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Transition-metal-free chemo- and regioselective vinylation of azaallyls

Minyan Li[†], Osvaldo Gutierrez[†], Simon Berritt[†], Ana Pascual-Escudero[†], Ahmet Ye ilçimen[†], Xiaodong Yang[†], Javier Adrio[†], Georgia Huang[†], Eiko Nakamaru-Ogiso[#], Marisa C. Kozlowski[†], and Patrick J. Walsh^{‡,†}

[†]Roy and Diana Vagelos Laboratories, Penn/Merck Laboratory for High-Throughput Experimentation, University of Pennsylvania, Department of Chemistry, 231 South 34th Street, Philadelphia, Pennsylvania 19104, USA

[#]EPR laboratory, University of Pennsylvania, Department of Biochemistry and Biophysics, 422 Curie Boulevard, Philadelphia, Pennsylvania 19104, USA

[‡]Institute of Advanced Synthesis (IAS), School of Chemistry and Molecular Engineering (SCME), Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), Nanjing Tech University (Nanjing Tech), 30 South Puzhu Road, Nanjing 211816, P. R. China

Abstract

Direct C(sp³)–C(sp²) bond-formation under transition-metal-free conditions offers an atom-economical, inexpensive, and environmentally benign alternative to traditional transition metal-catalyzed cross-coupling reactions. A new chemo- and regioselective coupling protocol between 3-aryl-substituted-1,1-diphenyl-2-azaallyl derivatives and vinyl bromides has been developed. This is the first transition-metal-free cross-coupling of azaallyls with vinyl bromide electrophiles and delivers allylic amines in excellent yields (up to 99%). This relatively simple and mild protocol offers a direct and practical strategy for the synthesis of high-value allylic amine building blocks that does not require the use of transition metals, special initiators, or photoredox catalysts. Radical clock experiments, EPR studies and DFT calculations point to an unprecedented substrate-dependent coupling mechanism. Furthermore, an EPR signal was observed when the *N*-benzyl benzophenone ketimine was subjected to silylamide base, supporting formation of radical species upon deprotonation. The unique mechanisms outlined herein could pave the way for new approaches to transition-metal-free C–C bond formations.

TOC image

Cross-coupling under transition-metal-free conditions is an attractive and economic alternative to traditional transition metal-catalyzed methods. Metal-free coupling of azaallyls has now been

Data availability statement

All relevant data are included with the manuscript, supplementary information and are available from the corresponding authors on reasonable request.

Author contributions

M.L. and P.J.W. conceived and designed the experiments. M.L., S.B., A.P.E., A.Y., X.Y., J.A., G.H. performed the research. O.G. and M.C.K. designed and performed the DFT computational study. M.L. and E.N.O. performed the EPR study. M.L., O.G., M.C.K. and P.J.W. wrote the paper.

demonstrated with vinyl bromide electrophiles, delivering allylic amines in excellent yields. Moreover, evidence supporting dual reaction pathways triggered by ketimine anions and radicals is described.

Transition metal-catalyzed coupling reactions are among the most widely used, robust, and efficient methods for carbon-carbon and carbon-heteroatom bond-formations. The impact of these transformations has extended well beyond organic synthesis into biology, materials science, and engineering and was highlighted by the Nobel Prize in 2010.^{1,2} The development of transition-metal-free protocols would offer an inexpensive and environmentally benign alternative to accomplish C–C and C–heteroatom bond constructions.³ In this regard, we focused our attention on transition-metal-free assembly of allylic amines, which are key building blocks in the synthesis of complex natural products and are prevalent in biologically active compounds.⁴ To date, approaches to the synthesis of allylic amine derivatives generally rely on transition metals, including amination reactions,^{5,6} some nucleophilic additions of organometallic reagents to imines,^{7,8} and catalyzed Overman rearrangements,⁹ among others.^{10,11}

Our team,^{12–15} and others,^{16–21} have been interested in the synthesis of amines via an umpolung approach involving the functionalization of 2-azaallyl anions. Recently, we reported the synthesis of both allylic amines and enamines through the transition-metal catalyzed arylation of 1,1-diphenyl-3-arylallyl-2-azaallyl anions (shown retrosynthetically in Figure 1a, path a).¹³ We envisioned an alternative route to the same allylic imines via vinylation of 1,1-diphenyl-3-aryl-2-azaallyl anions (Figure 1a, path b). Transition metal-catalyzed vinylation methods are less common,^{22–28} especially in the absence of preformed organometallic reagents (Figure 1b). We anticipated that the vinylation of azaallyl anions (Figure 1a, path b) would occur in a similar manner to the transition metal-catalyzed arylation of the same azaallyl anions. To our surprise, however, we found that the path b vinylation of 1,1-diphenyl-3-aryl-2-azaallyl anions occurred rapidly when no palladium catalyst was added.

Herein, we report the first transition-metal-free C(sp³)-C(sp²) coupling of vinyl bromide electrophiles with 2-azaallyl anions and azaallyl radicals (Figure 1c). Specifically, we describe coupling of 1,1-diphenyl-3-aryl-2-azaallyl anions with vinyl bromides to afford the *E* vinylation products in high yields with excellent chemo- and regioselectivity. Notably, the vinylation reaction outperforms a rapid background reaction arising from the base promoted elimination of the vinyl bromide to form a terminal alkyne. In addition, the base/solvent

combination efficiently promotes the metal-free vinylation but does not deprotonate the product (Figure 1d). Thus, neither product deprotonation/isomerization, which will form a more stable conjugated byproduct, nor product deprotonation/cyclization, is observed. Additional experiments, EPR studies and calculations provide a preliminary picture of the mechanistic landscape of the observed vinylations.

Results

We reported previously the arylation of 1,1-diphenyl-3-arylallyl-2-azaallyl anions via *in situ* deprotonation of ketimine substrates ($\text{ArCH}_2\text{N}=\text{CPh}_2$) followed by palladium-catalyzed arylation with $\text{Ar}'\text{-X}$ to give $\text{ArAr}'\text{CHN}=\text{CPh}_2$.^{12–15} Under these conditions, deprotonation of the product was not observed, as judged by the absence of isomerized product ($\text{ArAr}'\text{C}=\text{NCHPh}_2$).^{19,29} Key to preventing product deprotonation was the use of hindered bases $[\text{MN}(\text{SiMe}_3)_2$ ($\text{M} = \text{Li}, \text{Na}$)] at room temperature. To explore the analogous vinylation reaction, we investigated the deprotonative cross-coupling of ketimine **1a** and β -bromostyrene **2a** using microscale high-throughput screening (0.01 mmol) of 23 electronically diverse mono- and bidentate phosphine ligands in the presence of $\text{Pd}(\text{OAc})_2$, $\text{NaN}(\text{SiMe}_3)_2$ and THF at room temperature for three hours. To our surprise, a considerable amount of the targeted vinylated product (**3aa**) was found in the control vial, which contained no added transition-metal or ligand (see Supplementary information page 10, high throughput experimentation screenings). Validation on a larger scale (0.1 mmol) provided further support for a transition-metal-free process; specifically, reactions conducted without addition of catalyst led to the vinylation product **3aa** in 51% assay yield (AY) in THF as determined by ^1H NMR spectroscopy (Table 1, entry 1). Increasing the concentration from 0.1 M to 0.2 M (entry 2) resulted in an increase to 65% AY. We next tested 5 solvents [CPME (cyclopentyl methyl ether), THF, 2-Me-THF, DME (dimethoxyethane) and 1,4-dioxane, entries 3–7]. Surprisingly, the reaction was complete in just 10 min in DME, giving 98% AY of **3aa** (entry 6). Further optimization of the base ratio revealed that 2 equiv of $\text{LiN}(\text{SiMe}_3)_2$ and a 30 min reaction time resulted in 98% isolated yield (entry 9).

Reaction Scope

With the optimized reaction conditions (entry 9, Table 1), the scope of the *N*-benzyl group on the ketimine was examined (Figure 2a). Overall, some tuning of the reaction parameters, such as the base, reagent ratios, concentration and reaction times, was necessary for certain substrates. Nonetheless, vinylation of ketimine substrates bearing electron-donating (4-Me, **1b** and 4-OMe **1c**) and electron-withdrawing [4-F (**1d**), 4-Cl (**1e**), 3,5-di-F (**1f**) and 3,5-di- CF_3 (**1g**)] *N*-benzyl derived groups with β -bromostyrene (**2a**) proceeded in excellent yields. The sterically demanding 2-tolyl substituted ketimine (**1h**) underwent coupling, albeit in lower yield (61%), even when performed with 3 equiv $\text{LiN}(\text{SiMe}_3)_2$ and an extended reaction time (8 h). For more acidic heterocyclic 2-pyridyl **1i** (77%), 3-pyridyl **1j** (71%) and 2-thiophenyl **1k** (82%) ketimine substrates, 0.05 M concentration was optimal with 1.5 equivalent of $\text{LiN}(\text{SiMe}_3)_2$ to prevent deprotonation, isomerization and cyclization (Figure 1d).

We next determined the scope in the vinyl bromide component and found it to be broad (Figure 2b). *trans*- β -Aryl vinyl bromides bearing neutral (4-C₆H₄-*t*Bu) and electron donating (4-C₆H₄-OMe) groups furnished coupling products **3ab** and **3ac** in 92 and 98% yield, respectively. 4-Fluoro- (**2d**) and 4-trifluoromethyl-substituted vinyl bromides (**2e**) afforded the coupled products **3ad** and **3ae** in 96 and 70% yield. The reactions also proceeded well with substitution at the 3-position of the β -bromostyrene, such as 3-OMe (**2f**) and 3-CF₃ (**2g**), giving the products in 98 and 75% yield, respectively. *trans*- β -2-Tolyl vinyl bromide (**2h**) was an excellent substrate, affording the product in 96% yield. Surprisingly, the aliphatic vinyl bromides 1-bromo-2-methylprop-1-ene (**2i**) and (bromomethylene)cyclohexane (**2j**) were successfully coupled with **1a** to afford **3ai** and **3aj** in 54–55% yield. Monitoring the reaction with **3aj** revealed that the transformation was complete in 15 min (see Supplementary Figure 1). Notably, product isomerization and/or cyclization were not detected for any of the examples in Figure 2a–b.

The vinylation is amenable to a telescoped imine synthesis/vinylation protocol on gram-scale (Figure 2c). For example, the sequential one-pot synthesis of 2-thiophenyl ketimine **1k**, followed by vinylation with **2a** successfully afforded product **3ka** in 90% yield (1.02 g). Finally, hydrolysis of the vinylated product **3ka** was performed to isolate the allylic amine **5ka** in 99% yield (Figure 2d).

Mechanistic Studies

Given the unexpected and unusual coupling of ketimines with vinyl bromides in the absence of added catalyst, a synergistic computational and experimental study was undertaken to gain insight into the mechanistic possibilities. Several reasonable mechanisms can be envisioned (Figure 3a), including those involving alkyne intermediates, cycloadditions, addition/eliminations, substitutions and carbene insertions.

Of relevance to pathway i in Figure 3a, in the absence of ketimine the vinyl bromide undergoes rapid (one hour at room temperature) NaN(SiMe₃)₂ promoted background elimination to yield the corresponding alkyne. Mixing the terminal alkyne and imine **1a** under the same conditions as those used in the vinylation did not result in formation of the vinylated product **3aa** (ii, Figure 3b). These results indicate that the alkyne is not an intermediate en route to the vinylation product, discounting the pathway i in Figure 3a.

Addition of the silylamide base is expected to cause rapid deprotonation of the *N*-benzyl ketimine giving rise to an ketimine anion (Figure 3a).^{30,31} It is known that azaallyl anions undergo cycloadditions with styrene and, therefore, this pathway was explored with β -bromostyrene.^{32,33} Two isomeric [3+2] reactions are possible from this intermediate (ii, Figure 3a), with the first leading to the observed product after elimination of bromide. However, significant steric interactions arise in this pathway between the vinyl aryl group and the diphenyl moiety of the azaallyl anion. The alternate cyclization pathway gives rise to the regioisomeric product, which was not observed. Computations undertaken on the azaallyl anion found the concerted [3+2] cyclization pathway to be higher in energy (see Supplementary Information) than the step-wise substitution mechanism described below (iv, Figure 3a).

Another possibility is the α -elimination of vinyl halides in the presence of $\text{MN}(\text{SiMe}_3)_2$ ($\text{M} = \text{Na}, \text{K}$) to form vinylidenes.^{34,35} A highly reactive vinylidene could then insert into the benzylic C–H bond of the ketimine. If this mechanism is operative in our system, the hydrogen of the vinyl motif would originate from a benzylic hydrogen of the ketimine **1a**. With this in mind, the deuterated ketimine **1a'** was prepared and investigated in the coupling with vinyl bromides **2i** and **2a**. The results (Figure 3c) indicate that vinyl hydrogens of the products are not deuterated, which excludes the α -elimination mechanism in iii, Figure 3a.

Our attention next turned to possible substitution pathways.^{36–38} Both stepwise and concerted ($\text{S}_{\text{N}}\text{V}$)^{39–42} substitutions have been reported for vinyl halides, but not with carbon-derived anions. Mechanisms are case-dependent with the nature of the nucleophile, the leaving group, and the electrophile substitution pattern all playing a role.⁴³ All attempts to calculate intermediates for the corresponding stepwise process (iv, Figure 3a) using functionals previously used to study $\text{S}_{\text{N}}\text{V}$ reactions (B3LYP and OPBE) led directly to dissociation back to starting materials or formation of vinylated product and bromide. DFT calculations did, however, reveal a concerted displacement with a low energetic barrier (11.7 kcal/mol) to deliver the vinylated product **B1** with concomitant release of bromide (Figure 4). A strong kinetic preference ($\Delta G^\ddagger > 7$ kcal/mol) for nucleophilic attack perpendicular to the carbon-carbon double bond ($\text{S}_{\text{N}}\text{V}$)^{39–42} at the less sterically encumbered β -position (**A1-B1-TS** vs **A1-C1-TS**) was found. Notably, both product regioisomers (**B1** and **C1**) are nearly isoenergetic.

These computational results are in accord with both the experimentally observed reactivity (20 min – 3 h at room temperature) and regioselectivity ($> 20:1$ dr) using bromostyrene. However, experiments with the *Z*-bromostyrene **2a'** at room temperature yield a near 2:1 ratio of *E*- and *Z*-products, albeit in low yield (14%) due to rapid competing elimination of *Z*-bromostyrene **2a'** to form alkyne (see Supplementary Figure 5). The anionic-pathway $\text{S}_{\text{N}}\text{V}$ shown in Figure 4 is a concerted and stereospecific process,^{36–38} which is inconsistent with the stereochemical scrambling observed. These results motivated us to examine alternative pathways.

We speculated that an azaallyl radical **A0** (Figure 5a)^{44–46} could participate in the process. This azaallyl radical could form by electron transfer from the azaallyl anion (**A1**) to a molecule of ketimine **1a** (Figure 5a).⁴⁷ DFT calculations for azaallyl radical recombination with a putative vinyl radical^{45,48} showed very small energetic barriers (ca. 11 kcal/mol), indicating that such a process is facile. The energy difference between the competing transition states, however, indicates negligible levels of *E/Z* product regioselectivity, which is inconsistent with experiments (see Supplementary Information for structures).

Transition states could also be located for the addition of azaallyl radical **A0** to *trans*-bromostyrene (Figure 5b), which proceeds in a stepwise manner with an overall barrier of 18.0 kcal/mol (via **TS-1a**) to yield radical intermediate **Int-1a**, and eventually to the observed regioisomer (Figure 5b). The transition state **TS-2a**, which leads to the unobserved regioisomer is much higher in energy (23.2 kcal/mol) due to increased steric interactions between the diaryl moiety of the azaallyl radical and β -bromostyrene.

From **Int-1a**, a scan for dissociation of Br• and formation of observed product **P-1a** was computed to be prohibitively high in energy (>35 kcal/mol; see Supplementary Information for scan). Alternatively, radical intermediate **Int-1a** can undergo single electron reduction to generate a negatively charged species, which facilitates the heterolytic cleavage of the C–Br bond to generate Br[−] and the observed product **P-1a**. In support of this hypothesis, all optimizations of anionic version of **Int-1a** led directly to dissociation of Br[−] and formation of **P-1a**. This result implies that once radical **Int-1a** undergoes single electron reduction, it quickly dissociates bromide leading to the observed product, consistent with the highly exergonic (−47 kcal/mol) nature of the net process. This process also converts radical anion **A2** back to ketimine **1a**. The product regioisomers **P-1a** and **P-2a** are nearly isoenergetic, and hence the regioselectivity derives from the kinetic preference of **TS-1a** over **TS-2a**. In contrast to the azaallyl anion pathway (Figure 5b), the pathway involving the radical intermediates **Int-1a** accounts for the stereochemical scrambling from *Z*-bromostyrene **2a'** (bond rotation more rapid than reduction/elimination).

The mechanism in Figure 5 proposes radical intermediates (**A0** and **A2**). To probe for the presence of radicals, an electron paramagnetic resonance (EPR) study was undertaken. In these experiments, DME solutions of NaN(SiMe₃)₂ were added to DME solutions of ketimine **1a** and the samples were allowed to react for ~5 min at rt before freezing in liquid nitrogen. The EPR spectra were acquired in DME glass at 190 K and microwave power of 1 mW. No signal was detected in samples with only base in DME or DME alone. In contrast, for the deprotonations of **1a**, EPR spectra showed clear signals for the presence of radical species (see Supplementary Figure 2). The observation of an EPR signal is supportive of one or more radicals, but definitive conclusions concerning the nature of the radical species must await future investigations. Despite numerous studies of azaallyl anions in the literature, to the best of our knowledge this is the only evidence of radical formation upon deprotonation of ketimines.

Given the evidence for the presence of radicals, which we propose to be the azaallyl radical (**A0**) and the ketimine radical anion (**A2**), an effort was made to distinguish the azaallyl anion S_NV and azaallyl radical additions by calculating the reaction barriers (Figure 5c). Based on the computations, similar trends were observed for both mechanisms, as listed in Figure 5d. Thus, *E*-β-bromostyrene was predicted to react more readily than the *Z*-isomer or *E*-β-chlorostyrene. Experimentally, *E*-β-bromostyrene reacted at −40 °C to afford the vinylation product in 96% assay yield (i, Figure 5d) while *Z*-β-bromostyrene generated the *E*-product in 6% yield (no *cis*-product observed and elimination dominating the reaction, ii, Figure 5d). At room temperature, coupling of *E*-β-chlorostyrene afforded product in 98% assay yield. For substrates lacking a β-aryl group, reaction is expected to slow according to both mechanisms, but to a far larger degree for the azaallyl anion mechanism.^{39–42} As illustrated in Figure 2b, 1-bromo-2-methylprop-1-ene (**2i**) and (bromomethylene)cyclohexane (**2j**) underwent reaction, albeit more slowly (12 h) and with reduced yields (54 and 55%, respectively). Although there are well-documented errors associated with determining accurate quantitative barriers with charged species, computations employing the commonly used B3LYP functional, which has been used by others to study S_NV reactions, predicted prohibitively high barriers (>36 kcal/mol) for the

azaallyl anion **AI** and 1-bromo-2-methylprop-1-ene in both gas-phase and in implicit solvent. Moreover, the greater reactivity of 1-bromo-2-methylprop-1-ene (Figure 2b, 2i) vs *E*-1-bromo-prop-1-ene (iv, Figure 5d) also seemingly runs counter to the azaallyl anion mechanism; a build-up of negative charge would be less favorable with two methyl substituents as is the case for the former.

The EPR results support the presence of radicals, but do not indicate if they are involved in the vinylation reactions. To probe for the direct participation of radicals in the vinylations, we next examined the reactions of radical clock-containing styryl and non-styryl substrates. We prepared the radical clock **2k** (Figure 5e) to test for the intermediacy of radical intermediates in the reaction with β -bromostyrene derivatives. As outlined in Figure 5b, **Int-1a** possesses a stabilized benzylic radical. Thus, a second aryl group was built into the substrate such that, in the event the benzylic radical analogous to **Int-1a** is formed, ring-opening would also give a stabilized benzylic radical. The reaction of the *E*-styryl radical clock **2k** with ketimine **1a** in the presence of $\text{LiN}(\text{SiMe}_3)_2$ furnished a mixture of *Z* and *E* vinylated products in a 1:1 ratio (i, Figure 5e, overall 60% yield). An alkyne side-product was observed in 28% isolated yield, which we propose is derived from the α -elimination-migration mechanism. Thus, no cyclopropane ring-opened products were detected, suggesting that the reaction of styryl substrates does not proceed through radical intermediates. Furthermore, the scrambling of the double bond geometry is inconsistent with an anionic concerted $\text{S}_{\text{N}}\text{V}$ substitution mechanism. Based on these results, the pathway favored is the addition/elimination, wherein the azaallyl anion adds to the styrene to generate a benzylic carbanion that can rotate about the single bond before elimination, giving rise to the observed products (see structure of the proposed intermediate in i, Figure 5e). Unfortunately, we were unable to locate such an intermediate computationally without an additional anion-stabilizing group.

To probe the participation of radicals with aliphatic vinyl bromides, radical clock **2l** was prepared and isolated as the pure *E*-isomer (see Supplementary Information page 19, synthesis of radical clock **2l** for details). Reaction with of *E*-**2l** (ii, Figure 5e) with ketimine **1a** in the presence of $\text{LiN}(\text{SiMe}_3)_2$ led to a complex mixture, as determined by ^1H NMR. Further, no clean products could be isolated from this mixture. We propose that ring-opening occurs to give a reactive radical. These results suggest the presence of radical addition mechanism for aliphatic vinyl bromides.

Based on the computational, spectroscopic (EPR), and experimental results, both azaallyl anion and radical exist under the reaction conditions. To rationalize these observations, we propose substrate dependent reactions with different electrophiles. Thus, with aliphatic vinyl bromides the azaallyl radical addition mechanism best fits with the experimental and computational results. In contrast, for the styryl vinyl bromides, the data is most consistent with the anionic pathway.

Conclusion

In summary, we report a unique transition-metal free coupling of 1,1-diphenyl-3-aryl-2-azaallyl anions with vinyl bromides to afford allylic amine derivatives, which are of great

importance in the pharmaceutical industry. High regioselectivities and yields of *E*-vinylation products were observed. The vinylation reaction outcompetes a rapid background reaction arising from the elimination of the styryl bromides to form alkynes. Several mechanistic possibilities were explored both experimentally and with DFT calculations. EPR studies indicate the presence of radicals, which we have tentatively assigned to be the azaallyl radical and imino-ketyl radical anion species. The detection of radicals is consistent with the unusual azaallyl radical addition mechanism with aliphatic vinyl bromides. For styryl bromides, a radical clock-bearing substrate reacted without ring opening, but with loss of the double bond stereochemistry. This observation disfavors the radical mechanism and is better explained by an anionic addition-elimination mechanism. Further studies are underway to broaden this class of reactions utilizing ketimine derivatives in the absence of added transition metal catalyst, and definitively assign the structures of the radical species observed by EPR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Overview of allylic amines synthesis and vinylation reactions

a. Retrosynthesis of allylic amines. **b.** Prior metal catalyzed vinylation reactions of carbanions generated *in-situ*. **c.** Transition metal-free vinylation of azaallyl-anions. **d.** Possible byproducts derived from product deprotonation/isomerization and deprotonation/cyclization.

Figure 2. Overview of reaction scope

a, Scope of ketimines in the vinylation reaction. ^aUnless otherwise noted, reactions were conducted on a 0.1 mmol scale using 1 equiv of ketimine **1** and 2 equiv of **2a** at 0.2 M. Isolated yields after chromatographic purification. ^b2 equiv of LiN(SiMe₃)₂, 30 min. ^c3 equiv of LiN(SiMe₃)₂, 3 h. ^d2 equiv of LiN(SiMe₃)₂, 6 h. ^e0.05 M. ^f1.2 equiv of LiN(SiMe₃)₂, 0.05 M, 15 min. ^g2 equiv of LiN(SiMe₃)₂, 8 h. ^h0.05 M, 3 h.). **b**, Scope of vinyl bromides in transition metal-free vinylation. ^aReactions conducted on a 0.1 mmol scale using 1 equiv **1a** (0.2 M), 2 equiv LiN(SiMe₃)₂, and 2 equiv vinyl bromides at 0.2 M. Isolated yields after chromatographic purification. ^b2 equiv LiN(SiMe₃)₂ ^c0.1 M. ^d3 equiv NaN(SiMe₃)₂, 12 h, 0.1 M. ^e3 equiv NaN(SiMe₃)₂, 15 min, 60 °C.). **c**, Gram-scale sequential one-pot imine synthesis/vinylation protocol. **d**, Ketimine hydrolysis.

Figure 3. Overview of Mechanistic Study

a, Possible mechanisms for vinylation of benzyl ketimines. (i.) Elimination-addition pathway. (ii.) [3+2] cycloaddition between ketimine anion and vinyl bromide, followed by ring opening. (iii.) Carbene insertion. (iv.) Addition-elimination or substitution. **b**. Probing the intermediacy of an alkyne. **c**. Probing the vinyldene insertion mechanism.

Figure 4. M06-2X/6-31G(d)-CH₂Cl₂(CPCM) geometries of competing transition states for azaallyl anion S_NV reaction with styryl bromide. Gibbs free energies (blue) are in kcal/mol relative to isolated reactants. Selected distances (red) are in Å.

c

a	b	c	d	e
radical: 18.0	19.3	20.7	21.5	25.5
anionic: 11.7	15.1	15.5	28.0	33.2

d

Figure 5. Overview of possible radical mechanism

a. Proposed formation of ketimine radical A0 and ketimine radical anion A2 via a SET process. **b.** Gibbs free energy (M06-2X/6-31G(d)-CH₂Cl₂(CPCM)) profile for the azaallyl radical additions. Energies (kcal/mol) are relative to isolated reactants. Substituent effects of electrophile on the radical and anionic addition barriers (free energies in kcal/mol at 298 K) were calculated using M06-2X/6-31G(d)-CH₂Cl₂(CPCM). Selected Mulliken spin densities with hydrogens summed into heavy atoms are listed in blue. Selected distances are in Å. **c.** Substituent effects of electrophile on the radical and anionic addition barriers (free energies in kcal/mol at 298 K) were calculated using M06-2X/6-31G(d)-CH₂Cl₂(CPCM). **d.** Substrate study of vinylation. **e.** Radical clock study.

Table 1

Optimization of the transition metal-free vinylation.^{a,b}

Entry	Base (equiv)	Solvent	Time (min) (min)	Conc.	3aa (%)
1	NaN(SiMe ₃) ₂ (3)	THF	180	0.1 M	51
2	NaN(SiMe ₃) ₂ (3)	THF	180	0.2 M	65
3	NaN(SiMe ₃) ₂ (3)	CPME	10	0.2 M	0
4	NaN(SiMe ₃) ₂ (3)	THF	10	0.2 M	32
5	NaN(SiMe ₃) ₂ (3)	2-Me THF	10	0.2 M	0
6	NaN(SiMe ₃) ₂ (3)	DME	10	0.2 M	98
7	NaN(SiMe ₃) ₂ (3)	Dioxane	10	0.2 M	0
8	LiN(SiMe ₃) ₂ (3)	DME	10	0.2 M	99
9	LiN(SiMe ₃) ₂ (2)	DME	10	0.2 M	98 ^c
10	LiN(SiMe ₃) ₂ (1.5)	DME	10	0.2 M	54
11	LiN(SiMe ₃) ₂ (1)	DME	30	0.2 M	21

^aReactions conducted on a 0.1 mmol scale.^bAssay yields determined by ¹H NMR spectroscopy of the reaction mixture on a 0.1 mmol scale using an internal standard.^cIsolated yield after chromatographic purification.