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Letter

Pd-Catalyzed Rearrangement of *N*-Alloc-*N*-allyl Ynamides *via* Auto-Tandem Catalysis: Evidence for Reversible C−N Activation and Pd(0)-Accelerated Ketenimine Aza-Claisen Rearrangement

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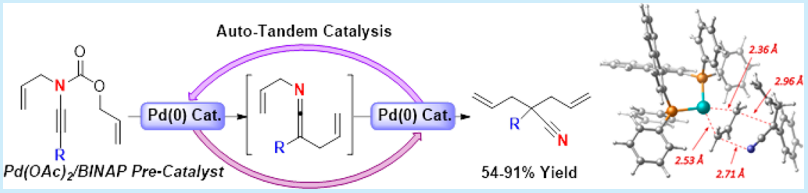
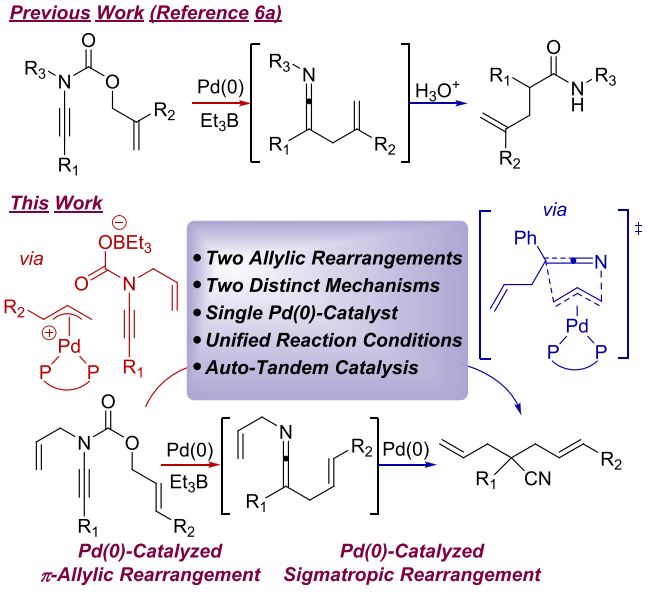


ABSTRACT: An auto-tandem catalytic double allylic rearrangement of *N*-alloc-*N*-allyl ynamides was developed. This reaction proceeds through two separate and distinct catalytic cycles with both decarboxylative Pd−π-allyl and Pd(0)-promoted aza-Claisen rearrangements occurring. A detailed mechanistic study supported by computations highlights these two separate mechanisms. Previously unreported reversible C−N ionization and a Pd(0)-catalyzed [3,3]-sigmatropic rearrangement were discovered. This study provides new reaction pathways for both π-allyl and sigmatropic rearrangements.

The ability of a single catalytic entity to perform two or more mechanistically distinct reactions is a powerful strategy in synthesis. This approach, termed auto-tandem catalysis (ATC) by Fogg and dos Santos,[1] can provide a very direct and atom-efficient route to complex molecules.[2] Their definition of an ATC reaction requires a single catalyst, which is present at the reaction outset, to proceed through two different mechanistic cycles without the need for a chemical trigger to alternate between these mechanisms.[3] As such, these are mechanistically distinct from cascade reactions that intercept catalyst-bound intermediates and/or use bifunctional/cooperative catalysts.[4] The use of the ATC approach is especially impactful when sequential C−C bond-forming events occur during the reactions.[5] Importantly, ATCs allow the *in situ* formation and use of unstable or sensitive organic intermediates that would not be amenable to a linear synthetic approach. Aside from their synthetic utility, these reactions are mechanistically intriguing, with a single catalyst providing orthogonal reactivity between substrates and intermediates in a single reaction sequence. Herein we report the development of a new ATC reaction that performs both π-allyl and sigmatropic allylic rearrangements mediated by a single palladium(0) catalyst. Of particular note are the previously unreported Pd(0)-catalyzed aza-Claisen rearrangement and reversible π-allylic ionization of neutral allyl amines.

We previously disclosed the Pd-catalyzed decarboxylative rearrangement of *N*-alloc ynamides to form ketenimines, which were trapped with nucleophiles (Scheme 1).[6,7] We envisaged that if *N*-alloc-*N*-allyl ynamides were utilized, two sequential

Scheme 1. Rearrangement of *N*-Alloc-*N*-allyl Ynamides in C−C Bond-Forming ATC Reactions



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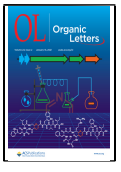
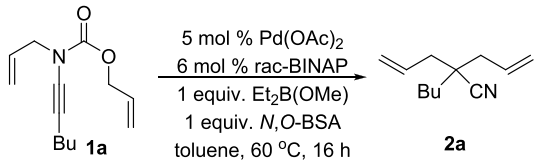


palladium-catalyzed allylic rearrangements could occur through an *N*-allyl ketenimine intermediate. This approach would provide a unique method for the synthesis of quaternary nitriles bearing two independent allyl groups.[8] More importantly, we hypothesized that both allylic rearrangements could be performed by a single palladium catalyst through two distinct mechanisms, one π-allylic and one sigmatropic. Although the uncatalyzed thermal ketenimine aza-Claisen rearrangement has been previously reported,[9] we reasoned that a catalyst-accelerated variant could be developed. While electrophilic Pd(II) complexes have been reported to promote a range of sigmatropic rearrangements,[10] these proceed *via* a π-Lewis acidic pathway, requiring either a strongly nucleophilic migrating group or a strongly electrophilic palladium π-Lewis acid.[11] Tunge has reported a suite of Pd-catalyzed π-allylic rearrangements to form nitriles; these generate π-allyl intermediates and nitrile α-anions *in situ* (*via* decarboxylative and deacylative routes).[12] While the use of protonated allyl amines as π-allyl donors has been established,[13] the activation of neutral allyl amines has not been reported and represents a new mode of reactivity. The rearrangement of butyl derivative **1a** was optimized with a $Pd(OAc)_2$/BINAP catalyst system, with $Et_2B(OMe)$ and *N*,*O*-BSA proving optimal (Table 1). Both

Table 1. Optimization Studies



entry	change from optimized conditions	yield (%)[a]
1	none	72 (56[b])
2	no *N*,*O*-BSA	24
3	BEt_3 instead of $Et_2B(OMe)$	42
4	no borane ($Et_2B(OMe)$ or BEt_3)	n.r.
5	(*S*)-SEGPHOS as the ligand	32
6	Trost ligands (ANDEN or DACH)	n.r.
7	Xantphos as the ligand	63

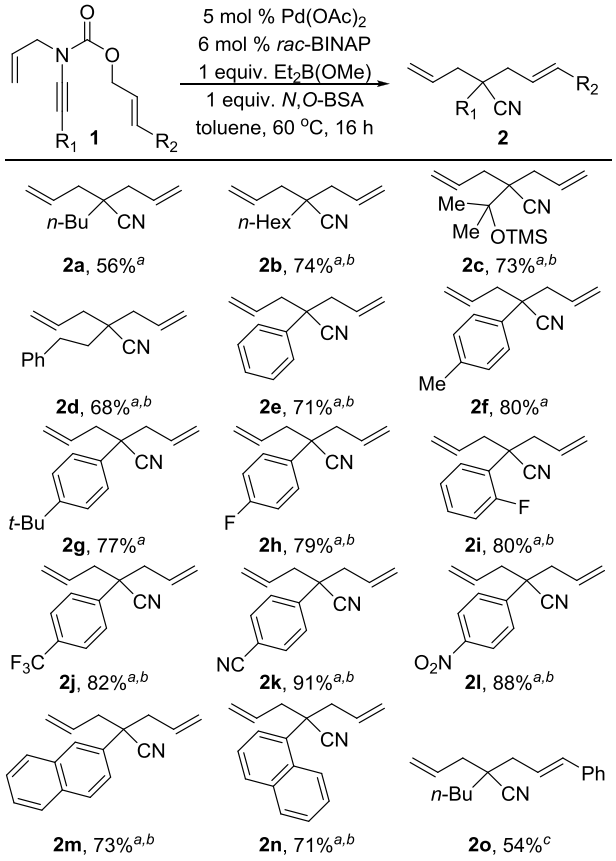
[a]Determined by ^{1}H NMR analysis with mesitylene as an internal standard. [b]Isolated yield.

the *N*,*O*-BSA and $Et_2B(OMe)$ additives were crucial for high efficiency. Et_3B provided products in lower yield, and the absence of borane led to no reaction. Other bidentate ligands, such as SEGPHOS or Xantphos, were effective, whereas both Trost ligand scaffolds led to no reaction.

Following optimization, we embarked on a substrate scope study to examine the generality of the reaction. Quaternary nitriles bearing unsubstituted alkyl groups (**2a**, **2b**), highly substituted alkyl groups (**2c**), and phenethyl (**2d**) were formed in good yields. Aryl alkyne substrates (**1e**–**m**) were particularly efficient for this reaction. Interestingly, there was little difference in efficiency between aryl alkynes substituted by electron-neutral (**1e**), σ-donating (**1f**, **1g**), or σ-withdrawing (**1h**–**j**) groups. When mesomeric π-withdrawing groups were present (**1k**, **1l**), enhanced reactivity was observed, and excellent yields of the products were obtained. The use of polyaromatic-substituted alkynes was demonstrated, with 2-naphthyl-substituted **1m** and the more hindered 1-naphthyl analogue **1n** reacting with similar reactivity. Substitution at R_2 could also be tolerated, with **1o** bearing a cinnamyl-substituted *N*-alloc group reacting with similar efficiency as **1a**. This reaction provided quaternary nitrile **2o** with high levels of linear regioselectivity.

As uncatalyzed sigmatropic ketenimine aza-Claisen rearrangements were previously reported,[9] we examined whether both rearrangement reactions were indeed catalyzed by a single palladium catalyst. Two distinct substrate classes were chosen, with butyl (**1a**) and phenyl (**1e**) substrates being the focus of our studies (Scheme 2). Deuterium-labeled analogues (**3** and **4**)

Scheme 2. Substrate Scope



[a]Average isolated yield over two reactions. [b]The reaction was performed on a 1 mmol scale. [c]Isolated as a 10:1 mixture of regioisomers.

were prepared in which CH_2 was independently replaced with CD_2 at the *N*-allyl (**3**) and *N*-alloc (**4**) positions. These were then subjected to the optimized reaction conditions, and the position of the deuterium was tracked (Scheme 3a). When the deuterated *N*-allyl analogues (**3**) were utilized, two reactivity patterns were observed. The butyl substrate (**3a**) provided a single regioisomer **5a** with the deuterium exclusively at the terminal vinylic position. With the phenyl analogue (**3b**), deuterium scrambling was observed in a **5b**:**6b** ratio of 1.2:1. These results clearly demonstrate a divergence in mechanisms between the two substrates (**3a** and **3b**) and indicate that a dissociative allylic pathway occurs for **3b** that is not accessible to **3a**. Of note is the slight excess of the terminal vinylic deuterium isomer (**5b**). The origin of the selectivity in **3b** could be produced by either two competing (concerted and dissociative) mechanisms or a secondary kinetic isotope effect in a rapidly isomerizing (Curtin–Hammett) system. In the latter case, it would suggest the facile formation of a π-allyl intermediate followed by a higher-energy C–C bond-forming step with

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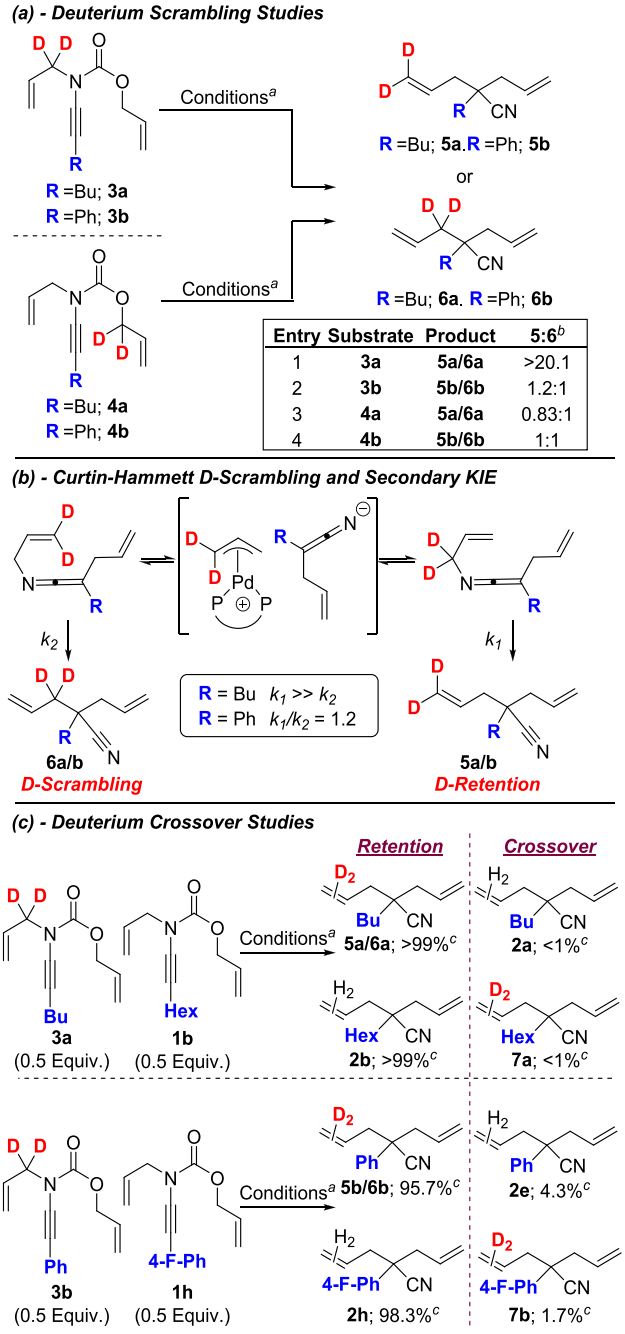
Scheme 3. Deuterium-Labeling and Crossover Experiments



[a]Conditions: 5 mol % $Pd(OAc)_2$, 6 mol % *rac*-BINAP, $Et_2B(OMe)$ (1 equiv), *N*,*O*-BSA (1 equiv), toluene, 60 °C, 16 h. [b]Ratios were determined by ^1H NMR analyses of unpurified reaction mixtures. [c]Percentages represent the isotopic makeup of individual products and were measured by GCMS/HRMS of unpurified reaction mixtures. Values are corrected for natural isotopic abundance.

rehybridization from sp^3 to sp^2 determining the selectivity (Scheme 3b). When deuteration was installed on the *N*-alloc group (**4**), isotopic scrambling was observed in both cases. The butyl analogue **4a** provided a slight excess of the allylic CD_2 compound **6a**, whereas the phenyl analogue **4b** provided equimolar quantities of **5b** and **6b.** These results are consistent with our previous mechanistic experiments and indicate that the *N*-alloc rearrangement proceeds *via* a more classical dissociative π-allylic mechanism.[6a]

Crossover studies were performed using 0.5 equiv each of **3** and a structurally similar unlabeled compound (**1b** and **1h**) to probe whether any solvent-separated dissociation or π-allyl ligand exchange was occurring (Scheme 3c). The competition reaction of butyl (**3a**) and hexyl (**1b**) ynamides provided no evidence of dissociation, with complete retention of the deuterium label in the butyl substrate. Phenyl (**3b**) and 4-fluorophenyl (**1h**) ynamides gave trace amounts of deuterium crossover. This suggests that the dissociative pathway for **3b** that leads to deuterium scrambling is short-lived and/or that solvent separation is not favored. Thus, we focused our efforts on determining the exact nature of the previously unknown palladium-catalyzed ketenimine aza-Claisen step.

To further elaborate our mechanistic insight, we conducted computational studies on ketenimines **8a** and **8e**,[14] which are derived from **1a** and **1e**, respectively.[15] Because of the large ligand, we applied the two-layer quantum-mechanical (QM)/semiempirical (SE) ONIOM model to the palladium complexes.[16] The QM layer was treated with M06L/6-31+G(d) (C, H, P, B, O)/LANL2DZ (ECP Pd)[17] and the SE layer with PM6. Single-point (SP) energies of these optimized structures were calculated utilizing M06L/6-311++G(2d,2p) (C, H, P, B, O)/LANL2DZ (ECP Pd). The solvation by toluene was taken into account using C-PCM.[18] Transition states (TSs) were located using the nudged elastic band (NEB) method implemented in ORCA 4.2.1[19] at the M06L level with thedef2-SV(P) basis set followed by the ONIOM/SP process described above. Conformational flexibility was addressed through the mixed torsional/low mode method and relaxed torsion scans (see the Supporting Information (SI) for full details).

Using phenyl ketenimine **8e** as an initial model, we explored both catalytic and uncatalyzed pathways for the sigmatropic rearrangement and discovered a complex potential energy surface. The uncatalyzed ketenimine aza-Claisen rearrangement of **8e** proceeded through an early transition state analogous to those described by Walters.[9] This rearrangement is significantly faster with the free ketenimine rather than *via* a Lewis acid−base adduct with the borane additive (not shown in Scheme 3; see the SI for details). In the palladium-catalyzed routes (Scheme 4),[20] coordination of ketenimine **8e** with the Pd(0) catalyst to form **9** is exergonic by 11.7 kcal/mol. π-Allylic ionization mechanisms were examined with and without the borane additive bound. Direct ionization of **9** to form π-allyl species **10** (*via* **TS-ION**) was readily accessible with a TS energy of just 11.4 kcal/mol. Once again, the borane adduct route was significantly higher in energy than the direct ionization of **9.** As a result, we do not believe that the borane additive participates in the ketenimine rearrangement of **8e** and is only necessary to perform the initial π-allyl rearrangement of **1e**. The structure of **10** is a heavily distorted η^3-π-allyl tight ion pair, which can easily isomerize between the η^3 and η^1 haptomers (**10** and **12**), leading to the deuterium scrambling observed in Scheme 2. Bond rotation is required to form the reactive conformer **13**, which can rearrange *via* an inner-sphere C−C bond formatting mechanism (**TS-IS**). The palladium-bound rearranged nitrile **13** is formed with an overall TS energy of 15.8 kcal/mol from **9**.

A concerted Pd(0)-catalyzed pericyclic process was also investigated. This mechanism, which is also consistent with experimental data, proceeds through highly ordered **TS-**[**3,3**]**-Pd** and is 1.9 kcal/mol lower in energy than the **TS-IS** route. The deuterium scrambling and crossover described in Scheme 3 can be reconciled by rapid and reversible ionization through **TS-ION**, which is 2.5 kcal/mol lower than **TS-**[**3,3**]**-Pd**. The

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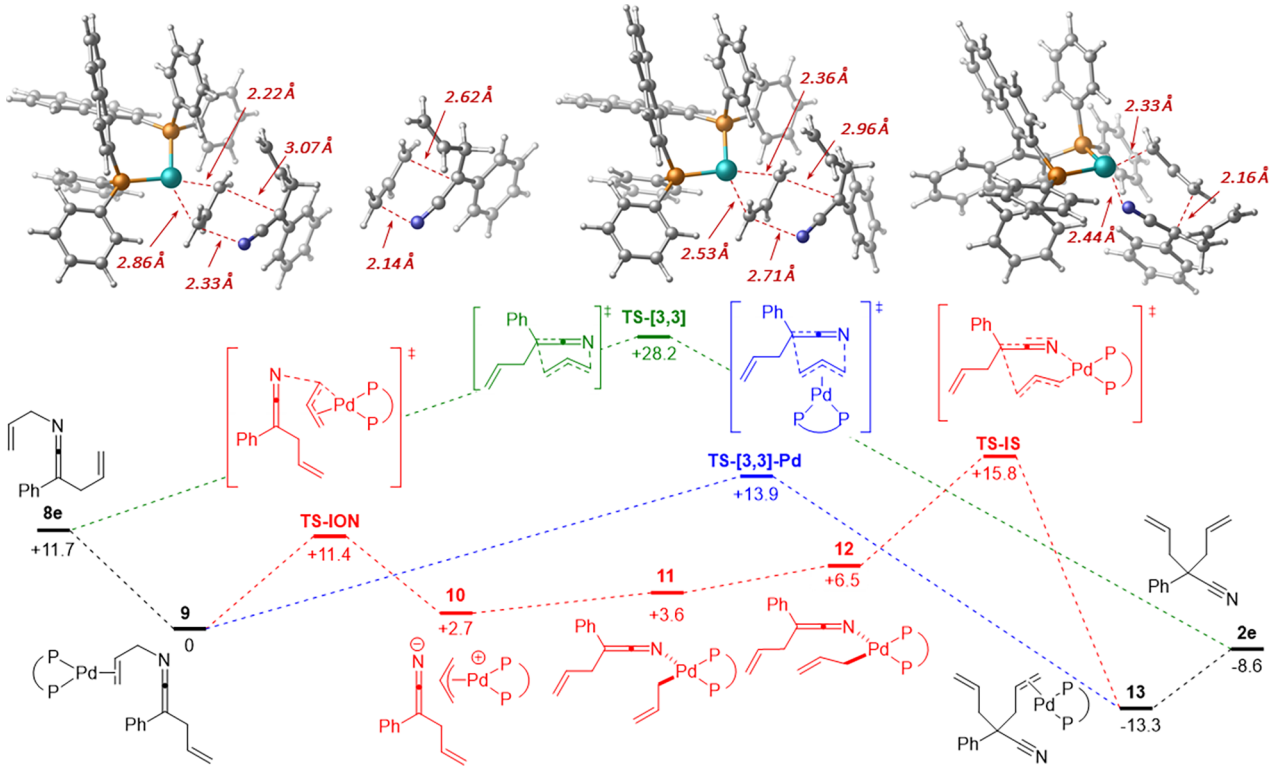
Scheme 4. Summary of the DFT Study Examining Catalytic and Uncatalyzed Mechanisms[a]



[a]Geometries/frequencies were obtained using the QM/SE ONIOM model (M06L/6-31+G(d) (C, H, P, B, O)/LANL2DZ (ECP Pd):PM6). TSs were located using the NEB method in ORCA 4.2.1 at the M06L/def2-SV(P) level and confirmed by intrinsic reaction coordinate calculations. All of the SP energies were calculated using C-PCM (toluene) at the M06L/6-311++G(2d,2p) (C, H, P, B, O)/LANL2DZ (ECP Pd) level. See the SI for full details.

structure of **TS-[3,3]-Pd** is a hybrid between π-allylic and sigmatropic processes, where the reaction is aided by donation of electron density from the Pd(0) center into the C−N σ^* orbital, leading to a later TS than the uncatalyzed variant **TS-[3,3]**. When one examines the migrating allylic portion, the three carbon atoms are almost trigonal-planar, and the terminal C−Pd bond lengths (2.36 and 2.53 Å) indicate substantial interactions between the Pd catalyst and both termini. This effect can be seen more clearly when the HOMO and LUMO coefficients are examined (Figure 1). There is significant overlap of the d orbitals of the Pd(0) atom (in the HOMO) with the σ^* orbital of the C−N bond (in the LUMO). Additionally, both the forming C−C and breaking C−N σ bonds are significant contributors to the HOMO, indicative of a sigmatropic process. Furthermore, the HOMO and LUMO contain two and four nodes, respectively, indicating an aromatic TS. The HOMO/LUMO gap is just −0.87 eV, demonstrating facile transfer of electron density between these two molecular orbitals. As the $\Delta\Delta G^{\ddagger}$ between the **TS-[3,3]-Pd** and **TS-IS** routes is 1.9 kcal/mol, representing an 18:1 difference in relative rates at 60 °C, we believe that the Pd(0)-assisted [3,3]-sigmatropic and inner-sphere mechanisms both occur, with the former being the much faster pathway.

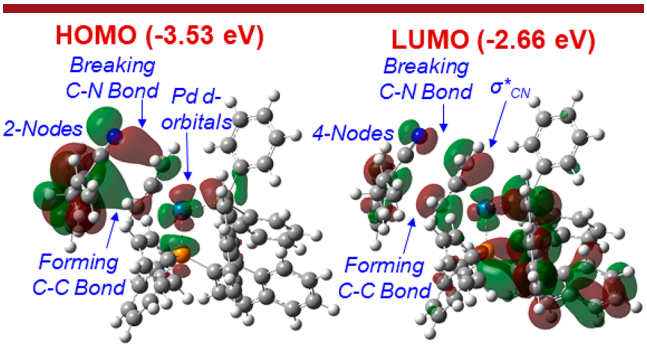


Figure 1. Calculated molecular orbitals for **TS-[3,3]-Pd**

Analogous computational studies performed on butyl ketenimine **8a** indicate that the reaction proceeds through a similar Pd(0)-catalyzed [3,3]-sigmatropic rearrangement, but the ionization pathway is much higher in energy because of the lower stability of the ketenimine anion formed in ionized intermediate **10**. As this dissociative mechanism is no longer in operation, both deuterium isomerization and crossover pathways are no longer accessible (see the SI for details).

In conclusion, we have developed a highly efficient auto-tandem catalytic process to form substituted nitriles from *N*-alloc-*N*-allyl ynamides. This reaction proceeds through two mechanistically distinct allylic rearrangement reactions, with both π-allylic and sigmatropic processes promoted by a single Pd(0) source. Computations and experimental mechanistic data helped elucidate these pathways. This study identified two new reaction mechanisms, including the π-allylic ionization of neutral C−N bonds and a Pd(0)-catalyzed aza-Claisen rearrangement. These Pd(0)-catalyzed sigmatropic rearrangements have potential to be incorporated in many other ATC reactions.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04078.

Experimental procedures, $^{1}H/^{13}C$ NMR spectra, computational methods, and Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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