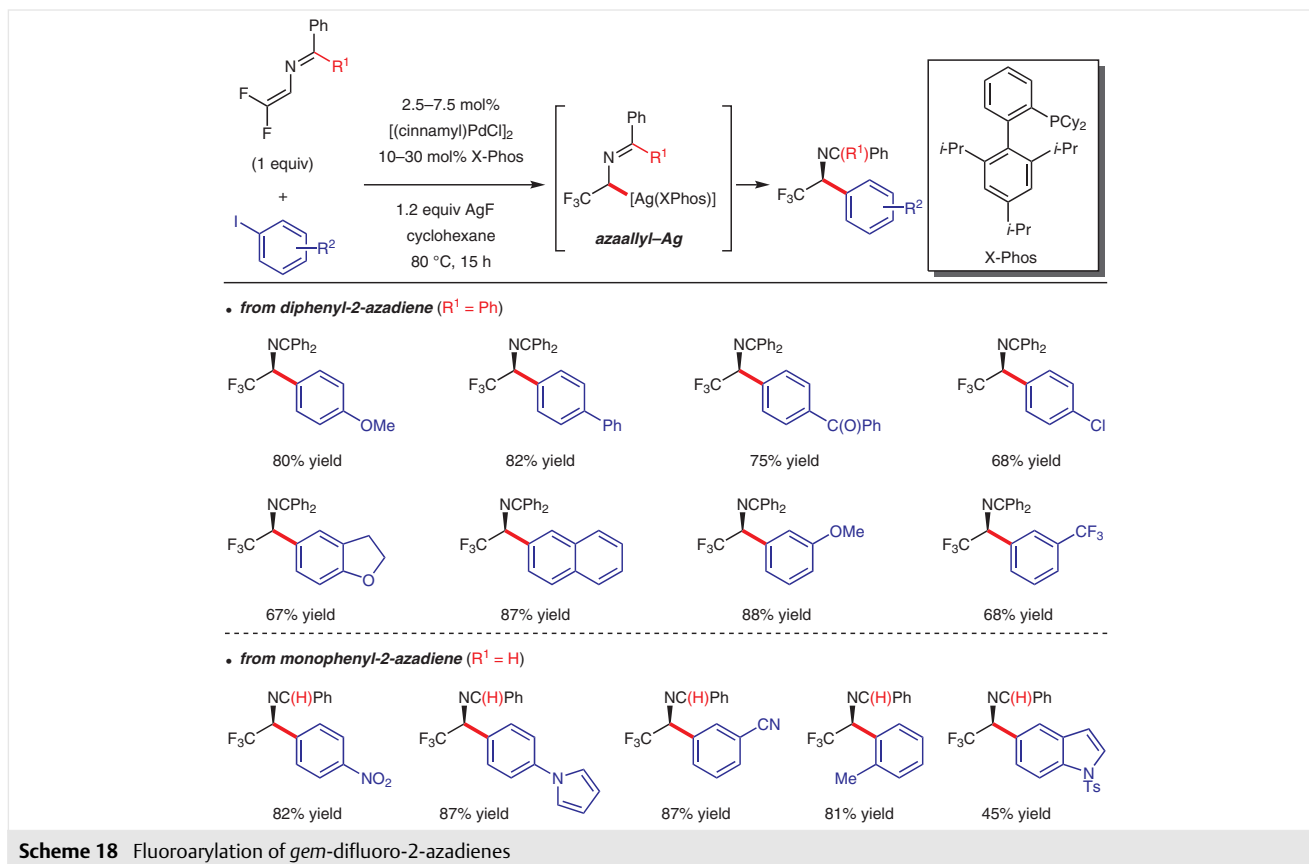
We sought to develop an aryl cross-coupling route that would afford  $\alpha$ -trifluoromethylated benzylic amines. However, strongly alkaline conditions proved incompatible for a direct deprotonation/cross-coupling strategy with *N*-(2,2,2-trifluoroethyl)imines via azaallyl anions (Scheme 16). Instead, a *gem*-difluoroazadiene along with numerous decomposition products were obtained.



With this azadiene byproduct in mind, we were inspired by recent work from the Loh laboratory involving fluoroarylation of *gem*-difluorovinylarenes (Scheme 17).<sup>86,87</sup> Reactions are proposed to proceed by addition of silver fluoride to the alkene, generating a benzylic silver intermediate that transmetalates to the Pd-based catalyst.



Similarly, we found that silver fluoride uniquely serves as a fluoride source in reactions with what might be classified as a *Z*-type *gem*-difluoro-2-azadiene (Scheme 18).<sup>88</sup> The process is catalyzed by XPhos and affords an azaallyl–Ag intermediate that we characterized by means of NMR spectroscopy. This metastable silver species, in equilibrium with its azadiene precursor, then leads to the desired benzylic amine after transmetalation to Pd and reductive elimination. Several electron-rich and some electron-deficient



aryl iodides engaged in reactions with a diphenyl-containing difluoroazadiene. Halogen, trifluoromethyl groups, and non-enolizable ketones are tolerated.

Protonation of the azaallyl–Ag intermediate by adventitious water was an issue in some couplings as the resulting byproduct proved difficult to separate from the desired benzylic amines. This protonation process was exacerbated and the overall catalytic efficiency was lower with more-challenging couplings involving *ortho*-substituted aryl iodides, more-electron-deficient partners (e.g., 1-iodo-4-nitrobenzene or 3-iodobenzonitrile), or indolyl iodides. We reasoned that reducing the steric hindrance of the azaallyl–Ag species might facilitate cross-coupling, so we switched to a monophenyl-containing difluoroazadiene (Scheme 18). With this new reagent, product yields improved by an average of 45%, and the protonation side reaction was no longer observed. Note that couplings that worked well with the *diphenyl* difluoroazadiene, which led to products containing the more-robust benzophenone-protected amine, were not improved significantly. Future efforts in our laboratory will be aimed at developing additional transformations with difluoroazadienes and to rendering these processes enantioselective.

## 6 Summary and Outlook

We have developed a new concept for generating nucleophilic  $\alpha$ -aminoalkyl transition-metal species through additions of M–X to 2-azadienes, first applying it in Cu–phosphine-catalyzed enantioselective reductive coupling reactions (addition of Cu–H) to give 1,2-amino alcohols or diamines. We have also utilized this idea in Pd-catalyzed fluoroarylation of difluoroazadienes, themselves transformed into azaallyl–Ag intermediates by Ag–F addition to generate valuable  $\alpha$ -trifluoromethylated benzylic amines. These strategies arm organic chemists with new methods for the design and synthesis of chiral amines, potentially permitting the exploration of new chemical space in the process. Our future work will therefore focus on the discovery of additional reactions that furnish myriad chiral amine scaffolds by employing 2-azadienes in novel ways.

## Funding Information

Our research was generously supported by the National Institutes of Health (GM124286), the American Chemical Society PRF (57565-DNI1), and Duke University.

## Acknowledgment

We are grateful to our colleagues and collaborators who have made important contributions to the development of new reactions with 2-azadienes: Paige Daniel, Chibueze Onyeagusi, Luke Tseng, and Anthony Ribeiro.

## References

- (1) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753.
- (2) (a) Vesely, J.; Rios, R. *Chem. Soc. Rev.* **2014**, *43*, 611. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626. (c) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. (d) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
- (3) (a) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2013**, *47*, 696. (b) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11686. (c) Boyce, G. R.; Greszler, S. N.; Johnson, J. S.; Linghu, X.; Malinowski, J. T.; Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Steward, K. M. *J. Org. Chem.* **2012**, *77*, 4503. (d) Smith, A. B. III.; Wuest, W. M. *Chem. Commun.* **2008**, 5883. (e) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
- (4) (a) Wang, R.; Ma, M.; Gong, X.; Panetti, G. B.; Fan, X.; Walsh, P. J. *Org. Lett.* **2018**, *20*, 2433. (b) Patel, N. R.; Kelly, C. B.; Siegenfeld, A. P.; Molander, G. A. *ACS Catal.* **2017**, *7*, 1766. (c) Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6776. (d) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404. (e) Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 16986.
- (5) (a) Okamoto, S.; Ariki, R.; Tsujioka, H.; Sudo, A. *J. Org. Chem.* **2017**, *82*, 9731. (b) Okamoto, S.; Kojiyama, K.; Tsujioka, H.; Sudo, A. *Chem. Commun.* **2016**, 52, 11339. (c) Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 8828.
- (6) (a) Kizu, T.; Uraguchi, D.; Ooi, T. *J. Org. Chem.* **2016**, *81*, 6953. (b) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768.
- (7) Ye, C.-X.; Melcamu, Y. Y.; Li, H.-H.; Cheng, J.-T.; Zhang, T.-T.; Ruan, Y.-P.; Zheng, X.; Lu, X.; Huang, P.-Q. *Nat. Commun.* **2018**, *9*, 410.
- (8) Murphy, J. A. *J. Org. Chem.* **2014**, *79*, 3731.
- (9) (a) Lei, Y.; Yang, J.; Qi, R.; Wang, S.; Wang, R.; Xu, Z. *Chem. Commun.* **2018**, 54, 11881. (b) Li, M.; Berritt, S.; Matuszewski, L.; Deng, G.; Pascual-Escudero, A.; Panetti, G. B.; Poznik, M.; Yang, X.; Chruma, J. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2017**, *139*, 16327. (c) Li, M.; Gutierrez, O.; Berritt, S.; Pascual-Escudero, A.; Yeşilçimen, A.; Yang, X.; Adrio, J.; Huang, G.; Nakamaru-Ogiso, E.; Kozłowski, M. C. *Nat. Chem.* **2017**, *9*, 997.
- (10) (a) Sukhorukov, A. Y.; Sukhanova, A. A.; Zlotin, S. G. *Tetrahedron* **2016**, *72*, 6191. (b) Ballini, R.; Gabrielli, S.; Palmieri, A.; Petrini, M. *Curr. Org. Chem.* **2011**, *15*, 1482.
- (11) (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (b) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854.
- (12) (a) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
- (13) (a) López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13170. (b) Kondo, M.; Nishi, T.; Hatanaka, T.; Funahashi, Y.; Nakamura, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 8198. (c) Lin, S.; Kawato, Y.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 5183.
- (14) (a) Hayashi, M.; Iwanaga, M.; Shiomi, N.; Nakane, D.; Masuda, H.; Nakamura, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 8411. (b) Ortín, I.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3462.
- (15) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156.
- (16) (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366. (b) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, 47, 6784. (c) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845. (d) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321. (e) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.
- (17) (a) Tang, S.; Zhang, X.; Sun, J.; Niu, D.; Chruma, J. J. *Chem. Rev.* **2018**, *118*, 10393. (b) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (c) Katritzky, A. R.; Piff, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665.
- (18) (a) Li, Z.; Hu, B.; Wu, Y.; Fei, C.; Deng, L. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 1730. (b) Hu, B.; Deng, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 2233. (c) Chen, P.; Zhang, J. *Org. Lett.* **2017**, *19*, 6550. (d) Hu, L.; Wu, Y.; Li, Z.; Deng, L. *J. Am. Chem. Soc.* **2016**, *138*, 15817. (e) Chen, P.; Yue, Z.; Zhang, J.; Lv, X.; Wang, L.; Zhang, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 13316. (f) Wu, Y.; Hu, L.; Li, Z.; Deng, L. *Nature* **2015**, *523*, 445.
- (19) (a) O'Brien, P. *Chem. Commun.* **2008**, 655. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.
- (20) (a) DiPucchio, R. C.; Roşca, S.-C.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 3469. (b) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946. (c) McGrew, G. I.; Stanciu, C.; Zhang, J.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 11510. (d) Murai, T.; Aso, H.; Kato, S. *Org. Lett.* **2002**, *4*, 1407.
- (21) (a) Zhu, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 4500. (b) Li, M.; Yücel, B.; Adrio, J.; Bellomo, A.; Walsh, P. J. *Chem. Sci.* **2014**, *5*, 2383.
- (22) (a) Liu, J.; Cao, C.-G.; Sun, H.-B.; Zhang, X.; Niu, D. *J. Am. Chem. Soc.* **2016**, *138*, 13103. (b) Qian, X.; Ji, P.; He, C.; Zirimwabagabo, J.-O.; Archibald, M. M.; Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2014**, *16*, 5228.
- (23) (a) McCarver, S. J.; Qiao, J. X.; Carpenter, J.; Borzilleri, R. M.; Poss, M. A.; Eastgate, M. D.; Miller, M. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2017**, *56*, 728. (b) Li, C.; Wang, J.; Barton, L. M.; Yu, S.; Tian, M.; Peters, D. S.; Kumar, M.; Yu, A. W.; Johnson, K. A.; Chatterjee, A. K.; Yan, M.; Baran, P. S. *Science* **2017**, *356*, eaam7355; DOI: 10.1126/science.aam7355. (c) Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J. E.; Zhong, J. Z.; Mills, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 260. (d) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (e) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035. (f) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 322. (g) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801. (h) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304. (i) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832. (j) Joe, C. L.; Doyle, A. G. *Angew. Chem. Int. Ed.* **2016**, *55*, 4040. (k) El Khatib, M.; Serafim, R. A. M.; Molander, G. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 254. (l) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437.

- (24) (a) Li, M.; González-Esguevillas, M.; Berritt, S.; Yang, X.; Bellomo, A.; Walsh, P. *J. Angew. Chem. Int. Ed.* **2016**, *55*, 2825. (b) Spangler, J. E.; Kobayashi, Y.; Verma, P.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 11876. (c) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.
- (25) (a) Trost, B. M.; Li, X. *Chem. Sci.* **2017**, *8*, 6815. (b) Trost, B. M.; Mahapatra, S.; Hansen, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6032.
- (26) (a) Reznichenko, A. L.; Hultzs, K. C. *J. Am. Chem. Soc.* **2012**, *134*, 3300. (b) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 8361. (c) Herzog, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940.
- (27) Barluenga, J.; Joglar, J.; González, F. J.; Fustero, S. *Synlett* **1990**, 129.
- (28) (a) Alves, M. J.; Durães, M. M.; Fortes, A. G. *Tetrahedron Lett.* **2003**, *44*, 5079. (b) Ntirampebura, D.; Ghosez, L. *Synthesis* **2002**, 2043. (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4051. (d) Bayard, P.; Sainte, F.; Beaudegnies, R.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 3799. (e) Demoulin, A.; Gorissen, H.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409.
- (29) (a) Palacios, F.; Perez de Heredia, I.; Rubiales, G. *J. Org. Chem.* **1995**, *60*, 2384. (b) Barluenga, J.; Tomás, M.; Ballesteros, A.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1987**, 1195.
- (30) (a) Palacios, F.; Alonso, C.; Tobillas, C.; Rubiales, G. *Heterocycles* **2004**, *64*, 229. (b) Palacios, F.; Alonso, C.; Rubiales, G.; Tobillas, C.; Ezpeleta, J. M. *Heterocycles* **2003**, *61*, 493. (c) Palacios, F.; Alonso, C.; Amezuza, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941. (d) Cheng, Y. S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678.
- (31) (a) Barluenga, J.; Joglar, J.; González, F. J.; Gotor, V.; Fustero, S. *J. Org. Chem.* **1988**, *53*, 5960. (b) Govindan, C. K.; Taylor, G. *J. Org. Chem.* **1983**, *48*, 5348.
- (32) (a) Barluenga, J.; Palacios, F.; González, F. J.; Fustero, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1596. (b) Barluenga, J.; Joglar, J.; Fustero, S.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1986**, 361.
- (33) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 598.
- (34) Shao, X.; Li, K.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 7083.
- (35) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617.
- (36) Trost, B. M.; Zhang, L.; Lam, T. M. *Org. Lett.* **2018**, *20*, 3938.
- (37) Monbaliu, J.-C. M.; Masschelein, K. G. R.; Stevens, C. V. *Chem. Soc. Rev.* **2011**, *40*, 4708.
- (38) Wulff, G.; Böhnke, H.; Klinken, H. T. *Liebigs Ann. Chem.* **1988**, *1988*, 501.
- (39) Tarzia, G.; Balsamini, C.; Spadoni, G.; Duranti, E. *Synthesis* **1988**, 514.
- (40) Barluenga, J.; Joglar, J.; Fustero, S.; Gotor, V.; Krüger, C.; Romão, M. J. *Chem. Ber.* **1985**, *118*, 3652.
- (41) Barluenga, J.; González, F. J.; Fustero, S.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1986**, 1179.
- (42) Paparin, J.-L.; Crévisy, C.; Grée, R.; Toupet, L. *J. Heterocycl. Chem.* **2000**, *37*, 411.
- (43) Bujak, P.; Krompiec, S.; Malarz, J.; Krompiec, M.; Filapek, M.; Danikiewicz, W.; Kania, M.; Gębarowska, K.; Grudzka, I. *Tetrahedron* **2010**, *66*, 5972.
- (44) Henry, K. M.; Townsend, C. A. *J. Am. Chem. Soc.* **2005**, *127*, 3300.
- (45) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592.
- (46) For cyclization of a Z-type 2-azadiene, see: Leijendekker, L. H.; Weweler, J.; Leuther, T. M.; Streuff, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 6103.
- (47) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599.
- (48) Barrett, A. G. M.; Seefeld, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1053.
- (49) (a) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902. (b) Courant, T.; Dagousset, G.; Masson, G. *Synthesis* **2015**, *47*, 1799.
- (50) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523.
- (51) Georg, G. I.; He, P.; Kant, J.; Mudd, J. *Tetrahedron Lett.* **1990**, *31*, 451.
- (52) Balsamini, C.; Duranti, E.; Mariani, L.; Salvatori, A.; Spadoni, G. *Synthesis* **1990**, 779.
- (53) Kauffmann, T.; Berg, H.; Kiippelmann, E.; Kuhlmann, D. *Chem. Ber.* **1977**, *110*, 2659.
- (54) Capra, J.; Le Gall, T. *Synlett* **2010**, 441.
- (55) Panunzio, M.; Zarantonello, P. *Org. Process Res. Dev.* **1998**, *2*, 49.
- (56) Barroso, M. T.; Kascheres, A. *J. Org. Chem.* **1999**, *64*, 49.
- (57) Böhme, H.; Ingendoh, A. *Chem. Ber.* **1979**, *112*, 1297.
- (58) Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947.
- (59) (a) Davidsen, S. K.; Philips, G. W.; Martin, S. F. *Org. Synth. Coll. Vol. VIII* 1993; 451. (b) Kauffmann, T.; Koch, U.; Steinseifer, F.; Vahrenhorst, A. *Tetrahedron Lett.* **1977**, *18*, 3341.
- (60) (a) Holmes, M.; Schwartz, L. A.; Krische, M. J. *Chem. Rev.* **2018**, *118*, 6026. (b) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, *354*, aah5133; DOI: 10.1126/science.aah5133.
- (61) (a) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48. (b) Jordan, A. J.; Lalic, G.; Sadighi, J. P. *Chem. Rev.* **2016**, *116*, 8318. (c) Deutsch, C.; Krause, N.; Lipschutz, B. H. *Chem. Rev.* **2008**, *108*, 2916. (d) Rendler, S.; Oestreich, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 498.
- (62) (a) Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 8428. (b) Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831.
- (63) (a) Gui, Y.-Y.; Hu, N.; Chen, X.-W.; Liao, L.-L.; Ju, T.; Ye, J.-H.; Zhang, Z.; Li, J.; Yu, D.-G. *J. Am. Chem. Soc.* **2017**, *139*, 17011. (b) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8126. (c) Lee, J.; Torke, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 821. (d) Han, J. T.; Jang, W. J.; Yun, J. *J. Am. Chem. Soc.* **2016**, *138*, 15146. (e) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 9787. (f) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144. (g) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5821. (h) Wang, Y.-M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5024.
- (64) (a) Liu, R. Y.; Zhou, Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2019**, *141*, 2251. (b) Tsai, E. Y.; Liu, R. Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 2007.
- (65) (a) Burchak, O. N.; Py, S. *Tetrahedron* **2009**, *36*, 7333. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121.
- (66) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875.
- (67) Tosaki, S.-y.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776.
- (68) Silverio, D. L.; Fu, P.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Tetrahedron Lett.* **2015**, *56*, 3489.
- (69) (a) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. *Angew. Chem. Int. Ed.* **2016**, *55*, 685. (b) Ma, J.; Harms, K.; Meggers, E. *Chem. Commun.* **2016**, *52*, 10183.
- (70) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 17735.
- (71) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073.

- (72) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. J. *Am. Chem. Soc.* **2003**, *125*, 8779.
- (73) (a) Lee, J.; Radomkit, S.; Torker, S.; Del Pozo, J.; Hoveyda, A. H. *Nat. Chem.* **2018**, *10*, 99. (b) Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017**, *139*, 12758.
- (74) (a) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. (b) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101. (c) Viso, A.; Fernandez de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167. (d) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. (e) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.
- (75) (a) Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3. (b) Pikul, S.; Corey, E. J. *Org. Synth. Coll. Vol. IX*; Wiley: London, **1998**, 387.
- (76) (a) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887. (b) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947.
- (77) (a) De Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067. (b) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269.
- (78) (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. (b) Cornwall, R. G.; Zhao, B.; Shi, Y. *Org. Lett.* **2013**, *15*, 796.
- (79) Wang, F.-L.; Dong, X.-Y.; Lin, J.-S.; Zeng, Y.; Jiao, G.-Y.; Gu, Q.-S.; Guo, X.-Q.; Ma, C.-L.; Liu, X.-Y. *Chem* **2017**, *3*, 979.
- (80) Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 4666.
- (81) Lipshutz, B. H.; Shimizu, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 2228.
- (82) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.
- (83) (a) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (b) Fioravanti, S. *Tetrahedron* **2016**, *72*, 4449.
- (84) (a) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6324. (b) Therkelsen, M.; Rasmussen, M. T.; Lindhardt, A. T. *Chem. Commun.* **2015**, *51*, 9651.
- (85) For an additional transformation, see: Yang, L.; Fan, W.-X.; Lin, E.; Tan, D.-H.; Li, Q.; Wang, H. *Chem. Commun.* **2018**, *54*, 5907.
- (86) Tang, H.-J.; Lin, L.-Z.; Feng, C.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2017**, *56*, 9872.
- (87) (a) Tian, P.; Wang, C.-Q.; Cai, S.-H.; Song, S.; Ye, L.; Feng, C.; Loh, T.-P. *J. Am. Chem. Soc.* **2016**, *138*, 15869. (b) Gao, B.; Zhao, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 638. (c) Gao, B.; Zhao, Y.; Ni, C.; Hu, J. *Org. Lett.* **2014**, *16*, 102.
- (88) Daniel, P. E.; Onyeagusi, C. I.; Ribeiro, A. A.; Li, K.; Malcolmson, S. *J. ACS Catal.* **2019**, *9*, 205.