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Synergistic *N*-Heterocyclic Carbene/Palladium-Catalyzed [3 + 2] Annulation of Vinyl Enolates with 1-Tosyl-2-vinylaziridine

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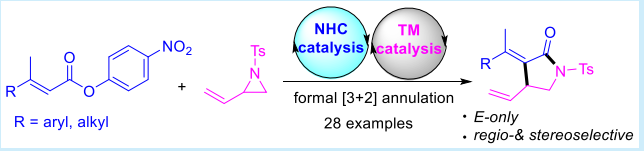
ABSTRACT: The synergistic combination of *N*-heterocyclic carbene organocatalysis and transition-metal catalysis for a formal [3 + 2] annulation between 3-substituted but-2-enoates and 1-tosyl-2-vinylaziridine was developed. This cooperative strategy provides a facile and efficient access to various functionalized (*E*)-3-ethylidene-4-vinylpyrrolidin-2-ones in a regioselective and stereoselective manner. The preliminary asymmetric studies were also performed, which indicated a potential for enantioselective annulation of vinyl enolate intermediates with transition-metal−π-allyl species.



Over the past decades, conventional transition-metal (TM) catalysis[1] and organocatalysis[2] have been widely explored and applied in the activation and functionalization of various chemical bonds to accomplish useful chemical transformations. Nevertheless, with the development of the modern organic synthesis, the traditionally single catalytic systems have also encountered some challenges, such as the activation efficiency for new types of substrates, and the control for the reactivity and selectivity. Aiming to get out of this dilemma, synergistic or cooperative catalysis, especially synergistic TM catalysis and organocatalysis, has drawn much attention and has been proven to be a general and effective strategy to realize inaccessible transformations by single catalytic approaches previously via independent activation of separate substrates simultaneously.[3]

In recent years, *N*-heterocyclic carbenes (NHCs) have emerged as efficient and powerful organocatalysts for the discovery of novel and unconventional synthetic transformations with readily access to a wide array of heterocycles and bioactive molecules.[4] Especially via umpolung activation mode, a variety of NHC-bound active intermediates have been approached and widely applied for chemical bond construction. However, because of the strong affinity of NHCs to TM centers through irreversible binding and coordination, a disruption of the individually desired catalytic activities of both NHCs and TMs usually happens (Scheme 1a).[5] Thus, the design and development of synergistic catalysis by merging NHCs with TMs remain a formidable challenge and only limited examples were explored (Scheme 1b).[6] In 2014, the Scheidt group[7] pioneered an intramolecular allylation and subsequent acylation reaction of NHC-bound Breslow intermediates for the construction of dihydrocoumarins derivatives co-catalyzed by NHC/palladium catalyst. Following this pioneering work, intermolecular allylation and benzylation of NHC-bound Breslow intermediates were also achieved by Ohmiya and co-workers.[8−11] Furthermore, other than Breslow intermediates, NHC-bound active species such as homoenolates, enolates, and azolium enamides have also been developed as C2 or C3 synthons for diverse [*n*+*m*] annulation[12−18] and arylation[19] reactions by synergistic NHC/TMs (Pd, Cu, Ir, Au) co-catalysis. In view of the importance of synergistic catalysis and the diversity of NHC-bound intermediates, it is still highly desirable to explore novel and efficient catalytic systems based on cooperative NHC/TM catalysis.

Recently, NHC-bound vinyl enolates derived from α,β-unsaturated acids or their esters, or (α-bromo)enals via γ-activation, have been used as reactive nucleophilic C4 synthons or C2 synthons to enable diverse annulation reactions at the γ- or α-position.[20] However, to the best of our knowledge, NHC/TM co-catalyzed reactions of vinyl enolates have not been reported yet. We envisioned that NHC-bound vinyl enolates would also be applicable in combination with TM-activated electrophiles to realize various formal [*n*+2] or [4+*m*] annulations (Scheme 1c). Herein, as part of our continuous efforts to enrich vinyl enolate chemistry,[21] we report an NHC/Pd co-catalyzed [3 + 2] annulation of α,β-unsaturated esters **1** with 1-tosyl-2-vinylaziridine **2**, a versatile substrate for the generation of Pd-π-allyl species,[22] for the facile construction of (*E*)-3-ethylidene-4-vinylpyrrolidin-2-one skeleton **3** that is frequently found in numerous synthetic compounds or natural products.[23] Notably, (*E*)-[3 + 2] adducts **3** were obtained exclusively in a regioselective and stereoselective manner, and the corresponding [4 + 3] adducts **4** were not observed.

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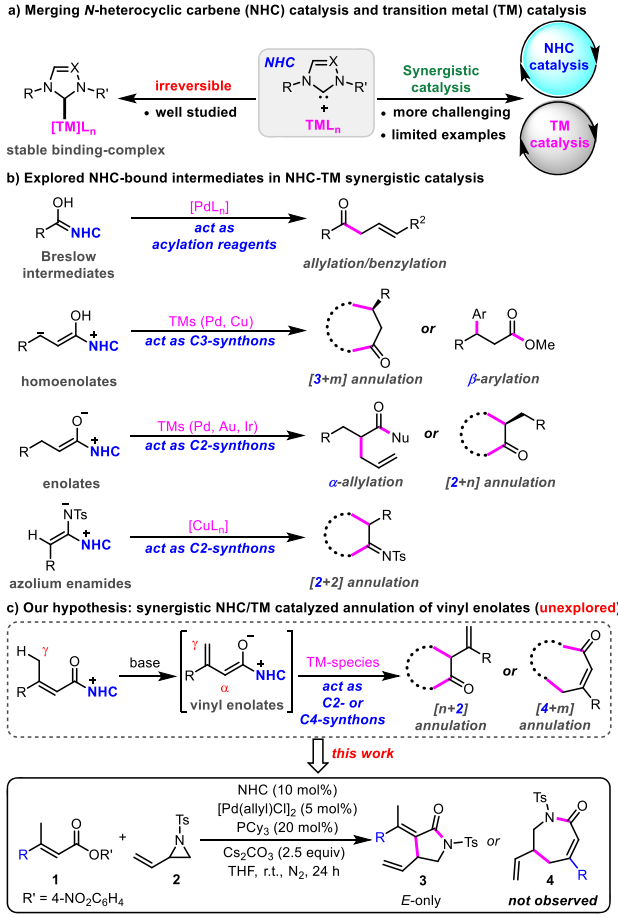
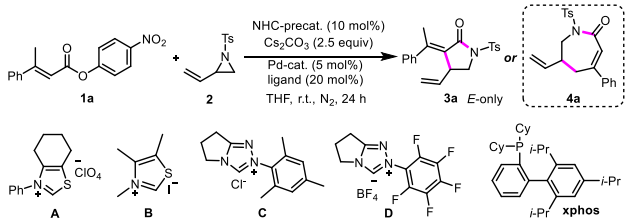
Scheme 1. Merged *N*-Heterocyclic Carbene and Transition-Metal Co-catalysis



We commenced the evaluation of our hypothesis by the reaction of 4-nitrophenyl-3-phenylbut-2-enoate **1a** with 1-tosyl-2-vinylaziridine **2** using Cs_2CO_3 as the base in THF under NHC/palladium co-catalysis (for details, see the Supporting Information (SI)). We were delighted to find that the reaction proceeded smoothly to give the formal [3 + 2] annulation product **3a** in 11% yield, rather than the [4 + 3] annulation product **4a**, in the presence of carbene precursor **A** and $Pd_2(dba)_3{\cdot}CHCl_3$ with PPh_3 as the ligand (Table 1, entry 1). Subsequent screening of other carbene precursors indicated that NHC precatalyst **D** displayed the best catalytic efficiency for this [3 + 2] annulation reaction (Table 1, entries 2−4). Notably, the control experiments showed that **3a** was not formed at all in the absence of either NHC or a palladium catalyst, indicating the synergistically catalytic roles of both carbene and the palladium catalyst (Table 1, entries 5 and 6). Different ligands, under the co-catalysis of carbene **D** and $Pd_2(dba)_3{\cdot}CHCl_3$, were then further examined (Table 1, entries 7−13). As a result, tricyclohexylphosphine (PCy_3) proved to be the best ligand for this annulation, and 38% yield of **3a** could be obtained (Table 1, entry 9). Encouraged by this result, we then tested various other palladium catalysts (Table 1, entries 14−20). Gratifyingly, a 46% yield of **3a** could be achieved when $[Pd(allyl)Cl]_2$ was used as the metallic catalyst in combination with PCy_3 (Table 1, entry 15). Lastly, we found that an excess amount of **2** was critical to this transformation, because of the dimerization of **2**, and the reaction yield could be enhanced to 75% (Table 1, entry 20).

Table 1. Selected Results for the Optimization of Reaction Conditions[a]



entry	NHC-precat.	Pd-cat.	ligand	yield of **3a**[b]
1	**A**	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	11
2	**B**	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	trace
3	**C**	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	0
4	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	21
5	–	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	0
6	**D**	–	–	0
7	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	$P(4\text{-FPh})_3$	13
8	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	$P(4\text{-MePh})_3$	26
9	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	PCy_3	38
10	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	P^tBuCy_2	14
11	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	xphos	0
12	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	P^tBu_3	0
13	**D**	$Pd_2(dba)_3{\cdot}CHCl_3$	P^nHex_3	30
14[c]	**D**	$Pd(PPh_3)_2Cl_2$	PCy_3	0
15	**D**	$[Pd(allyl)Cl]_2$	PCy_3	46
16[c]	**D**	$Pd(PPh_3)_4$	PCy_3	38
17[c]	**D**	$Pd(TFA)_2$	PCy_3	0
18[c]	**D**	$Pd(tBu_3P)_2$	PCy_3	38
19[c]	**D**	$Pd(OAc)_2$	PCy_3	14
20[d]	**D**	$[Pd(allyl)Cl]_2$	PCy_3	75

[a]Reaction conditions: **1a** (0.12 mmol, 1.2 equiv); **2** (0.1 mmol, 1.0 equiv); NHC-precat. (10 mol %); Cs_2CO_3 (2.5 equiv); Pd-cat. (5 mol %); ligand (20 mol %); THF, 2 mL; N_2; rt; 24 h. [b]Isolated yields. [c]ligand (10 mol %). [d]**1a** (0.2 mmol, 1.0 equiv); **2** (0.6 mmol, 3.0 equiv); THF, 4 mL. dba, dibenzylideneacetone; Cy, cyclohexyl; ^{n}Hex, *n*-hexyl; TFA, trifluoroacetate.

Note that the configuration of the C=C double bond of the product can be established by NMR analysis of **3a**, which is a known compound.[24]

With the optimal reaction conditions in hand, the substrate scope of the annulation between 3-substituted-(4-nitrophenyl)but-2-enoates **1** and 1-tosyl-2-vinylaziridine **2** was investigated as shown in Scheme 2. Inspiringly, a wide array of 3-(substituted phenyl)-(4-nitrophenyl)but-2-enoates were compatible to the present annulation system. The nature and position of the substituents on the phenyl ring seemed to have certain impact on the reaction results. Substrates bearing either electron-withdrawing groups or electron-donating groups at the *para* position of the phenyl ring could be well-tolerated, affording the corresponding desired products **3b−3i** in moderate to good yields. However, when a cyclic amino group was anchored on the *para* position of the phenyl ring, only 28% yield was achieved for the corresponding product **3j**. In terms of 3-(*meta*-substituted phenyl)-(4-nitrophenyl)but-2-enoates, substrates with electron-withdrawing groups, such as halogens (**3k−3m**) and methoxy group (**3o**) were found to be better than those bearing an electron-donating group, such as methyl (**3n**). When it comes to 3-(*ortho*-substituted phenyl)-(4-nitrophenyl)but-2-enoates, the steric effect from the substituents was obvious. The yields decreased significantly with the increase of the volume of substituents at the *ortho*

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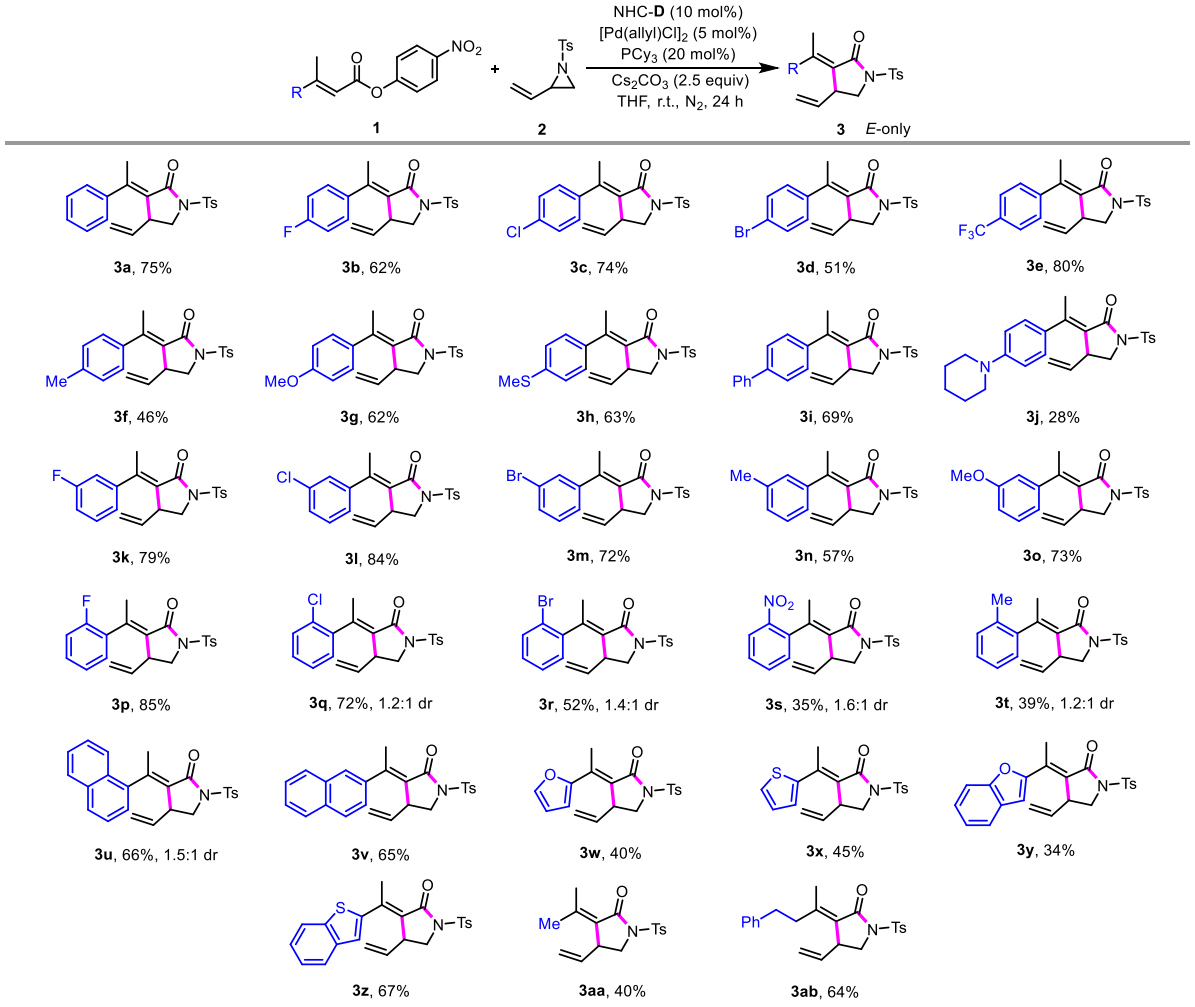
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), **NHC-D** (10 mol %), Cs_2CO_3 (2.5 equiv), [Pd(allyl)]Cl_2 (5 mol %), PCy_3 (20 mol %), THF, 4 mL, rt, 24 h; isolated yields are based on **1**.

position (**3p**−**3t**). Furthermore, atropisomerism was observed for products **3q**−**3t** bearing bigger groups at ortho position, because of the generation of a chiral axial. Similarly, the reaction of 3-(1-naphthyl) enoate gave the corresponding product **3u** in 66% yield with a diastereomeric ratio (dr) of 1.5:1. 3-(2-Naphthyl and 2-heteroaryl phenyl) enoates were also applicable to the present protocol. Although lower yields were obtained for 2-(2-furyl)-, 2-(2-thienyl)-, and 2-(2-benzofuryl)-substituted enoates (**3w**−**3y**), upper-medium yields could be obtained for 2-naphthyl and 2-benzothienyl-derived enoates (**3v** and **3z**). Lastly, 3-alkyl-(4-nitrophenyl) but-2-enoates were also tested to evaluate the generality of our present reaction system. Fortunately, medium yields could be achieved under the identical reaction conditions for two typical aliphatic substrates (**3aa** and **3ab**).

To further explore the synthetic utility of this methodology, a scale-up synthesis of product **3a** and several synthetic applications were then performed (see Scheme 3). Product **3a** was obtained in a maintained yield with a 1 mmol scale under the standard conditions (see Scheme 3a). Moreover, **3d** could be used for late-stage modification for different synthetic purposes. For example, the Suzuki coupling with phenylboronic acid and Hartwig-Buchwald coupling with piperidine could proceed smoothly to afford the target compounds **3i** and **3j**, respectively (Scheme 3b), indicating the generality for late-stage functionalization of the annulation products. In addition, the *N*-protecting group could also be easily removed under mild conditions to produce pyrrolidin-2-one derivative **5** in a good yield (see Scheme 3c). Under catalytic hydrogenation conditions, the two C═C double bonds of product **3a** were completely reduced together, giving a *trans*-reduced product **6** in a high yield (Scheme 3c). Finally, a preliminary asymmetric annulation study was performed (Scheme 2d). Unsatisfyingly, after the screening of various reaction parameters (for details, see the SI), **3a** could be obtained in 31% yield with 65% enantiomeric excess (ee) in the presence of chiral carbene precursor **E**, using chiral diamine **F** as the additive.

A tentative mechanism of the NHC/palladium co-catalyzed annulation of vinyl enolates with 1-tosyl-2-vinylaziridine was proposed as outlined in Scheme 4.[7a,13−15] Herein, this synergistic annulation was successfully realized through the concomitant catalytic generation of two reactive species: a nucleophilic NHC-bound vinyl enolate **II** and a highly electrophilic Pd-π-allyl species **IV**. The nucleophilic attack of carbene **D′** generated upon the deprotonation of **D** with Cs_2CO_3 to **1a** afforded the acyl azolium intermediate **I**. Subsequent deprotonation of γ-H of **I** with a base produced NHC-bound vinyl enolate **II**. In a parallel palladium catalytic

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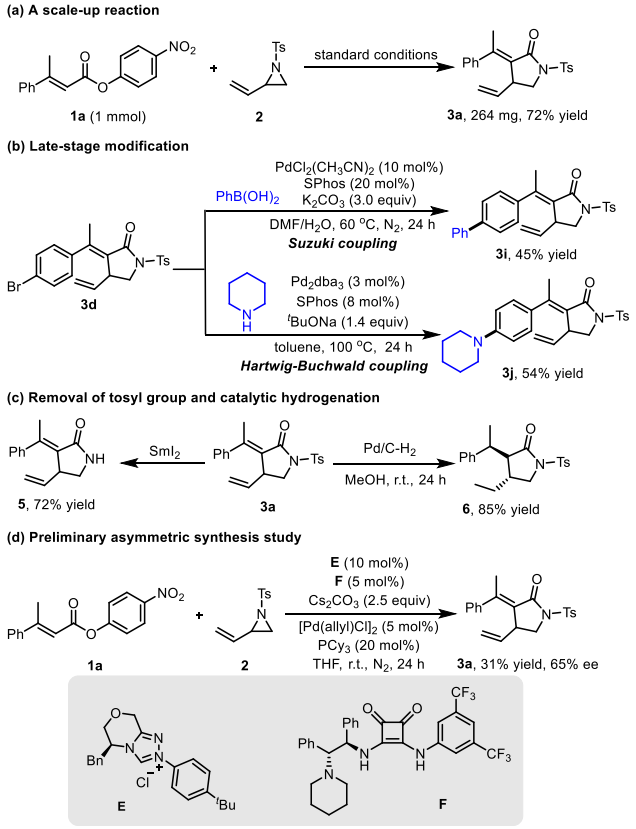
Scheme 3. Synthetic Applications and Preliminary Enantioselective Study



cycle, through the coordination of **2** to the palladium catalyst, an active electrophilic Pd-π-allyl species **IV** could be generated via the ring opening of aziridine. At this point, the NHC-bound vinyl enolate **II** could undergo a nucleophilic attack to the *in-situ*-formed Pd-π-allyl species **IV** with the formation of intermediate **V**. Following this C−C bond formation, the release of the Pd(0) gave rise to acyl azolium **VI**. This species then underwent a *N*-acylation annulation to produce the cyclic intermediate **VII** and regenerate carbene **D′** for the next catalytic cycle. Lastly, tautomerization of **VII** furnished the more stable final product **3a**.

In conclusion, we have demonstrated the first [3 + 2] annulation reaction of NHC-bound vinyl enolates with a Pd-π-allyl species via a dual organo-metal catalytic process. Under the properly optimized conditions, the free carbene catalyst and the Pd catalyst could work well independently to accomplish their own catalytic roles without quenching each other. The rapid and stereoselective construction of (*E*)-3-ethylidene-4-vinylpyrrolidin-2-one skeletons could be achieved successfully in medium to good yields with excellent compatibility of functional groups. In addition, encouraged by the preliminary results of the asymmetric study, further enantioselective annulation of NHC-bound vinyl enolates with diverse transition metal-π-allyl species and other synthetic applications are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02935.

General information, experimental procedures, compound characterizations, and NMR spectra (PDF)

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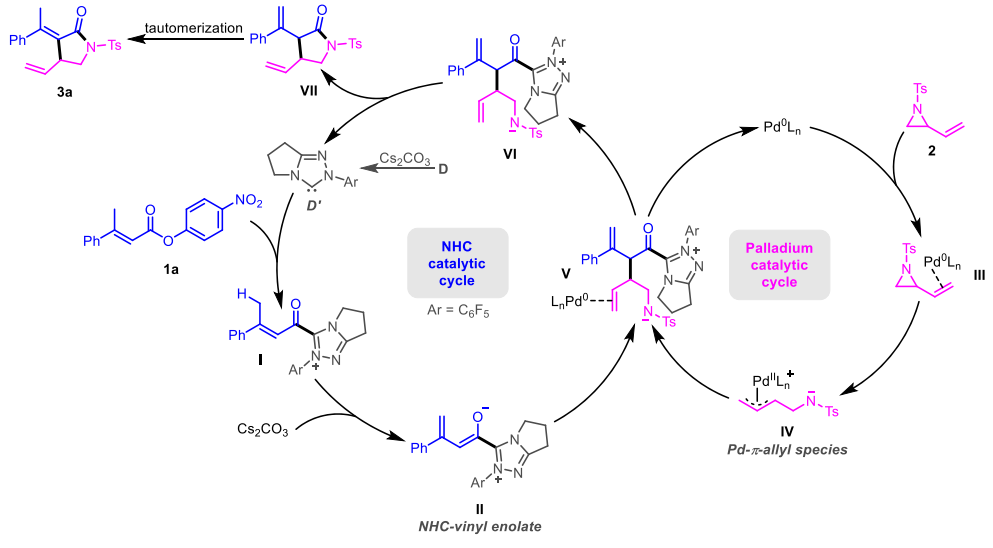
Scheme 4. Proposed Reaction Mechanism



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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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