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Evidence for a Sigmatropic and an Ionic Pathway in the Winstein Rearrangement

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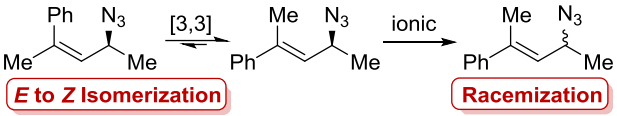


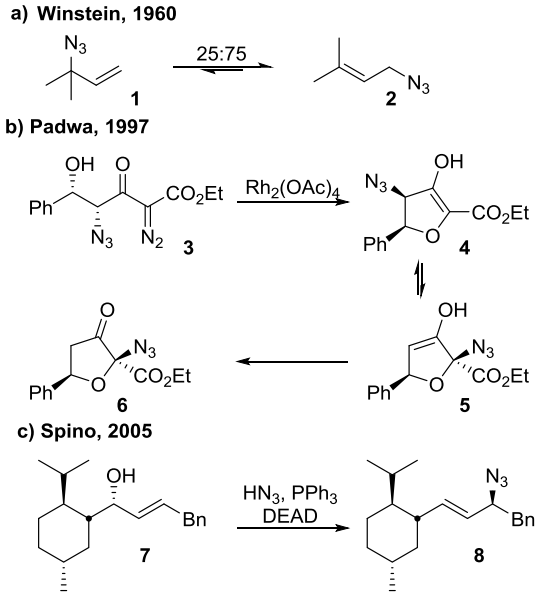
ABSTRACT: The spontaneous rearrangement of allylic azides is thought to be a sigmatropic reaction. Presented herein is a detailed investigation into the rearrangement of several allylic azides. A combination of experiments including equilibrium studies, kinetic analysis, density functional theory calculations, and selective ^{15}N-isotopic labeling are included. We conclude that the Winstein rearrangement occurs by the assumed sigmatropic pathway under most conditions. However, racemization was observed for some cyclic allylic azides. A kinetic analysis of this process is provided, which supports a previously undescribed ionic pathway.

Introduction

Sigmatropic rearrangements are central to organic chemistry and their synthetic applications are numerous. Famous examples include the Cope,[1] Claisen,[1] Wittig,[2] Carroll[3], Sommelet-Hauser[4], Mislow-Evans[5], Meisenheimer[6], and Overman[7] rearrangements or modifications thereof.[8–10] In principle, all of these reactions are reversible. However, the most heavily utilized sigmatropic rearrangements have a clear thermodynamic driving force. Most also require heating to achieve efficient reactivity. When viewed in this light, the Winstein rearrangement of allylic azides is an oddity because i) it occurs at or near room-temperature and ii) it results in an equilibrium mixture of allylic azides (Scheme 1a).[11] This is because the azide functional group is dipolar and symmetric. A C-N, N=N, and C=C bond is present in both the starting material and product of the azide rearrangement, making it near thermo-neutral. This parallels the Cope rearrangement, where, in most cases, the starting material and product are similar in energy, resulting in an equilibrium distribution.[12] This also parallels the rearrangement of allylic acetates.[13–15] These unusual properties make the allylic azide rearrangement an interesting candidate for further study.

The rearrangement of allylic azides was first described by Winstein and co-workers (Scheme 1a).[11] In hindsight, this rearrangement was likely observed but not recognized until later by VanderWerf and Heasley.[16,17] Winstein's initial report describes the rate constant and equilibrium constant for the rearrangement of prenyl azide and crotyl azide. These parameters were minimally sensitive to solvent polarity, indicating a relatively neutral transition state and implying a sigmatropic process. Le Noble found that at high pressure the reaction's activation volume was consistent with a neutral pathway.[18] Padwa provided the first evidence for stereoselectivity.[19] A single diastereomer was isolated from a tandem insertion rearrangement sequence (Scheme 1b). Spino observed stereoselectivity during a tandem Mitsunobu reaction rearrangement sequence (Scheme 1c).[20] A few reports describe an analysis of crotyl and prenyl systems computationally and concluded that the process is cyclic.[21–23] These observations are all consistent with a concerted [3,3] sigmatropic mechanism for the allylic azide rearrangement and the [3,3] mechanism has been generally accepted.

Scheme 1. Winstein Rearrangement



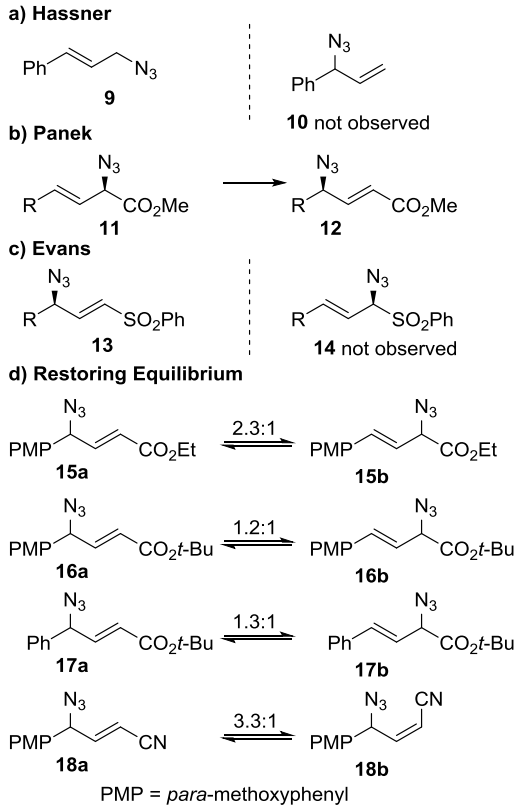
A unique aspect of the allylic azide rearrangement is the abnormally low activation barrier, which allows this process to occur at ambient temperature. The Winstein rearrangement has limited synthetic applications due to difficulties controlling the rearrangement.[24–30] We have an ongoing interest in using the Winstein rearrangement and became interested in more precisely defining the parameters of the rearrangement on a broader set of allylic azides.[31–33] Presented herein is a summary of several experiments that more fully define the energetics and mechanism of this rearrangement. We investigated the effect of competitive conjugation on the equilibrium constant. A rearrangement with ^{15}N isotopically labeled allylic azide unambiguously confirms the [3,3] pathway. We describe a pathway for the *E* to *Z* isomerization of trisubstituted alkenes. These results led to us to probe whether racemization of chiral allylic azides could occur. Under certain conditions, these allylic azides racemize. A kinetic analysis supports an ionic pathway. Each of these pathways is supported by DFT calculations. These combined experiments indicate that more than one pathway is operable for allylic azide isomerization.

Results and Discussion:

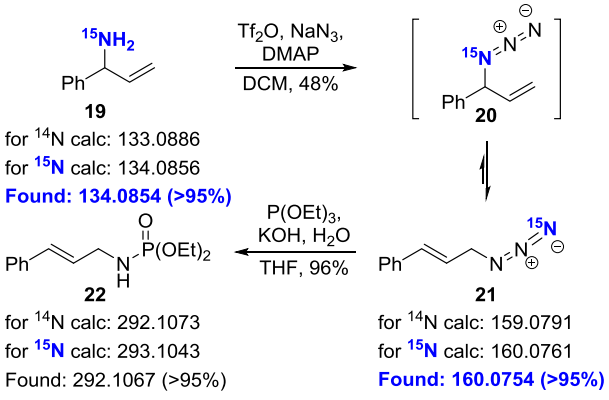
Effect of Conjugation on K_{eq}. Scattered reports provide insight into biasing the azide rearrangement. Hassner originally synthesized cinnamyl azide and reported only a single isomer (Scheme 2a).[34] In this example, conjugation to the phenyl ring strongly influences the equilibrium and results in a single observable isomer.[35] Panek observed a similar effect with γ-azido-α,β-unsaturated esters (Scheme 2b) and Evans made an analogous observation with 3-azido-vinyl sulfones (Scheme 2c).[36,37] In all cases, the conjugated compound is favored. This is reminiscent of strategies to render the Cope rearrangement effectively irreversible by forming a conjugated product.[38] We were interested in re-establishing a detectible equilibrium with conjugated azides. To this end, compounds **15** through **18** were synthesized (Figure 2d). Each allylic terminus is substituted with a different group for conjugation. After isolation, samples were incubated at 40 °C for 48h to allow equilibration and then analyzed. The observed equilibrium ratio ranges from 2.3:1 to 1.2:1 for azides **15** through **17**, indicating that a detectible equilibrium can be re-established if both termini stabilize the system through conjugation. The effect seemed insensitive to the nature of the aryl (**16** vs **17**). For nitriles **18a** and **18b**, the other isomer was not detected. The remainder of this report describes allylic azides that are conjugated to an aryl ring. These systems were intentionally designed to minimize the number of isomers present in the mixture as a means of simplifying analysis.

^{15}N-Labelling Experiment. One means to unambiguously discern between a [1,3], [3,3], and ionic mechanism is to isotopically label one end of the azide group. Sodium azide containing a ^{15}N-label is commercially available; however, either end of the azide anion could attack an electrophilic carbon center. This would likely generate a 1:1 mixture of proximal and distal ^{15}N-azides, which would be difficult to analyze. Instead, we turned our attention to an alternate approach (Scheme 3). We synthesized ^{15}N-amine **19** in two steps from potassium ^{15}N-phthalimide. The ^{15}N-label was evident by ^{15}N NMR and by HRMS. Images of all mass spectra are included in the supporting information. The amine was subjected to diazo-transfer conditions, which formed azide **20**. This azide spontaneously rearranged to afford ^{15}N-cinnamyl azide (**21**), which was isolated as a single isomer due to conjugation. The label was again clearly evident by NMR, IR, and HRMS. Reduction of the azide liberated N_2 and afforded phosphoramidate **22**. Analysis of this product by NMR and HRMS indicated the complete loss of the ^{15}N label. An authentic sample of ^{15}N-**22** was synthesized by a separate route. This experiment provides direct evidence for the [3,3] mechanism of the Winstein rearrangement.

Scheme 2. Effects of Conjugation on K_{eq}



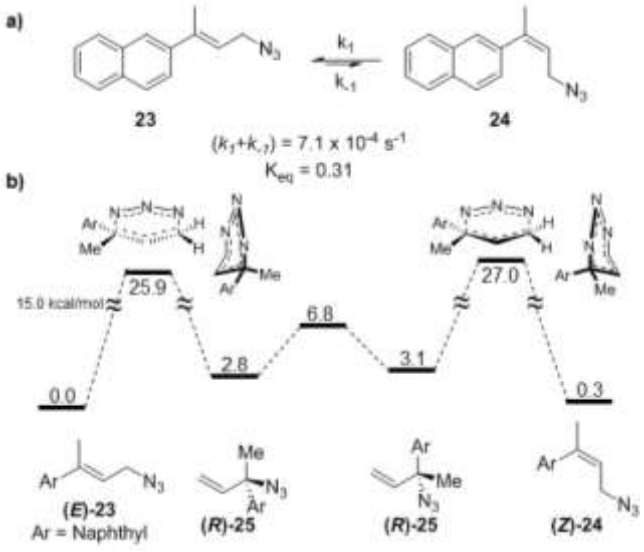
Scheme 3. Rearrangement of ^{15}N-Labeled Allylic Azide



***E* to *Z* Isomerization.** Many allylic azides are isolated as a mixture of alkene isomers.[11,24,27,39,40] Typically, the ob-

served distribution of isomers is related to the relative thermodynamic stability of the alkenes. Little is known regarding the mechanism of alkene isomerization via the Winstein rearrangement.[22] Labadie et. al, investigated several isoprenyl azides.[23] That report concluded that allylic azides conjugated to an aryl ring do not rearrange. This is contrary to a prior report that *cis*-cinnamyl azide isomerizes to *trans*-cinnamyl azide.[41] We observed that azide **23** forms a mixture of *E* and *Z* isomers upon standing (Scheme 4a). The naphthyl containing compound was studied because the isomers were separable by column chromatography.[42] We conducted a kinetic analysis of the *E* to *Z* isomerization by ^{1}H NMR at 75 °C in C_6D_6. The observed rate constant (k_1+k_{-1}) was 7.2 x 10^{-4} s^{-1} and the observed ratio of **23**:**24** was 3.2:1 at equilibrium (equilibrium reached after 90 min). The same approximate values were measured by monitoring the reverse *Z* to *E* rearrangement (k_1+k_{-1} = 6.9 x 10^{-4} s^{-1}, average reported in Scheme 4). The observed rate is slower than that reported by Winstein for crotyl azide.

Scheme 4. Equilibration of Azides 23 and 24



a) Values determined by ^{1}H NMR. b and c) Free energies (kcal/mol, 1 M standard state, 75 °C) computed at the SMD($CHCl_3$)/M06-2X/6-311+G(2df,p)//SMD($CHCl_3$)/ M06-2X/6-31G(d) level of theory. The vertical scale has been compressed by 15.0 kcal/mol between the ground states and transition states.

We turned to density functional theory (DFT) calculations to describe the pathway for the observed alkene isomerization (Scheme 4b). These calculations were conducted at the M06-2 level of theory, both in the gas phase and accounting for solvation effects implicitly with the SMD solvation model (e.g., chloroform, as shown in Scheme 4, see Computational Details).[43,44] The analysis indicates a three step process: (1) endothermic rearrangement to benzylic azide **25**, (2) sigma bond rotation, and (3) a second Winstein rearrangement to the conjugated isomer **24**. The calculated barriers and relative stationary point energetics are in good agreement with the experimental data. In both rearrangements, the transition-state structure is a fairly flat half chair (C-N-N-N-C in plane and C-C-C pucker). The rearrangement is relatively synchronous (CN bond lengths of 2.036 and 2.069 Å). This study did not address if the transition state is pericyclic or pseudopericyclic.[15,45,46] These results indicate that the Winstein rearrangement is kinetically viable on conjugated systems, even though the isomeric benzylic azide is present at too small a concentration to be readily detected by ^{1}H NMR.

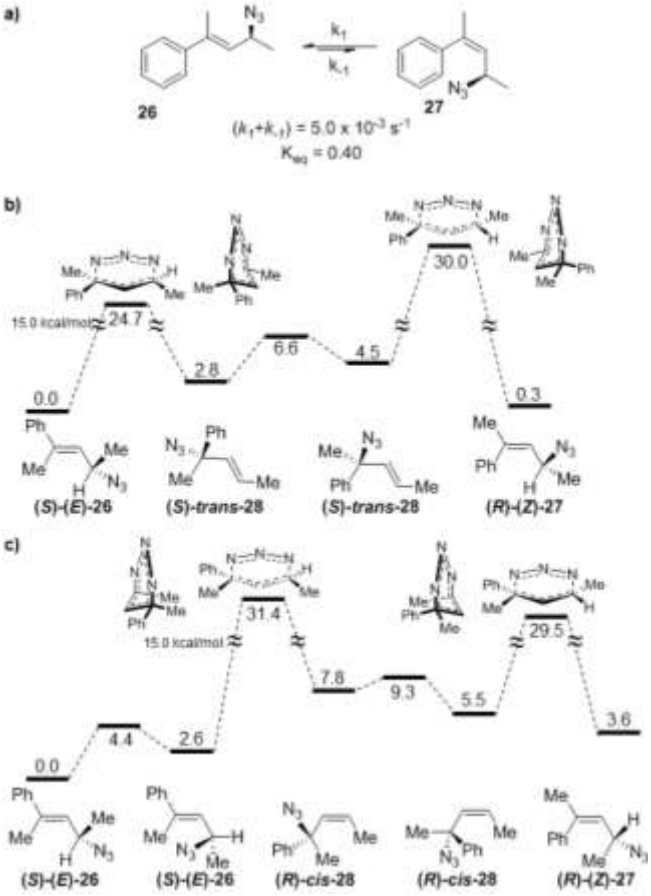
Chiral Acyclic Allylic Azide. These results led us to consider whether azide **26** could racemize through the Winstein rearrangement (Scheme 5). Stereoselectivity is a key feature to effectively utilizing allylic azides in synthetic contexts.[20] Racemization can occur readily if one isomer is achiral (see SI for the calculated profile for crotyl azide) or if the product is the enantiomer of the starting material.[32,47] It was unclear whether a system such as azide **26** would racemize via a sigmatropic process. The examples from Padwa and Spino (Scheme 1b-c) document that racemization was not observed in those instances. However, the example from Padwa is cyclic, cannot form *E*/*Z* mixtures, and it is effectively irreversible (kinetically mediated). The example from Spino contains a *trans* alkene, which may not be able to adopt multiple reactive conformations. Azide **26** rapidly forms a mixture of *E*/*Z* isomers, with a rate constant (k_1+k_{-1}) of 5.0 x 10^{-3} s^{-1} in C_6D_6 at 75 °C and a 2.5:1 equilibrium ratio of **26**:**27**. Equilibrium is reached considerably faster for compounds **2**6 and **27** (after 20 min) relative to **23** and **24** (90 min). The observation that an additional methyl group speeds the rearrangement is consistent with Winstein's work where k_{rel} for prenyl/crotyl azides ranged from 2.6-3.6 in a variety of solvents.[11] To determine if racemization occurs, we used semi-preparative chiral HPLC to isolate enantioenriched azide **26** (>99:1 er). The equilibration of compound **26** was monitored by ^{1}H NMR at 75 °C. Once equilibrium was reached, the enantiopurity of the sample was measured by chiral HPLC. Only a single enantiomer was observed for both the *E* isomer (>99:1 er) and *Z* isomer (>99:1 er). This indicates that racemization via a sigmatropic process is unlikely.

We investigated the [3,3] mechanism computationally (Scheme 5b-c). The lowest energy pathway is similar to that shown for compounds **23** and **24,** where a three step process is responsible for the alkene isomerization (Scheme 5b). The azide rearranges to *trans*-azide **28**, undergoes a bond rotation, and then rearranges for a second time to afford (*Z*)-azide **27**. For compounds **26** and **27**, a second sigmatropic pathway was identified, which is similar to the first except in the order of events. In the second pathway (Scheme 5c), (*E*)-azide **26** undergoes a sigma bond rotation and then a rearrangement to afford *cis*-azide **28**. This azide undergoes a second bond rotation and subsequent rearrangement to afford (*Z*)-azide **27**. In both pathways, the initial azide was intentionally assigned as (*S*)-(*E*)-azide **26** and the product of both pathways was (*R*)-(*Z*)-azide **27**. The stereoselectivity in both pathways is consistent with the experimental findings.

A third ionic pathway was identified which was significantly higher in energy. The azide ionizes to form free azide anion and a stabilized allylic cation (Scheme 6). In the gas phase and in chloroform, this pathway was significantly higher in energy relative to the sigmatropic pathway (134.3

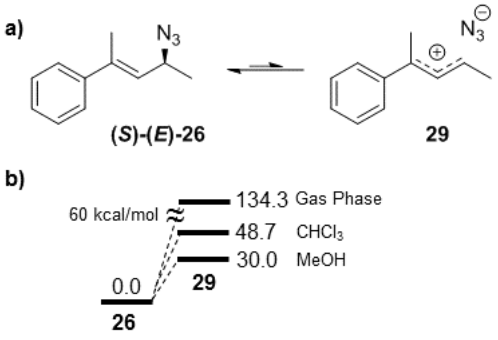
and 48.7 kcal/mol, respectively). However, in methanol, the ionic pathway was calculated to be much closer in energy to the sigmatropic pathway, at only 30.0 kcal/mol. This prompted further exploration.

Scheme 5. Equilibration of Chiral Allylic Azide



a) Values determined by ^{1}H NMR. b and c) Free energies (kcal/mol, 1 M standard state, 75 °C) computed at the SMD($CHCl_3$)/M06-2X/6-311+G(2df,p)//SMD($CHCl_3$)/M06-2X/6-31G(d) level of theory. The vertical scale has been compressed by 15.0 kcal/mol between the ground states and transition states.

Scheme 6. Relative Ionization Energies of Azide 26



Free energies (kcal/mol, 1 M standard state, 75 °C) computed at the M06-2X/6-311+G(2df,p)//M06-2X/6-31G(d) level of theory for gas-phase and SMD-solvated reaction coordinates. The vertical scale has been compressed by 60.0 kcal/mol between chloroform and gas phase.

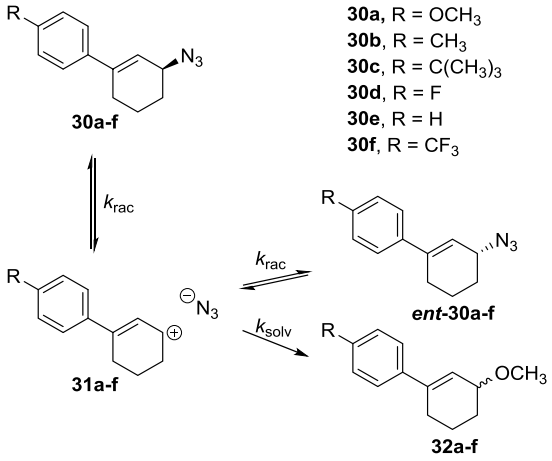
Identifying a Racemization Pathway. To examine the proposed ionic pathway, a new series of allylic azides was investigated (Scheme 7). These allylic azides are readily prepared from cyclohexenone. The cyclohexyl ring prevents *E* to *Z* isomerization and simplifies analysis. These azides could be easily separated by semi-preparative chiral HPLC. Once characterized, azide **30e** was subjected to prolonged heating in a variety of solvents. After one week at 100 °C no or negligible racemization was observed in hexanes, toluene, chloroform, and tetrahydrofuran. In these solvents, even after prolonged heating, these allylic azides can be thought of as static structures that are configurationally and isomerically stable. However, rapid racemization was observed in methanol at 100 °C. As an example, for azide 30b (4-Me), the er decreased considerably after only 1h from >99:1 er to 74:26 er and full racemization occurred within 8h. Solvent-dependent racemization is consistent with the pathway identified by DFT.

Intrigued by the observed racemization, we conducted a more detailed kinetic analysis. The rate of racemization was determined by chiral HPLC. Using the method of initial rates[48], the rate was found to be first order in azide. Several analogous substrates were synthesized and subjected to the same analysis. A Hammett plot was generated for racemization (Figure 1). Therate of racemization is highly correlated with the Hammett parameter σ^+ (R^2 = 0.99, ρ = - 3.9). The relative energies of the ions (**31a-f**) were calculated at the SMD/M06-2X level. The ion stabilities ranged from 21.4 – 30.0 kcal/mol (SMD(MeOH)) and the stabilities were also correlated to σ^+ (see SI). This analysis is consistent with rate determining formation of an ion pair.

A more detailed analysis revealed a byproduct of the racemization process, identified as the corresponding methyl ether. At all-time points, the methyl ether is racemic. The appearance of this product is consistent with an ionic solvolysis reaction. Adding exogenous tetrabutylammonium azide did not noticeably inhibit the formation of the methyl ether. The rate of methyl ether formation is also correlated with the Hammett parameter σ^+ (Figure 2, R^2 = 0.92, ρ = - 3.1). When heated in methanol, acyclic azide **26** also racemizes, indicating that other azides can participate in this process.

Conclusion: Presented herein is a description of two competing pathways for the rearrangement of allylic azides. A ^{15}N-labeling experiment, supported by DFT calculations, indicates that under most circumstances, the rearrangement is sigmatropic. A pathway for the isomerization of a chiral allylic azide, with a trisubstituted alkene, is reported to occur without racemization. A second ionic pathway is available in highly polar media and we observed it in methanol. This reaction is Hammett constant (σ^+) correlated and is kinetically consistent with a solvolysis mechanism.

Scheme 7. Racemization and Solvolysis of Cyclic Azides



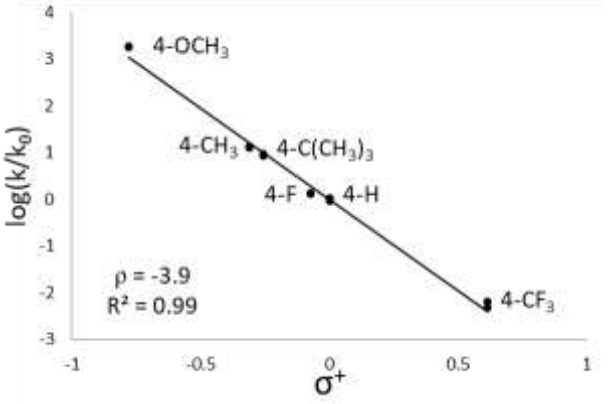


Figure 1. Plot of log(k/k$_0$) vs σ$^+$ for substituent effects on the racemization of azides **30a-f** in MeOH. Rates were measured in duplicate, replicates shown.

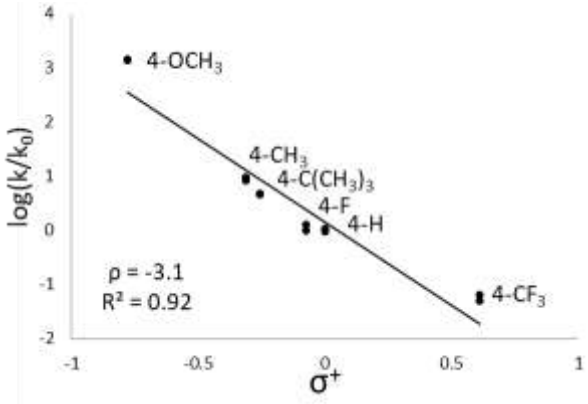


Figure 2. Plot of log(k/k$_0$) vs σ$^+$ for substituent effects on the solvolysis of azides **30a-f** in MeOH. Rates were measured in duplicate, replicates shown.

Experimental Section:

Azide Safety. Azides are known to be high-energy materials, and explosions have been reported when working with azides. In the course of this work, no issues were encountered. All of the azides synthesized in this report have C/N ratios equal to or above the recommended guideline of 3 C/N. Precautionary blast shields were used for all reactions using or producing more than 1 mmol of azide. Blast shields were used both in the fume hood and during rotary evaporation. All waste and aqueous solutions, which could be contaminated with azide were kept in individually labeled containers and were kept STRICTLY free of acid to avoid the accidental production of HN_3.

General Methods. All reactions used magnetic stirring. All reactions conducted at elevated temperatures used aluminum block heating. Temperatures reported are based on an external thermocouple. All commercially available reagents were used without further purification. Dry THF and DCM were obtained from a commercial solvent system utilizing activated alumina columns under an argon pressure. Thin-layer chromatography (TLC) was used to monitor reaction progress. TLC was performed using pre-coated glass or plastic plates with silica gel impregnated with a fluorescent indicator (254 nm). Visualization was achieved using UV light, PMA, or $KMnO_4$ stains. Organic solutions were concentrated by rotary evaporation under reduced pressure. Flash chromatography was performed on an automated system utilizing normal phase pre-column load cartridges and gold high performance columns. All proton (^{1}H) nuclear magnetic resonance spectra (NMR) were recorded on a 400 MHz or 500 MHz spectrometer. All carbon (^{13}C) nuclear magnetic resonance spectra were recorded on a 100 MHz or 125 MHz NMR spectrometer. All phosphorous (^{31}P) nuclear magnetic resonance spectra were recorded on a 162 MHz NMR spectrometer. All nitrogen (^{15}N) nuclear magnetic resonance chemical shifts were measured using ^{1}H-^{15}N Heteronuclear Multiple Bond Correlation (HMBC) on a 93 MHz spectrometer. Data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), integration, and coupling constant in Hertz (Hz). Infrared (IR) spectra were taken with KBr plates. IR spectra were reported in cm^{-1}. Mass spectrometry was conducted at the University of Minnesota Mass Spectometry Laboratory. Details on HPLC analysis and purification are included in the supporting information.

ethyl (E)-4-azido-4-(4-methoxyphenyl)but-2-enoate (**15a**) and ethyl (*E*)-2-azido-4-(4-methoxyphenyl)but-3-enoate (**15b**). Azides **15a** and **15b** were synthesized via a multistep sequence that is outlined here. A procedure was adapted from a known method for the addition of ethyl propiolate to 4-methoxybenzaldehyde and the product was isolated (700 mg, 73%).[49] Characterization data for this compound has been reported. The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file.

This product was reduced using an adapted procedure.[50] To an ice-cold suspension of $LiAlH_4$ (33 mg, 0.9 mmol) in THF (2.5 mL), a solution of ethyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate (200 mg, 0.9 mmol) in THF (2.5 mL) was added dropwise. After 10 min, the ice bath was removed. After 30 min, the reaction was quenched by addition of 1M HCl. The resulting solution was extracted with DCM (3 × 10 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc in hexanes) afforded ethyl (*E*)-4-hydroxy-4-(4-methoxyphenyl)but-2-enoate (82 mg, 41%) as an oil. Characterization data for this compound has been reported. The

material obtained from this method provided an identical ^{1}H NMR spectrum.[51] An image of the ^{1}H NMR spectrum is supplied in the accompanying file.

To a solution of ethyl 4-hydroxy-4-(4-methoxyphenyl)but-2-enoate (67 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) was added $TMSN_3$ (0.8 mL, 0.6 mmol) and $Zn(OTf)_2$ (23 mg, 0.063 mmol) at room temperature. The vessel was sealed. After 20 min, the reaction mixture was filtered through silica and washed with CH_2Cl_2. The resulting solution was concentrated under reduced pressure. Purification by column chromatography (gradient elution 0-15% EtOAc in hexanes) afforded a mixture of azide **15a** and **15b** (**15a** : **15b** = 2.0 : 1) as an oil (52 mg, 70%): Major isomer (**15a**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.98-6.89 (m, 3H), 6.14 (d, *J* = 15.4 Hz, 1H), 5.16 (d, *J* = 5.5 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); Minor isomer (**15b**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2H), 6.98-6.89 (m, 2H), 6.73 (d, *J* = 15.8 Hz, 1H), 6.17-6.12 (m, 1H), 4.53 (d, *J* = 7.7 Hz, 1H), 4.33-4.27 (m, 2H), 3.84 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); Mixture: ^{13}C NMR (125 MHz; $CDCl_3$) δ 169.1, 165.9, 160.1, 160.0, 144.1, 135.5, 128.9, 128.4, 128.2, 122.5, 118.3, 114.4, 114.1, 65.0, 63.9, 62.1, 60.7, 55.3, 14.2, 14.1; IR (KBr, thin film, cm^{-1}) 2980, 2838, 2103, 1720, 1608, 1513, 1255, 1176; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{15}N_3O_3Na^+$ 284.1006, found 284.0998.

tert-butyl (E)-4-azido-4-(4-methoxyphenyl)but-2-enoate (**16a**) and *tert-butyl (E)-2-azido-4-(4-methoxyphenyl)but-3-enoate* (**16b**). Azides **16a** and **16b** were synthesized via a multi-step sequence following the procedures for compounds **15a** and **15b**, *tert*-butyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate was isolated as an oil (840 mg, 87%): ^{1}H-NMR (500 MHz; $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 5.47 (s, 1H), 3.80 (s, 3H), 3.49 (s, 1H), 1.50 (s, 9H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 159.8, 152.6, 131.2, 128.2, 114.1, 84.5, 83.9, 78.8, 63.7, 55.3, 28.0; IR (KBr, thin film, cm^{-1}) 3400, 2981, 2936, 2838, 2237,1707, 1612, 1513, 1255, 1156; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{18}O_4Na^+$ 285.1097, found 285.1097.

Tert-butyl 4-hydroxy-4-(4-methoxyphenyl)but-2-enoate was isolated as an oil (220 mg, 56%): ^{1}H-NMR (400 MHz; $CDCl_3$) δ 7.29-7.26 (m, 2H), 6.94 (dd, *J* = 14.4, 4.7 Hz, 1H), 6.92-6.88 (m, 2H), 6.05 (dd, *J* = 15.6, 1.7 Hz, 1H), 5.29 (dd, *J* = 4.9, 1.3 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 165.8, 159.6, 147.5, 133.3, 128.0, 122.0, 114.2, 80.6, 73.2, 55.3, 28.1; IR (KBr, thin film, cm^{-1}): 3409, 2977, 2933, 1710, 1512, 1249, 1152; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{20}O_4Na^+$ 287.1254, found 287.1249.

Allylic azides **16a** and **16b** were isolated as an oil (1.3 : 1, 160 mg, 65%): Major isomer (**16a**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.85 (dd, *J* = 15.4, 5.4 Hz, 1H), 6.06 (d, *J* = 15.4 Hz, 1H), 5.13 (d, *J* = 5.2 Hz, 1H), 3.84 (s, 3H), 1.51 (s, 9H); Minor isomer (**16b**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 15.8 Hz, 1H), 6.14 (dd, *J* = 15.8, 7.5 Hz, 1H), 4.38 (d, *J* = 7.4 Hz, 1H), 3.84 (s, 3H), 1.54 (s, 9H); Mixture: ^{13}C NMR (126 MHz; $CDCl_3$) δ 168.2, 165.1, 160.0, 143.0, 135.0, 128.9, 128.6, 128.3, 128.2, 124.3, 118.8, 114.4, 114.1, 83.2, 80.9, 65.0, 64.3, 55.3, 28.1, 28.0; IR (KBr, thin film, cm^{-1}) 2978, 2933, 2102, 1716, 1512, 1252, 1152; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{19}N_3O_3Na^+$ 312.1319, found 312.1320.

tert-butyl (E)-2-azido-4-phenylbut-3-enoate (**17a**) *and tert-butyl (E)-4-azido-4-phenylbut-2-enoate* (**17b**). Azides **17a** and **17b** were synthesized via a multi-step sequence that is outlined here. A procedure was adapted from a known method[52] for the addition of *tert*-butyl propiolate to benzaldehyde and the product was isolated as an oil (755 mg, 75%): ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.52 (d, *J* = 7.1 Hz, 2H), 7.42-7.36 (m, 3H), 5.54 (s, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 152.6, 138.8, 128.79, 128.78, 126.7, 84.2, 84.0, 79.0, 64.2, 28.0; IR (KBr, thin film, cm^{-1}) 3401, 2981, 2935, 2238, 1707, 1278, 1155; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{16}O_3Na^+$ 255.0992, found 255.0991.

This product was reduced using an adapted procedure.[50] To an ice-cold suspension of $LiAlH_4$ (57 mg, 1.7 mmol) in THF (4 mL), a solution of *tert*-butyl 4-hydroxy-4-phenylbut-2-ynoate (350 mg, 1.7 mmol) in THF (4mL) was added dropwise. After 15 min, the reaction was quenched by addition of 1M HCl. The resulting solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc in hexanes) afforded *tert*-butyl (*E*)-4-hydroxy-4-phenylbut-2-enoate (200 mg, 56%) as an oil. Characterization data for this compound has been reported. The material obtained from this method provided an identical ^{1}H NMR spectrum.[53] An image of the ^{1}H NMR spectrum is supplied in the accompanying file.

This product was acetylated using an adapted procedure.[54] To a solution of *tert*-butyl (*E*)-4-hydroxy-4-phenylbut-2-enoate (100 mg, 0.4 mmol) in CH_2Cl_2 (0.8 mL) was added acetic anhydride (80 μL, 0.8 mmol), followed by pyridine (30 μL, 0.4 mmol). After 24 h, the reaction was quenched by addition of 1M HCl. The resulting solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc in hexanes) afforded *tert*-butyl (*E*)-4-acetoxy-4-phenylbut-2-enoate as an oil (75 mg, 64%): ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.41-7.36 (m, 5H), 6.92 (dd, *J* = 15.6, 5.2 Hz, 1H), 6.40 (dd, *J* = 5.2, 1.6 Hz, 1H), 5.97 (dd, *J* = 15.6, 1.7 Hz, 1H), 2.15 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 169.7, 165.2, 143.4, 137.4, 128.8, 128.7, 127.4, 123.6, 80.9, 74.3, 28.1, 21.1; IR (KBr, thin film, cm^{-1}) 2979, 2934, 1744, 1716, 1659,1456, 1369, 1230, 1153; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{20}O_4Na^+$ 299.1254, found 299.1253.

The azide was installed using a known procedure.[55] Allylic azides **17a** and **17b** were isolated as an oil (43 mg, 46% yield): Major isomer (**17a**): ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.45-7.32 (m, 5H), 6.86 (dd, *J* = 15.4, 5.9 Hz, 1H), 6.07 (dd, *J* = 15.4, 1.6 Hz, 1H), 5.18 (dd, *J* = 5.9, 1.3 Hz, 1H), 1.51 (s, 9H); Minor isomer (**17b**): ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.45-7.32 (m, 5H), 6.77 (d, *J* = 15.8 Hz, 1H), 6.27 (dd, *J* = 15.8, 7.3 Hz, 1H), 4.42 (d, *J* = 7.3 Hz, 1H), 1.54 (s, 9H); Mixture: ^{13}C NMR (125 MHz; $CDCl_3$): δ 168.2, 165.0, 142.7, 136.7, 135.6, 135.3, 129.1, 128.9, 128.7, 128.6, 127.5, 126.8, 124.7, 121.2, 83.3, 81.0, 65.5, 64.1, 28.1, 28.0; IR (KBr, thin film, cm^{-1}) 2979, 2931, 2104, 1716, 1253, 1152; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{17}N_3O_4Na^+$ 282.1213, found 282.1216.

(E)-4-azido-4-(4-methoxyphenyl)but-2-enenitrile (**18a**) and *(Z)-4-azido-4-(4-methoxyphenyl)but-2-enenitrile* (**18b**). Azides **18a** and **18b** were synthesized via a two step sequence. Following a known procedure[56], (*E*)-4-(4-methoxyphenyl)-2-((trimethylsilyl)oxy)but-3-enenitrile was isolated crude as an orange oil (698 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 15.7 Hz, 1H), 6.08 (dd, *J* = 15.7, 6.2 Hz, 1H), 5.12 (d, *J* = 6.2 Hz, 1H), 3.85 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 133.6, 128.3, 127.7, 121.3, 118.6, 114.2, 62.5, 55.3, 0.0; IR (KBr, thin film, cm^{-1}) 2959, 2838, 1607, 1513, 1255, 1176, 845; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{14}H_{19}NO_2Na^+$ [M + Na]$^+$: 284.1077, found 284.1067.

Starting from *(E)-4-(4-methoxyphenyl)-2-((trimethylsilyl)oxy)but-3-enenitrile* and following the procedure above for the azide installation for compounds **15** and **16** , a mixture of azides **18a** and **18b** (17 mg, 38%) was isolated as an oil. Major isomer (**18a**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.71 (dd, *J* = 16.0, 4.6 Hz, 1H), 5.76 (dd, *J* = 16.0, 2.0 Hz, 1H), 5.18 (dd, *J* = 4.6, 2.1 Hz, 1H), 3.85 (s, 3H); Minor isomer (**18b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.99 – 6.92 (m, 2H), 6.55 (dd, *J* = 10.9, 9.2 Hz, 1H), 5.56 – 5.49 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 160.2, 150.7, 150.3, 129.1, 128.2, 127.0, 116.6, 114.7, 114.7, 101.0, 100.8, 64.8, 64.2, 55.4, 55.4; IR (KBr, thin film, cm^{-1}) 2839, 22640, 2103, 1608, 1512, 1252; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{11}H_{10}N_2O^+$ [M – N_2]$^+$: 186.0788, found 186.0782.

(3-azidoprop-1-en-1-yl)benzene (**9**). A procedure was adapted from a known method[57] and the product was isolated (32 mg, 60%) . The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file. The data provided here is for comparison to the ^{15}N-labeled compound:^{1}H NMR (500 MHz; $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.73 (m, 2H), 7.48-7.46 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.31-7.28 (m, 1H), 6.67 (ddd, *J* = 17.3, 9.0, 7.6 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 5.40 (d, *J* = 9.3 Hz, 1H), 5.37 (d, *J* = 16.8 Hz, 1H); IR (KBr, thin film, cm^{-1}) 3031, 1769, 1715, 1468, 1382, 1352, 989, 718; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{13}NO_2Na^+$ 286.0838, found 286.0832.

The procedure to deprotect the phthalimide is based off of a known method.[58] To a solution of 2-(1-phenylallyl)isoindoline-1,3-dione (0.10 g, 0.40 mmol) in EtOH (5 mL) was added ethanolamine (0.24 mL, 3.8 mmol). The solution was sealed and heated to 40 °C. After 18 h, the solution was poured over 6 M HCl (10 mL) and extracted with CH_2Cl_2 (1 x 10 mL). The aqueous layer was then basified with NaOH (pH > 10) and the resulting solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting compound was isolated as a yellow oil (23 mg, 44%) and was used without further purification. The material obtained from this method provided an identical ^{1}H NMR spectrum to previous report.[59] An image of the ^{1}H NMR spectrum is supplied in the accompanying file. The data provided here is for comparison to the ^{15}N-labeled compound: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.39-7.34 (m, 4H), 7.30-7.26 (m, 1H), 6.05 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H), 5.27 (d, *J* = 16.9 Hz, 1H), 5.14 (d, *J* = 10.2 Hz, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 1.63 (s, 2H); IR (KBr, thin film, cm^{-1}): 3368, 3271, 3062, 3027, 2856, 1639, 1601, 1492, 1452, 995, 919, 701; HRMS (EI-TOF) *m/z*: [M]$^+$ calcd for $C_9H_{11}N^+$ 133.0886, found 133.0848, [M - H]$^+$ calcd for $C_9H_{10}N^+$ 132.0803, found 132.0803.

Using a known diazotransfer procedure,[60] the product was isolated (24 mg) in 44% yield. The material obtained from this method provided an identical ^{1}H NMR spectrum to a previous report.[34] An image of the ^{1}H NMR spectrum is supplied in the accompanying file. The data provided here is for comparison to the ^{15}N-labeled compound; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.44-7.43 (m, 2H), 7.38-7.35 (m, 2H), 7.32-7.28 (m, 1H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.27 (dt, *J* = 15.8, 6.6 Hz, 1H), 3.98 (d, *J* = 6.6 Hz, 2H); IR (KBr, thin film, cm^{-1}) 3029, 2923, 2100, 1493, 1448, 1236, 968; HRMS (EI-TOF) *m/z*: [M]$^+$ calcd for $C_9H_9N_3^+$ 159.0791, found 159.0747, [M - N_3]$^+$ calcd for $C_9H_9^+$ 117.0699, found 117.0693.

1-phenylprop-2-en-1-amine-^{15}N (**19**). Using the procedure above for compound **9** with phthalimide-^{15}N potassium salt (98 atom % ^{15}N), 2-(1-phenylallyl)isoindoline-1,3-dione-^{15}N was isolated (340 mg) in 74% yield as an oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31-7.28 (m, 1H), 6.68 (dddd, *J* = 17.8, 10.2, 7.6 Hz, $J_{N\text{-}H}$ = 1.1 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 5.40 (d, *J* = 10.2 Hz, 1H), 5.37 (d, *J* = 17.6 Hz, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 167.6 (d, $J_{C\text{-}N}$ = 11.9 Hz), 138.6, 134.3, 134.0, 131.9 (d, $J_{C\text{-}N}$ = 7.9 Hz), 128.6, 127.83, 127.77, 123.3, 119.1, 56.8 (d, $J_{C\text{-}N}$ = 8.6 Hz); ^{15}N NMR (93 MHz; $CDCl_3$, using ^{1}H-^{15}N HMBC) δ 171; IR (KBr, thin film, cm^{-1}) 3467, 3062, 3031, 1767, 1716, 1612, 1468, 1382, 1086; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{13}{}^{15}NO_2Na^+$ 287.0809, found 287.0816.

Using the phthalimide deprotection procedure used for the synthesis of **9**, ^{15}N-1-phenylprop-2-en-1-amine (**19**) was isolated (110 mg, 61%) as an oil and used without further purification: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.37-7.34 (m, 4H), 7.28-7.27 (m, 1H), 6.05 (ddd, *J* = 17.0, 9.1, 7.3 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 5.14 (d, *J* = 9.2 Hz, 1H), 4.55 (d, *J* = 7.1 Hz, 1H), 1.57 (s, 2H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 144.5, 142.3 (d, $J_{C\text{-}N}$ = 4.2 Hz), 128.6, 127.1, 126.6, 113.7 (d, $J_{C\text{-}N}$ = 6.6 Hz), 58.4 (d, $J_{C\text{-}N}$ = 16.3 Hz); ^{15}N NMR (93 MHz; $CDCl_3$, using ^{1}H-^{15}N HMBC) δ 38; IR (KBr, thin film, cm^{-1}) 3362, 3284, 3081, 3062, 3027, 2852, 1639, 1601, 1492, 1452, 918, 701; HRMS (EI-TOF) *m/z*: [M]$^+$ calcd for $C_9H_{11}{}^{15}N^+$ 134.0856, found 134.0829, calcd for $C_9H_{10}{}^{15}N^+$ [M -H]$^+$ 133.0778, found 133.0774.

^{15}N-(3-azidoprop-1-en-1-yl)benzene (**21**). Using the diazotransfer procedure for the synthesis of **9**, the product was isolated as an oil (45 mg, 80%): ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (m, 1H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.28 (dt, *J* = 15.7, 6.6 Hz, 1H), 3.98 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 136.0, 134.6, 128.7, 128.2, 126.6, 122.4, 53.0; ^{15}N NMR (93 MHz; $CDCl_3$, using ^{1}H-^{15}N HMBC) δ 214; IR (KBr, thin film, cm^{-1}) 3028, 2923, 2077, 1493, 1448, 968; HRMS (EI-TOF) *m/z*: [M]$^+$ calcd for $C_9H_9N_3^+$ 160.0761, found 160.0767, [M - N_3]$^+$ calcd for $C_9H_9^+$ 117.0699, found 117.0694.

^{15}N-Diethyl cinnamylphosphoramidate (**22**).To a solution of ^{15}N-(3-azidoprop-1-en-1-yl)benzene (**21**) (21 mg, 0.12 mmol) in THF (0.5 mL) was added triethyl phosphite (24 µL, 0.14 mmol). After 3 h, KOH (97 mg, 1.7 mmol) in water (0.25

mL) was added, and the solution was heated to 40 °C. After 2 h, the solution was heated to 80 °C. After an additional 2 h, the solution was poured over water (5 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil (29 mg, 86%) was used without further purification: ^{1}H-NMR (400 MHz; $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.28-7.23 (m, 1H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.0 Hz, 1H), 4.16-4.06 (m, 4H), 3.74-3.68 (m, 2H), 2.88 (td, $J_{H\text{-}P}$ = 17.0, 7.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 136.6, 131.0, 128.6, 127.64, 127.5 (d, $J_{C\text{-}P}$ = 7.3 Hz), 126.3, 62.4 (d, $J_{C\text{-}P}$ = 5.3 Hz), 43.5, 16.3 (d, $J_{C\text{-}P}$ = 7.1 Hz);^{31}P NMR (162 MHz; $CDCl_3$) δ 8.7; IR (KBr, thin film, cm^{-1}) 3246, 2983, 2932, 2906, 1702, 1450, 1238, 963; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{13}H_{20}NO_3PNa^+$ 292.1073, found 292.1067

3-phenylprop-2-en-1-amine. Using a known procedure,[61] 2-cinnamylisoindoline-1,3-dione was isolated (600 mg, 76%). The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file. The data provided here is for comparison to the ^{15}N-labeled compound:^{1}H NMR (400 MHz; $CDCl_3$) δ 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.39-7.37 (m, 2H), 7.33-7.24 (m, 3H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.28 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.47 (d, *J* = 6.5 Hz, 2H); IR (KBr, thin film, cm^{-1}) 3043, 3024, 1770, 1704, 1427, 1396, 1108, 727; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{13}NO_2Na^+$ 286.0838, found 286.0828.

Using the phthalimide deprotection procedure for the synthesis of **9**, the product was isolated (130 mg, 47%). The material obtained from this method provided an identical ^{1}H NMR spectrum to a previous report.[62]An image of the ^{1}H NMR spectrum is supplied in the accompanying file. The data provided here is for comparison to the ^{15}N-labeled compound: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.35 (dt, *J* = 15.7, 6.0 Hz, 1H), 3.50 (d, *J* = 5.8 Hz, 2H), 1.48 (s, 2H); IR (KBr, thin film, cm^{-1}) 3263, 3078, 2848, 1636, 1565, 1453, 965, 684; HRMS (EI-TOF) *m/z*: [M]$^+$ calcd for $C_9H_{11}N^+$ 133.0886, found 133.0879, [M – H]$^+$ calcd for $C_9H_{10}N^+$ 132.0808, found 132.0804.

(3-azidoprop-1-en-1-yl)benzene-^{15}N. Using the procedure for the synthesis of 2-cinnamylisoindoline-1,3-dione, with potassium ^{15}N-phthalimide, the product was isolated (510 mg, 89%): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.89 (t, *J* = 2.7 Hz, 2H), 7.74 (t, *J* = 2.7 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.32-7.29 (m, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.28 (dt, *J* = 15.1, 6.5 Hz, 1H), 4.47 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 168.0 (d, $J_{C\text{-}N}$ = 13.1 Hz), 136.2, 134.0, 133.8, 132.2 (d, $J_{C\text{-}N}$ = 7.5 Hz), 128.5, 127.9, 126.5, 123.3, 122.7, 39.7 (d, $J_{C\text{-}N}$ = 9.8 Hz); ^{15}N NMR (93 MHz; $CDCl_3$, using ^{1}H-^{15}N HMBC) δ 163; IR (KBr, thin film, cm^{-1}) 3024, 1769, 1702, 1469, 1381, 1095, 726; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{13}{}^{15}NO_2Na^+$ 287.0809, found 287.0801.

Using the phthalimide deprotection procedure for the synthesis of **9**, the product was isolated (42 mg, 56%) and used without further purification: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.35 (dt, *J* = 15.4, 6.3 Hz, 1H), 3.51 (d, *J* = 5.8 Hz, 2H), 1.84 (s, 2H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 137.2, 131.1, 129.5, 128.5, 127.3, 126.2, 44.3 (d, $J_{C\text{-}N}$ = 3.8 Hz); ^{15}N NMR (93 MHz; $CDCl_3$, using ^{1}H-^{15}N HMBC) δ 23; IR (KBr, thin film, cm^{-1}) 3258, 3021, 2838, 1632, 1565, 1435, 1395,957, 738; HRMS (EI-TOF) *m/z*: [M]$^+$ calcd for $C_9H_{11}{}^{15}N^+$ 134.0856, found 134.0845, [M – H]$^+$ calcd for $C_9H_{10}{}^{15}N^+$ 133.0778, found 133.0779.

Using the diazotransfer procedure for the synthesis of **9**, the product was isolated in (31 mg, 54%): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.31 (m, 1H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.28 (dt, *J* = 15.1, 6.5 Hz, 1H), 3.98 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 136.0, 134.6, 128.7, 128.2, 126.7, 122.4, 53.0 (d, $J_{C\text{-}N}$ = 4.1 Hz); ^{15}N NMR (93 MHz; $CDCl_3$, using ^{1}H-^{15}N HMBC) δ 73; IR (KBr, thin film, cm^{-1}) 3028, 2927, 2102, 1492, 1449, 1224, 968, 747, 693; HRMS (EI-TOF) *m/z*: [M]$^+$ calcd for $C_9H_9N_3^+$ 160.0761, found 160.0742, [M-N_3]$^+$ calcd for $C_9H_9^+$ 117.0699, found 117.0694

Diethyl cinnamylphosphoramidate-^{15}N. Using the procedure for the synthesis of **22**, the product was isolated (25 mg, 95%) and used without further purification; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.28-7.24 (m, 1H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.8 6.8 Hz, 1H), 4.11 (apparent q, *J* = 7.3 Hz, 4H), 3.71 (td, $J_{H\text{-}P}$ = 12.2, 7.0 Hz, 2H), 2.85 (apparent d, $J_{N\text{-}H}$ = 84 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 136.6, 131.0 (d, $J_{C\text{-}N}$ = 1.5 Hz), 128.6, 127.7, 127.6 (d, $J_{C\text{-}P}$ = 6.1 Hz), 126.3, 62.4 (d, $J_{C\text{-}P}$ = 5.4 Hz), 43.4 (d, $J_{C\text{-}N}$ = 8.3 Hz), 16.2 (d, $J_{C\text{-}P}$ = 7.1 Hz). (Note: $J_{C\text{-}P}$ vs $J_{C\text{-}N}$ were assigned by comparison to **22**); ^{15}N NMR (93 MHz; $CDCl_3$, using ^{1}H-^{15}N HMBC) δ 43; ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.68 (d, $J_{P\text{-}N}$ = 40.9 Hz); IR (KBr, thin film, cm^{-1}): 3211, 2981, 2904, 1444, 1237, 1031, 966; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{13}H_{20}{}^{15}NO_3PNa^+$ 293.1043; found 293.1047, [2M+Na]$^+$ calcd for $C_{26}H_{40}{}^{15}N_2O_6P_2Na^+$ 563.2195, found 563.2207.

2-(4-azidobut-2-en-2-yl)naphthalene. Using a known procedure[42] the product was isolated (520 mg, 65%). Characterization data for this compound has been reported. The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file.

5-azido-2,3,4,5-tetrahydro-1,1'-biphenyl (***rac*-30e**). Azides 30 were prepaired by a multi-step sequence that is outlined here. A procedure was adapted from a known method for the formation of tertiary alcohols and 3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol was isolated as an oil (1.38 g, 75%).[63] Characterization data for this compound has been reported. The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file.

To a solution of 3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (0.28 g, 1.6 mmol) in CH_2Cl_2 (7.0 mL) was added TMS-N_3 (0.41 mL, 3.2 mmol) and $Zn(OTf)_2$ (57 mg, 0.16 mmol) at room temperature. The vessel was sealed. After 20 min, the solution was quenched with triethylamine (0.5 mL) and MeOH (0.5 mL). The reaction mixture was filtered through basic alumina and washed with excess CH_2Cl_2. The resulting solution was concentrated under reduced pressure. Purification by column chromatography (gradient elution 0-15% EtOAc in hexanes) afforded ***rac*-30e** as an oil (0.25 g, 1.3 mmol, 79%). Characterization data for this compound has

been reported.[42] The material obtained from this method provided an identical ^{1}H NMR. An image of the ^{1}H NMR spectrum is supplied in the accompanying file.

(4-azidopent-2-en-2-yl)benzene (**26**). Following the azide formation procedure above for compound **30e**, the product (0.24 g, 57%) was isolated as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) (*E*-isomer) δ 7.47 – 7.42 (m, 2H), 7.40 – 7.35 (m, 2H), 7.33 – 7.30 (m, 1H), 5.73 (dq *J* = 9.0, 1.5 Hz, 1H), 4.49 (dq, *J* = 9.0, 6.6 Hz, 1H), 2.17 (d, *J* = 1.4 Hz, 3H), 1.37 (d, *J* = 6.6 Hz, 3H); ^{1}H NMR (500 MHz, $CDCl_3$) (*Z*-isomer) δ 7.50 – 7.15 (m, 5H), 5.47 (dq, *J* = 9.9, 1.6 Hz, 1H), 4.04 (dq, *J* = 9.9, 6.6 Hz, 1H), 2.12 (d, *J* = 1.4 Hz, 4H), 1.24 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (*E*-isomer) δ 142.5, 139.3, 128.3, 127.6, 126.7, 126.0, 55.5, 20.7, 16.6; ^{13}C NMR (125 MHz, $CDCl_3$) (*Z*-isomer) δ 141.5, 140.7, 128.4, 127.7, 127.3, 126.2, 56.0, 25.7, 20.8; IR (KBr, thin film, cm^{-1}) 2979, 2096, 1444, 1231; HRMS (CI-TOF) *m/z*: $[M - N_3]^+$ calcd for $C_{11}H_{13}^+$ 145.1012, found 145.1005.

5-azido-4'-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (***rac*-30a**). Following the procedure above for compound **30e,** 4'-methoxy-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (3.0 g, 47%) was isolated as a waxy solid. Characterization data for this compound has been reported.[63] The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file. With slight modifications, $Cu(hfac)_2$ instead of $Zn(OTf)_2$ with ice bath cooling, the product ***rac*-30a** (0.58 g, 86%) was isolated as a waxy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.07 – 6.01 (m, 1H), 4.12 – 4.10 (m, 1H), 3.84 (s, 3H), 2.53 – 2.48 (m, 1H), 2.44 – 2.39 (m, 1H), 2.00 – 1.91 (m, 2H), 1.84 – 1.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 141.8, 133.5, 126.6, 119.8, 113.7, 57.0, 55.3, 28.4, 27.4, 19.8; IR (KBr, thin film, cm^{-1}) 2935, 2836, 2089, 1607, 1513, 1251, 1037; HRMS (CI-TOF) *m/z*: $[M - N_3]^+$ calcd for $C_{13}H_{15}O^+$ 187.1117, found 187.1110.

5-azido-4'-methyl-2,3,4,5-tetrahydro-1,1'-biphenyl (***rac*-30b**). Following the above procedure for compound **30e,** 4'-methyl-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (3.9 g, 68%) was isolated as an oil. Characterization data for this compound has been reported.[63] The material obtained from this method provided and identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file. The product ***rac*-30b** (0.53 g, 71%) was isolated as an oil: ^{1}H NMR (400 MHz, CD_3CN) δ 7.41 – 7.34 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.10 (dt, *J* = 3.8, 1.8 Hz, 1H), 4.18 – 4.14 (m, 1H), 2.56 – 2.36 (m, 2H), 2.35 (s, 3H), 1.95 – 1.85 (m, 2H), 1.83 – 1.71 (m, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 142.1, 138.1, 137.7, 129.0, 125.2, 120.5, 56.9, 28.0, 26.9, 20.1, 19.5; IR (KBr, thin film, cm^{-1}) 2939, 2864, 2093, 1235; HRMS (CI-TOF) *m/z*: $[M - N_3]^+$ calcd for $C_{13}H_{15}^+$ 171.1168, found 171.1166.

5-azido-4'-(tert-butyl)-2,3,4,5-tetrahydro-1,1'-biphenyl (***rac*-30c**). Following the procedure above for compound **30e,** 4'-(tert-butyl)-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (1.3 g, 72%) was isolated as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (apparent d, *J* = 8.6 Hz, 2H), 7.39 (apparent d, *J* = 8.6 Hz, 2H), 6.05 (dt, *J* = 10.0, 3.7 Hz, 1H), 5.82 (d, *J* = 10.1 Hz, 1H), 2.22 – 2.07 (m, 2H), 2.06 – 1.99 (m, 1H), 1.91 (td, *J* = 10.0, 3.1 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.69 – 1.61 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 144.8, 132.4, 130.4, 125.2, 125.0, 72.0, 39.4, 34.4, 31.4, 25.1, 19.3; IR (KBr, thin film, cm^{-1}) 3050, 2817, 1571, 1401, 1161; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{22}ONa^+$ 253.1563, found 253.1574. Using ice bath cooling, ***rac*-30c** (0.26 g, 79%) was isolated as an oil: ^{1}H NMR (400 MHz, CD_3CN) δ 7.42 (s, 4H), 6.12 (dt, *J* = 3.8, 1.8 Hz, 1H), 4.19 – 4.13 (m, 1H), 2.58 – 2.46 (m, 1H), 2.46 – 2.36 (m, 1H), 1.95 – 1.85 (m, 2H), 1.84 – 1.67 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN) δ 150.8, 142.1, 138.1, 125.3, 125.1, 120.6, 56.9, 34.1, 30.5, 28.0, 26.9, 19.5; IR (KBr, thin film, cm^{-1}) 2960, 2866, 2093, 1162; HRMS (CI-TOF) *m/z*: $[M - N_3]^+$ calcd for $C_{16}H_{21}^+$ 213.1638, found 213.1631.

5-azido-4'-fluoro-2,3,4,5-tetrahydro-1,1'-biphenyl (***rac*-30d**). Following the procedure above for compound **30e,** 4'-fluoro-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (0.83 g, 68%) was isolated as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H), 7.02 (apparent triplet, *J* = 7.02, 2H), 6.04 (dt, *J* = 10.1, 3.7 Hz, 1H), 5.76 (d, *J* = 10.0, 1H), 2.23 (s, 1H), 2.19 – 2.03 (m, 2H), 2.02 – 1.92 (m, 1H), 1.89 – 1.72 (m, 2H), 1.66 – 1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (d, $J_{C\text{-}F}$ = 243.3 Hz), 143.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 132.1, 130.9, 127.2 (d, $J_{C\text{-}F}$ = 7.9 Hz), 114.7 (d, $J_{C\text{-}F}$ = 21.1 Hz), 71.9, 39.7, 25.0, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.5; IR (KBr, thin film, cm^{-1}) 3378, 2938, 1601, 1508, 1221, 1175, 833; HRMS (EI-TOF) *m/z*: $[M]^+$ calcd for $C_{12}H_{13}FO^+$ 192.0945, found 192.0951. The product ***rac*-30d** (0.17 g, 79%) was isolated as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 2H), 7.11 – 7.00 (m, 2H), 6.05 (dt, *J* = 3.6, 1.8 Hz, 1H), 4.14 – 4.08 (m, 1H), 2.55 – 2.35 (m, 2H), 2.03 – 1.90 (m, 2H), 1.88 – 1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5 (d, $J_{C\text{-}F}$ = 245.3 Hz), 141.5, 137.1 (d, $J_{C\text{-}F}$ = 3.4 Hz), 127.1 (d, $J_{C\text{-}F}$ = 7.8 Hz), 121.4 (d, $J_{C\text{-}F}$ = 1.5 Hz), 115.2 (d, $J_{C\text{-}F}$ = 21.2 Hz), 56.8, 28.2, 27.5, 19.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -114.6; IR (KBr, thin film, cm^{-1}) 2940, 2096, 1601, 1510, 1231, 1161, 826; HRMS (CI-TOF) *m/z*: $[M - N_3]^+$ calcd for $C_{12}H_{12}F^+$ 175.0918, found 175.0924.

5-azido-4'-(trifluoromethyl)-2,3,4,5-tetrahydro-1,1'-biphenyl (***rac*-30f**). Following the procedure above for compound **30e,** 4'-(trifluoromethyl)-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (1.4 g, 78%) was isolated as an oil. Characterization data for this compound has been reported.[63] The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file. The product ***rac*-30f** (0.42 g, 83%) was isolated as an oil: ^{1}H NMR (500 MHz, CD_3CN) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 6.24 (dt, *J* = 3.8, 1.8 Hz, 1H), 4.23 – 4.17 (m, 1H), 2.56 – 2.50 (m, 1H), 2.47 – 2.41 (m, 1H), 2.05 – 1.95 (m, 1H), 1.95 – 1.86 (m, 1H), 1.84 – 1.72 (m, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 144.9, 141.0, 128.8 (q, $J_{C\text{-}F}$ = 32.0 Hz), 126.0, 125.8, 125.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.5 (q, $J_{C\text{-}F}$ = 269.4 Hz), 56.7, 27.8, 26.8, 19.4; ^{19}F NMR (471 MHz, CD_3CN) δ -63.0; IR (KBr, thin film, cm^{-1}) 2934, 2836, 2091, 1606, 1513, 1250, 1181; HRMS (CI-TOF) *m/z*: $[M - N_3]^+$ calcd for $C_{13}H_{12}F_3^+$ 225.0886, found 225.0875.

5-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (**32e**). This procedure was adapted from a known method.[64] To a solution of 3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (189 mg, 1.08 mmol) in MeCN (5 mL) and MeOH (1 mL) was added salicylic acid (15 mg, 0.11 mmol). The resulting solution was heated at 40 °C. After 18 h, the reaction was diluted with ethyl acetate and quenched by the addition of saturated aqueous $NaHCO_3$. The resulting solution was extracted with

EtOAc (3 × 10 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (gradient elution 0-20% EtOAc in hexanes) afforded the product (150 mg, 0.797 mmol, 73%) as an oil. Characterization data for this compound has been reported.[64] The material obtained from this method provided an identical ^{1}H NMR spectrum. An image of the ^{1}H NMR spectrum is supplied in the accompanying file.

4',5-dimethoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (**32a**). Following the above procedure for compound **32e** at room temperature**,** the product **32a** (0.16 g, 81%) was isolated as a waxy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.13 (dt, *J* = 3.6, 1.7 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.81 (s, 3H), 3.45 (s, 3H), 2.52 – 2.42 (m, 1H), 2.42 – 2.32 (m, 1H), 2.00 – 1.82 (m, 2H), 1.81 – 1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 139.8, 134.1, 126.5, 122.7, 113.6, 75.0, 55.8, 55.2, 27.7, 27.6, 19.7; IR (KBr, thin film, cm^{-1}) 2935, 2834, 1607, 1513, 1462, 1250, 1181, 1097, 1037, 822; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$calcd for $C_{14}H_{18}O_2Na^+$ 241.1199, found 241.1206.

5-methoxy-4'-methyl-2,3,4,5-tetrahydro-1,1'-biphenyl (**32b**). Following the above procedure for compound **32e**, the product **32b** (0.16 g, 76%) was isolated as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (apparent d, *J* = 8.2 Hz, 2H), 7.15 (apparent d, *J* = 7.9 Hz, 2H), 6.16 (dt, *J* = 3.5, 1.8 Hz, 1H), 3.98 – 3.94 (m, 1H), 3.45 (s, 3H), 2.53 – 2.32 (m, 2H), 2.37 (s, 3H), 2.00 – 1.85 (m, 2H), 1.82 – 1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 138.7, 137.0, 128.9, 125.3, 123.5, 75.0, 55.8, 27.7, 27.5, 21.1, 19.6; IR (KBr, thin film, cm^{-1}) 2935, 2861, 1513, 1348, 1098, 808; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{18}ONa^+$ 225.1250, found 225.1253.

4'-(tert-butyl)-5-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (**32c**). Following the above procedure for compound **32e**, the product **32c** (0.18 g, 87%) was isolated as an oil: ^{1}H NMR (400 MHz, CD_3CN): δ 7.40 (s, 4H), 6.19 – 6.13 (m, 1H), 3.96 – 3.89 (m, 1H), 3.38 (s, 3H), 2.51 – 2.41 (m, 1H), 2.41 – 2.32 (m, 1H), 1.98 – 1.86 (m, 2H), 1.73 – 1.60 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN): δ 150.3, 139.4, 138.7, 125.2, 125.0, 124.0, 74.8, 55.0, 34.1, 30.6, 27.5, 27.3, 19.5; IR (KBr, thin film, cm^{-1}): 2947, 2866, 1159, 1104; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{24}ONa^+$ 267.1719, found 267.1721.

4'-fluoro-5-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (**32d**). Following the above procedure for compound **32e**, the product **32d** (0.15 mg, 82%) was isolated as a waxy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H), 7.02 (apparent t, *J* = 8.7 Hz, 2H), 6.13 (dt, *J* = 3.6, 1.8 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.45 (s, 3H), 2.52 – 2.41 (m, 1H), 2.39 – 2.31 (m, 1H) 2.01 – 1.87 (m, 2H), 1.81 – 1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, $J_{C\text{-}F}$ = 244.6 Hz), 139.5, 137.7 (d, $J_{C\text{-}F}$ = 3.3 Hz), 127.0 (d, $J_{C\text{-}F}$ = 7.9 Hz), 124.3, 115.0 (d, $J_{C\text{-}F}$ = 21.1 Hz), 74.9, 55.9, 27.8, 27.4, 19.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.4; IR (KBr, thin film, cm^{-1}) 2938, 2818, 1601, 1509, 1099, 825; HRMS (EI-TOF) *m/z*: $[M]^+$ calcd for $C_{13}H_{15}FO^+$ 206.1101, found 206.1093.

5-methoxy-4'-(trifluoromethyl)-2,3,4,5-tetrahydro-1,1'-biphenyl (**32f**). Following the above procedure for compound **32e** using 0.5 equiv. salicylic acid, the product **32f** (0.10 g, 52%) was isolated as a waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 6.25 (dt, *J* = 3.5, 1.8 Hz, 1H), 4.01 – 3.94 (m, 1H), 3.46 (s, 3H), 2.54 – 2.33 (m, 2H), 2.03 – 1.88 (m, 2H), 1.81 – 1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.3, 129.2 (q, 32.2 Hz), 126.5, 125.7 , 125.2 (q, 3.7 Hz), 124.3 (q, 270.1 Hz), 74.8, 56.0, 27.6, 27.3, 19.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5; IR (KBr, thin film, cm^{-1}) 2936, 2820, 1615, 1326, 1122, 1070; HRMS (EI-TOF) *m/z*: $[M]^+$ calcd for $C_{14}H_{15}F_3O^+$ 256.1070, found 256.1078.

Computational Details: All calculations were performed at the DFT level using the M06-2X density functional[44] as implemented in Gaussian09.[65] The 6-31G(d) basis set was used for all atoms.[66,67] The structure of reactants, intermediates, products, and transition states were fully optimized with the grid=ultrafine option in gas phase and in $CHCl_3$ (ε = 4.71) and MeOH (ε = 32.61) using the SMD approach.[43] Transition states were identified by having one imaginary frequency in the Hessian matrix. It was confirmed that transition states connect with the corresponding intermediates. All frequencies below 50 cm^{-1} were replaced by 50 cm^{-1} when accounting for thermal contributions to vibrational partition functions.[68] Single-point calculations were performed using the 6-311+G(2df,p) basis set.[69,70] Final values are reported as free energies computed at the specified temperature and 1 M standard state.

ASSOCIATED CONTENT

Supporting Information. Spectral images, kinetic data, HPLC traces, and calculated coordinates. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Lutz, R. P. Catalysis of the Cope and Claisen Rearrangements. *Chem. Rev.* **1984**, *84*, 206–243.

(2) Nakai, T.; Mikami, K. [2,3]-Wittig Sigmatropic

Rearrangements in Organic Synthesis. *Chem. Rev.* **1986**, *86*, 885–902.
(3) Wilson, S. R.; Price, M. F. The Ester Enolate Carroll Rearrangment. *J. Org. Chem.* **1984**, *49*, 722–725.
(4) Kantor, S. W.; Hauser, C. R. Rearrangements of Benzyltrimethylammonium Ion and Related Quaternary Ammonium Ions by Sodium Amide Involving Migration into the Ring. *J. Am. Chem. Soc.* **1951**, *73*, 4122–4131.
(5) Evans, D. A.; Andrews, G. C. Allylic Sulfoxides: Useful Intermediates in Organic Synthesis. *Acc. Chem. Res.* **1974**, *7*, 147–155.
(6) Albini, A. Synthetic Utility of Amine N-Oxides. *Synthesis* **1992**, 263–277.
(7) Overman, L. E. Allylic and Propargylic Imidic Esters in Organic Synthesis. *Acc. Chem. Res.* **1980**, *13*, 218–224.
(8) Nubbemeyer, U. Recent Advances in Asymmetric [3 ,3]-Sigmatropic Rearrangements. *Synthesis* **2003**, *7*, 961–1008.
(9) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. Toward a Symphony of Reactivity : Cascades Involving Catalysis and Sigmatropic Rearrangements. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 2556–2591.
(10) Editors, G.; Erik, P.; Davies, H. M. L. [3,3]-Sigmatropic Rearrangements: Recent Applications in the Total Synthesis of Natural Products. *Chem. Soc. Rev.* **2009**, *38*, 3133–3148.
(11) Gagneuz, A.; Winstein, S.; Young, W. G. Rearrangement of Allyl Azides. *J. Am. Chem. Soc.* **1960**, *82*, 5956–5957.
(12) Doering, W. V. E.; Roth, W. R. Thermal Rearrangements. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 115–122.
(13) Overman, L. E.; Fredrick, K. M. Palladium (II)-Catalyzed Rearrangement of Allylic Acetates. *Tetrahedron Lett.* **1979**, *20*, 321–234.
(14) Marion, N.; Gealageas, R.; Nolan, S. P. [(NHC)Au(I)]-Catalyzed Rearrangement of Allyic Acetates. *Org. Lett.* **2007**, *9*, 2653–2656.
(15) Kreiman, H. W.; Batali, M. E.; Jamieson, C. S.; Lyon, M. A.; Duncan, J. A. CASSCF Calculations Reveal Competitive Chair (Pericyclic) and Boat (Pseudopericyclic) Transition States for the [3,3] Sigmatropic Rearrangement of Allyl Esters. *J. Org. Chem.* **2018**, *83*, 1717–1726.
(16) VanderWerf, C. A.; Heisler, R. V; McEwen, W. E. The Reaction of Sodium Azide with Some Representative Epoxides. *J. Am. Chem. Soc.* **1954**, *76*, 1231–1235.
(17) VanderWerf, C. A.; Heasley, V. L. Studies on the Preparation and Rearrangements of Allylic Azides1. *J. Org. Chem.* **1966**, *31*, 3534–3537.
(18) Le Noble, W. J. The Effect of Pressure on the Equilibration of α- and γ-Methylallyl Azide. *J. Phys. Chem.* **1963**, *67*, 2451–2453.
(19) Padwa, A.; Sa, M. M. Intramolecular O-H Insertion Reaction of Azido Substituted Diazoesters and Its Relevance to the Mechanism of the Ailylic Azide Rearrangement. *Tetrahedron Lett.* **1997**, *38*, 5087–5090.
(20) Gagnon, D.; Lauzon, S.; Godbout, C.; Spino, C. Sterically Biased 3,3-Sigmatropic Rearrangement of Azides: Efficient Preparation of Nonracemic α-Amino Acids and Heterocycles. *Org. Lett.* **2005**, *7*, 4769–4771.
(21) Jabbari, A. Transition States and Activation Barriers for [3,3]-Sigmatropic Shift of Allyl Azides. *Org. Chem. J.* **2010**, *1*, 6–14.
(22) Kang, H.; Kang, Y. K. Allylic Azide Rearrangements Investigated by Density Functional Theory Calculations. *Bull. Korean Chem. Soc.* **2017**, *38*, 1419–1426.
(23) Porta, E. O. J.; Vallejos, M. M.; Bracca, A. B. J.; Labadie, G. R. Experimental and Theoretical Studies of the [3,3]-Sigmatropic Rearrangement of Prenyl Azides. *RSC Adv.* **2017**, *7*, 47527–47538.
(24) Askin, D.; Angst, C.; Danishefsky, S. A Total Syntheis of N-Acetylactinobolamine. *J. Org. Chem.* **1985**, *50*, 5005–5007.
(25) Liu, R.; Gutierrez, O.; Tantillo, D. J.; Aubé, J. Stereocontrol in a Combined Allylic Azide Rearrangement and Intramolecular Schmidt Reaction. *J. Am. Chem. Soc.* **2012**, *134*, 6528–6531.
(26) Vekariya, R. H.; Liu, R.; Aubé, J. A Concomitant Allylic Azide Rearrangement/Intramolecular Azide-Alkyne Cycloaddition Sequence. *Org. Lett.* **2014**, *16*, 1844–1847.
(27) Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. The Allylic Azide Rearrangement: Achieving Selectivity. *J. Am. Chem. Soc.* **2005**, *127*, 13444–13445.
(28) Craig, D.; Harvey, J. W.; O'Brien, A. G.; White, A. J. P. Claisen Rearrangements of Equilibrating Allylic Azides. *Org. Biomol. Chem.* **2011**, *9*, 7057–7061.
(29) Moynihan, L.; Chadda, R.; Mcardle, P.; Murphy, P. V. Allylic Azide Rearrangement in Tandem with Huisgen Cycloaddition for Stereoselective Annulation: Synthesis of C‐Glycosyl Iminosugars. *Org. Lett.* **2015**, *17*, 6226–6229.
(30) Mcardle, P.; Murphy, P. V. Allylic Azide Rearrangement in Tandem with Intramolecular Huisgen Cycloaddition for Iminosugar and Glycomimetic Synthesis : Functionalized Piperidine , Pyrrolidine , and Pyrrolotriazoles from D -Mannose. *Synthesis* **2017**, *49*, 2138–2152.
(31) Packard, M. H.; Cox, J. H.; Suding, V. P.; Topczewski, J. J. The Effect of Proximal Functionality on the Allylic Azide Equilibrium. *Eur. J. Org. Chem.* **2017**, 6365–6368.
(32) Ott, A. A.; Goshey, C. S.; Topczewski, J. J. Dynamic Kinetic Resolution of Allylic Azides via Asymmetric Dihydroxylation. *J. Am. Chem. Soc.* **2017**, *139*, 7737.
(33) Porter, M. R.; Shaker, R. M.; Calcanas, C.; Topczewski, J. J. Stereoselective Dynamic Cyclization of Allylic Azides : Synthesis of Tetralins, Chromanes, and Tetrahydroquinolines. *J. Am. Chem. Soc.* **2018**, *140*, 1211–1214.
(34) Hassner, A.; Fibiger, R.; Andisik, D. Synthetic Methods. 19. Lewis Acid Catalyzed Conversion of Alkenes and Alcohols to Azides. *J. Org. Chem.* **1984**, *49*, 4237–4244.
(35) Carlson, A. S.; Calcanas, C.; Brunner, R. M.; Topczewski, J. J. Regiocontrolled Wacker Oxidation of Cinnamyl Azides. *Org. Lett.* **2018**, *20*, 1604–1607.
(36) Panek, J.; Yang, M.; Muler, I. Sequential Diastereoselective Addition and Allylic Azide Isomerization of Syn- and Anti-α-Azido-β-(Dimethylphenylsilyl)-(E)-Hex-4-Enoates with Acetals: Asymmetric Synthesis of γ- Hydroxy-α-Amino Acid Synthons. *J. Org. Chem.* **1992**, *54*, 4063–4064.
(37) Doherty, W.; Evans, P. Aminooxylation Horner-Wadsworth-Emmons Sequence for the Synthesis of Enantioenriched γ-Functionalized Vinyl Sulfones. *J. Org. Chem.* **2016**, *81*, 1416–1424.
(38) Cope, A. C.; Hardy, E. M. The Introduction of Substituted Vinyl Groups. V. A Rearrangement Involving the Migration of an Allyl Group in a Three-Carbon System'. *J. Am. Chem. Soc.* **1940**, *62*, 441–444.
(39) Safi, M.; Fahrang, R.; Sinou, D. Palladium(0)-Catalyzed Azidation of Allyl Esters with Trimethylsilyl Azide. *Tetrahedron Lett.* **1990**, *31*, 527–530.
(40) Maag, H.; J, R. M. R. An Allylic Azide Route to 4'-Azido Carbocyclic Nucleosides. Synthesis of (±)-(1'α,2'α,3'β)- and (±)-(1'α,2'β,3'β)-1-[1-Azido-2-Hydroxy-1-(Hydroxymethyl)-3-Cyclopentyl]Thymine. *J. Org. Chem.* **1992**, *57*, 5823–5831.
(41) Banert, K.; Hagedorn, M.; Liedtke, C.; Melzer, A.; Schöffler, C. Reactions of Unsaturated Azides, 12 Azido-1,2,3-Triphenylpropenes of Varying Stabilities: A Corrigendum of Structure Assignment. *Eur. J. Org. Chem.* **2000**, 257–267.
(42) Goswami, P. P.; Suding, V. P.; Carlson, A. S.; Topczewski, J. J. Direct Conversion of Aldehydes and Ketones into Azides by Sequential Nucleophilic Addition and Substitution. *Eur. J. Org. Chem.* **2016**, 4805–4809.
(43) Marenich, A. V; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B.* **2009**, *113*, 6378–6396.
(44) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Function. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
(45) Sharma, S.; Rajale, T.; Unruh, D. K.; Birney, D. M. Competitive Pseudopericyclic [3,3]- and [3,5]-Sigmatropic Rearrangements of Trichloroacetimidates. *J. Org. Chem.* **2015**, *80*, 11734–11743.

(46) Sharma, S.; Rajale, T.; Cordes, D. B.; Hung-Low, F.; Birney, D. M. Experimental and Computational Studies on the [3,3]- and [3,5]- Sigmatropic Rearrangements of Acetoxycyclohexadienones: A Non- Ionic Mechanism for Acyl Migration. *J. Am. Chem. Soc.* **2013**, *135*, 14438.

(47) Klepper, F.; Jahn, E. M.; Hickmann, V.; Carell, T. Synthesis of the Transfer-RNA Nucleoside Queuosine by Using a Chiral Allyl Azide Intermediate. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 2325–2327.

(48) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill, Inc: New York, 1995.

(49) Yaragorla, S.; Dada, R.; Pareek, A.; Singh, G. A Calcium Catalysed Regioselective (5-Exo Dig) Tandem Process for the Synthesis of Fully Substituted Furans. *RSC Adv.* **2016**, *6*, 28865–28870.

(50) Heydenreuter, W.; Kunold, E.; Sieber, S. A. Alkynol Natural Products Target ALDH2 in Cancer Cells by Irreversible Binding to the Active Site. *Chem. Commun.* **2015**, *51*, 15784–15787.

(51) Rodríguez, S.; Kneeteman, M.; Izquierdo, J.; López, I.; González, F. V. V.; Peris, G. Diastereoselective Synthesis of γ-Hydroxy-α,β-Epoxyesters and Their Conversion into β-Hydroxy α-Sulfenyl γ-Butyrolactones. *Tetrahedron* **2006**, *62*, 11112–11123.

(52) Villeneuve, K.; Tam, W. Construction of Isochromenes via a Ruthenium-Catalyzed Reaction of Oxabenzonorbornenes with Propargylic Alcohols. *Organometallics* **2007**, *26*, 6082–6090.

(53) Pace, V.; Castoldi, L.; Alcántara, A. R.; Holzer, W. Robust Eco-Friendly Protocol for the Preparation of γ-Hydroxy-α,β-Acetylenic Esters by Sequential One-Pot Elimination–addition of 2-Bromoacrylates to Aldehydes Promoted by LTMP in 2-MeTHF. *Green Chem.* **2012**, *14*, 1859.

(54) Shen, M.; Tu, Y.; Xie, G.; Niu, Q.; Mao, H.; Xie, T.; Flowers, R. A.; Lv, X.; Wang, X. Allylsamarium Bromide-Mediated Cascade Cyclization of Homoallylic Esters. Synthesis of 2-(2-Hydroxyalkyl)Cyclopropanols and 2-(2-Hydroxyethyl)Bicyclo[2.1.1]Hexan-1-Ols. *J. Org. Chem.* **2015**, *80*, 52–61.

(55) Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. Palladium(0)-Catalyzed Azidation of Allyl Esters. Selective Synthesis of Allyl Azides, Primary Allylamines, and Related Compounds. *J. Org. Chem.* **1989**, *54*, 3292–3303.

(56) Dekamin, M. G.; Karimi, Z. Activation of Trimethylsilyl Cyanide by Potassium Phthalimide for Facile Synthesis of TMS-Protected Cyanohydrins. *J. Organomet. Chem.* **2009**, *694*, 1789–1794.

(57) Raskatov, J. A.; Spiess, S.; Gnamm, C.; Brödner, K.; Rominger, F.; Helmchen, G. Ir-Catalysed Asymmetric Allylic Substitutions with Cyclometalated (Phosphoramidite)Ir Complexes - Resting States, Catalytically Active (π-Allyl)Ir Complexes and Computational Exploration. *Chem. Eur. J.* **2010**, *16*, 6601–6615.

(58) Wang, H.; Matsuhashi, H.; Doan, B. D.; Goodman, S. N.; Ouyang, X.; Clark, W. M. Large-Scale Synthesis of SB-462795, a Cathepsin K Inhibitor: The RCM-Based Approaches. *Tetrahedron* **2009**, *65*, 6291–6303.

(59) Kresze, G.; Milnsterer, H. Bis(Methoxycarbonyl)Sulfur Diimide, a Convenient Reagent for the Allylic Amination of Alkenes. *J. Org. Chem.* **1983**, *48*, 3561–3564.

(60) Troyer, T. L.; Muchalski, H.; Hong, K. B.; Johnston, J. N. Origins of Selectivity in Brønsted Acid-Promoted Diazoalkane-Azomethine Reactions (The Aza-Darzens Aziridine Synthesis). *Org. Lett.* **2011**, *13*, 1790–1792.

(61) Lee, H. S.; Kim, K. H.; Kim, S. H.; Kim, J. N. Palladium-Catalyzed, Chelation-Assisted Stereo- and Regioselective Synthesis of Tetrasubstituted Olefins by Oxidative Heck Arylation. *Adv. Synth. Catal.* **2012**, *354*, 2419–2426.

(62) Dhami, A.; Mahon, M. F.; Lloyd, M. D.; Threadgill, M. D. 4-Substituted 5-Nitroisoquinolin-1-Ones from Intramolecular Pd-Catalysed Reaction of N-(2-Alkenyl)-2-Halo-3-Nitrobenzamides. *Tetrahedron* **2009**, *65*, 4751–4765.

(63) Li, J.; Tan, C.; Gong, J.; Yang, Z. Palladium-Catalyzed Oxidative Rearrangement of Tertiary Allylic Alcohols to Enones with Oxygen in Aqueous Solvent. *Org. Lett.* **2014**, *16*, 5370–5373.

(64) Mccubbin, J. A.; Voth, S.; Krokhin, O. V. Mild and Tunable Benzoic Acid Catalysts for Rearrangement. *J. Org. Chem.* **2011**, *76*, 8537–8542.

(65) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; B, M.; Petersson, G. A.; et al. Gaussian 09 Revision D.01. Gaussian Inc.: Wallingford CT 2009.

(66) Hehre, W. J.; Ditchfield, K.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian-Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1972**, *56*, 2257–2261.

(67) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XXIII. A Polarization-Type Basis Set for Second-Row Elements. *J. Chem. Phys.* **1982**, *77*, 3654–3665.

(68) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Use of Solution-Phase Vibrational Frequencies in Continuum Models for the Free Energy of Solvation. *J. Phys. Chem. B* **2011**, *115*, 14556–14562.

(69) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions. *J. Chem. Phys.* **1980**, *72*, 650–654.

(70) McLean, A. D.; Chandler, G. S. Contracted Gaussian Basis Sets for Molecular Calculations. I. Second Row Atoms, Z=11-18. *J. Chem. Phys.* **1980**, *72*, 5639–5648.