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Palladium(II)-Catalyzed Cross-Coupling of Diazo Compounds and Isocyanides to Access Ketenimines

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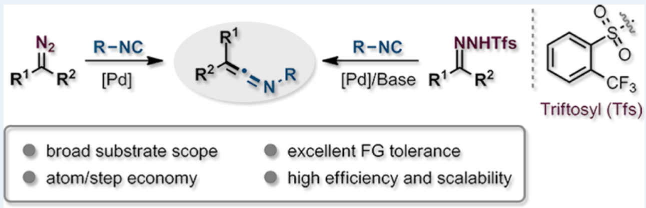

ABSTRACT: Diazo compounds and isocyanides are reactive functionalities and valuable building blocks commonly utilized in organic synthesis. Their cross-coupling for the synthesis of useful isolable ketenimines remains an unsolved challenge in synthetic chemistry. Herein, we report a general method for the preparation of ketenimines via a palladium-catalyzed cross-coupling of easily accessible diazo compounds with isocyanides. The reaction benefits from the use of readily available starting materials, a wide substrate scope, high functional group tolerance, and a high yield in products, and the resultant ketenimines are amenable to further functionalization. Experimental findings and DFT calculations unambiguously corroborate the initial formation of a Pd(II)−isocyanide complex as the active catalytic species, which enables the cross-coupling reaction via a migratory insertion of Pd(II)−carbene into isocyanide, with evidence suggesting that the oxidation state of Pd(II) remains unchanged during the reaction.

KEYWORDS: *palladium catalysis, cross-coupling, ketenimine, isocyanides, DFT calculations*

1. INTRODUCTION

Transition-metal catalyzed cross-coupling reactions of diazo compounds are widely used for the construction of cumulated double bonds[1] and reactive structural moieties with versatile synthetic applications.[2] As an established example, allenes can be obtained by copper-catalyzed cross-couplings of diazo species (or their precursors) and terminal alkynes.[3] The Wang group also reported an elegant palladium(0)-catalyzed carbonylation of diazo compounds with CO to yield ketenes.[4] However, the cross-coupling of diazo compounds[5] with isocyanides[6] to access isolable ketenimines remains largely unsuccessful (Figure 1a).[7] The transition-metal-catalyzed cascade reaction of diazo compounds with isocyanides is a notable recent achievement, formation of ketenimines was proposed, which further react without prior isolation.[8] Ketenimines contain two cumulated reactive functionalities (C=C and C=N bonds) and are versatile synthetic intermediates for the assembly of many nitrogen-containing compounds.[9] Despite the reliability and usefulness of these in situ-generating strategies,[8] the incompatibility between the reaction conditions for the generation of reactive ketenimines and their subsequent transformations somehow limit their application in organic synthesis.[9,10] Traditionally, isolated ketenimines can be prepared through the Wittig reaction of phosphoranes with isocyanates;[11] aza-Wittig reaction of ketenes with iminophosphoranes;[12] or cross-coupling reactions of isocyanides with stoichiometrically stabilized carbene complexes,[13] α-halophosphonates,[14] allyl carbonates, and α-haloketones[15] (Figure 1b). All these methods were constrained by significant shortcomings, such as poor accessibility or difficult processability of the substrates, narrow reaction scope, poor functional group tolerance, or a combination thereof. More efficient and greener methodologies for the rapid assembly of isolable ketenimines from readily available starting materials remain worth exploring.

In consideration of the increasing importance of ketenimines and our ongoing endeavors in diazo[16] and isocyanide chemistries,[17] we embarked on the investigation of a general and scalable ketenimination reaction via a palladium-catalyzed cross-coupling reaction between diazo compounds and isocyanides, whose results and mechanistic insights we are reporting herein (Figure 1c). This method can utilize either diazo compounds or *N*-triftosylhydrazones, affording high-quality ketenimines with or without an electron-withdrawing group (EWG) in high yields. Findings stemming from the synthesis, characterization, and reactivity of the putative palladium complex enabled a mechanistic understanding of this synthetically useful transformation. The data obtained from both experimental and DFT studies suggest that the formation and the subsequent migratory insertion of Pd(II)−carbenoid species were the key steps of this cross-coupling reaction. The oxidation state of palladium remains unchanged

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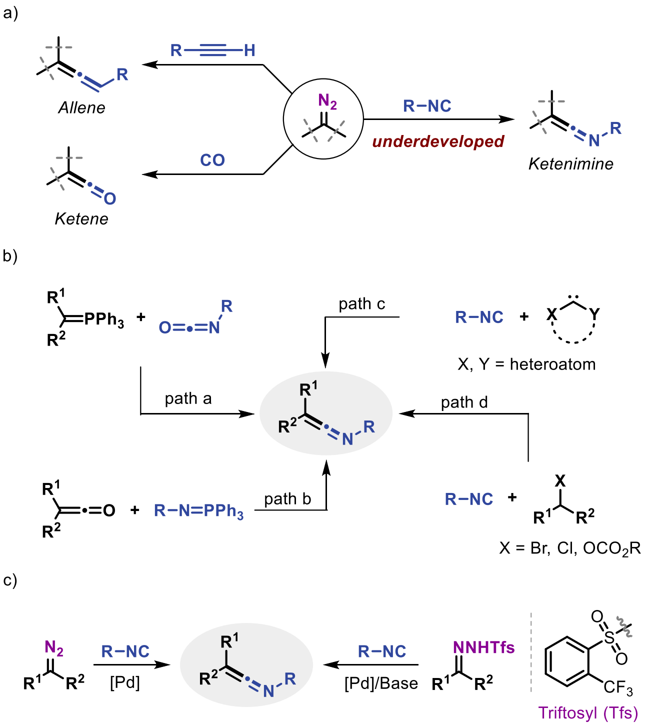


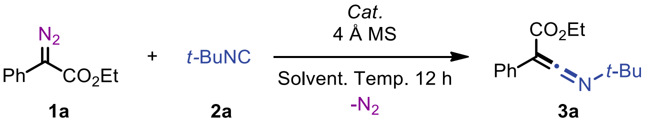
Figure 1. Synthetic strategies for the formation of cumulated double bonds. (a) Formation of cumulated double bonds from diazo compounds. (b) Synthesis of ketenimines by cross-coupling strategies (previous work). (c) Cross-coupling of diazo compounds with isocyanides (this work).

during the reaction, which is different from the previous reports proposing a Pd(II)/Pd(0) catalytic cycle.[6d,14,15,18]

2. RESULTS AND DISCUSSION

At the outset of this investigation, the parameters for the reaction of phenyldiazoacetate **1a** with *tert*-butyl isocyanide (*t*-BuNC) **2a** were screened. The reaction in the absence of any catalysts with 4 Å molecular sieves (MS) in 1,4-dioxane at 60 °C for 12 h afforded a trace amount of expected ketenimine **3a**, along with the unreacted phenyldiazoacetate being recovered (entry 1, Table 1). Commonly used transition metals in the catalytic generation of carbene from diazo compounds, AgOAc and $Cu(OAc)_2$, were demonstrated as ineffective catalysts, whereas $Rh_2(OAc)_4$ led to the formation of **3a** in very low yields (entries 2−4). Therefore, we turn our attention to palladium catalysts, which readily coordinate with isocyanide to form isocyanide-complexed Pd species and then react with diazo compounds.[8a,e−h] After some optimization work, it was found that $Pd(OAc)_2$ showed remarkable activity and delivered the desired product **3a** in 90% isolated yield (entry 8), in contrast to the moderate product yield recorded with $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and $Pd(PPh_3)_2Cl_2$ as catalysts (entries 5−7). Palladium catalysts were significantly superior to other transition-metal catalysts (entries 5−8 vs 2−4), indicating that the palladium catalyst prefers to coordinate with isocyanide to form isocyanide-complexed Pd species,[8a,e−h] rather than react with diazo compound to generate palladium carbene.[4] Changing the solvent to either CH_3CN or THF did not significantly impact the yield, whereas CH_2Cl_2 was unsuitable for the reaction (entries 9−11). The product yield was significantly lowered when decreasing the reaction temperature to 40 °C or increasing it to 80 °C (entries 12 and 13). A control reaction proved that 4 Å MS were necessary for this reaction; in their absence, the reaction led to poor conversion (entry 14).

Table 1. Optimization of the Reaction Conditions[a]



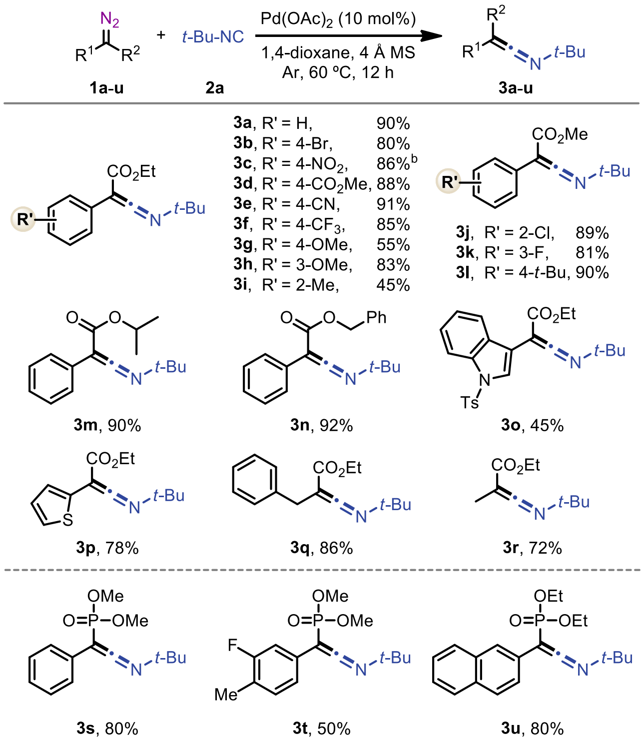
entry	cat.	amount (mol %)	solvent	*T* (°C)	yield (%)[b]
1			1,4-dioxane	60	trace
2	AgOAc	10	1,4-dioxane	60	trace
3	$Cu(OAc)_2$	10	1,4-dioxane	60	trace
4	$Rh_2(OAc)_4$	5	1,4-dioxane	60	31
5	$Pd_2(dba)_3$	10	1,4-dioxane	60	66
6	$Pd(PPh_3)_4$	10	1,4-dioxane	60	70
7	$Pd(PPh_3)_2Cl_2$	10	1,4-dioxane	60	67
8	$Pd(OAc)_2$	10	1,4-dioxane	60	97 (90)[c]
9	$Pd(OAc)_2$	10	CH_3CN	60	88
10	$Pd(OAc)_2$	10	THF	60	81
11	$Pd(OAc)_2$	10	CH_2Cl_2	60	trace
12	$Pd(OAc)_2$	10	1,4-dioxane	40	54
13	$Pd(OAc)_2$	10	1,4-dioxane	80	80
14[d]	$Pd(OAc)_2$	10	1,4-dioxane	60	55

[a]Reaction conditions: phenyldiazoacetate **1a** (0.3 mmol), **2a** (1.2 equiv), catalyst, and 4 Å MS (30.0 mg) in 1,4-dioxane (6.0 mL), 40, 60, or 80 °C, Ar, 12 h. [b]Yield calculated from the ^1H NMR spectrum with CH_2Br_2 as the internal standard. [c]Isolated yield. [d]Without 4 Å MS.

The reaction scope was first probed with respect to readily available stabilized diazo compounds, using *t*-BuNC (**2a**) as the coupling partner under the optimized conditions summarized in Table 1, entry 8, 10 mol % $Pd(OAc)_2$ in 1,4-dioxane at 60 °C with 4 Å MS (Scheme 1). A series of aryl ethyl diazoacetates possessing either electron-withdrawing (Br, NO_2, CO_2Et, CN, and CF_3) or electron-donating (OMe and Me) groups on the aryl ring (**1b**−**1i**) were suitable substrates, as they delivered the corresponding target products **3b**−**3i** in moderate to high yields. Aryl methyl diazoacetates (**1j**−**1l**), phenyl isopropyl diazoacetate (**1m**), and phenyl benzyl diazoacetate (**1n**) also yielded the corresponding ketenimines **3j**−**3n** in high yields. Ethyl diazoacetates **1o** and **1p** with a heterocyclic (indolyl and thienyl) substituent also reacted to afford **3o** and **3p** in 45 and 78% yields, respectively. Reaction with α-alkyl diazoacetates fared comparably. For example, benzyl- and methyl-substituted ethyl diazoacetates were coupled efficiently with **2a** to afford **3q** and **3r** in 86 and 72% yields, respectively. Excitingly, this transformation is not restricted to α-diazoacetates, in that α-diazophosphonates (**1s**−**1u**) effectively reacted to deliver the desired phosphonoketenimines **3s**−**3u** in moderate to high yields.[14]

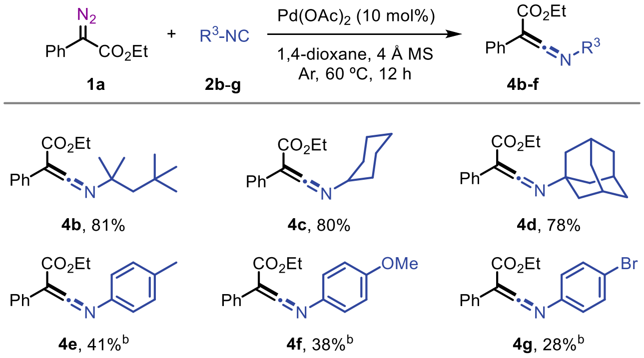
Subsequently, we turned our attention to varying the isocyanide component (Scheme 2). Under these conditions, readily available alkyl isocyanides such as 2-isocyano-2,4,4-trimethylpentane (**2b**), cyclohexyl isocyanide (**2c**), and 2-adamantyl isocyanide (**2d**) were coupled with **1a** to deliver products **4b**−**4d** in high yields (78−81%). Aryl isocyanides **2e**−**2g**, instead, required 5 mol % of preprepared 1,3-bis[2,6-di(propan-2-yl)phenyl]imidazolidin-2-ide,3-chloropyridine, dichloropalladium (PEPPSI-SIPR) as a catalyst to afford the corresponding coupling products **4e**−**4g**, albeit in a lower

Scheme 1. Reaction Scope of Diazo Compounds[a]



[a]Reaction conditions: **1a**−**1u** (0.3 mmol), **2a** (1.2 equiv), Pd(OAc)$_2$ (10 mol %), and 4 Å MS (30.0 mg) in 1,4-dioxane (6.0 mL) at 60 °C under Ar for 12 h; isolated yields. [b]18 h.

Scheme 2. Scope of Isocyanides[a]

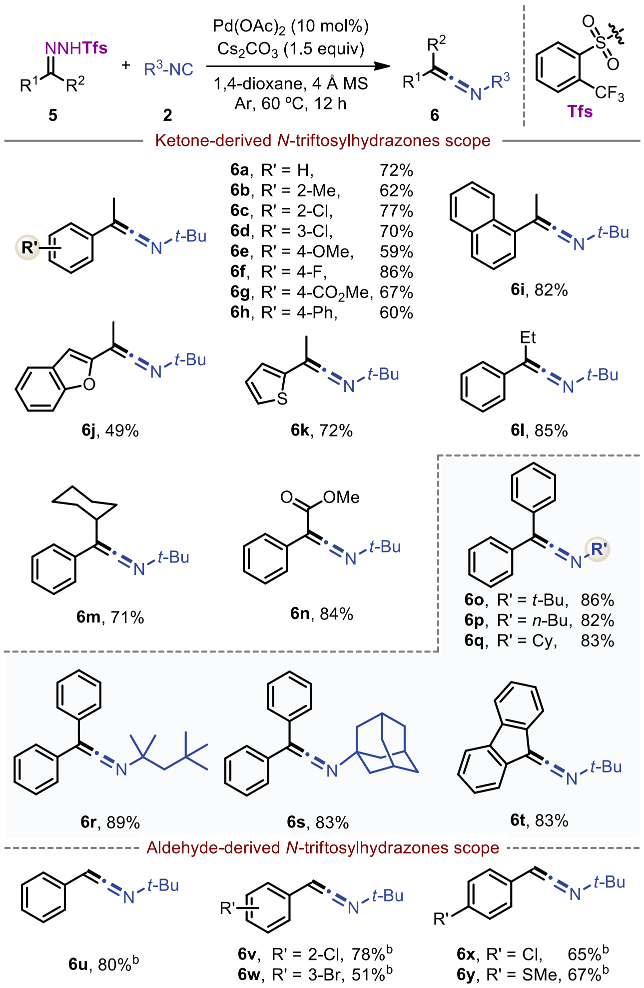


[a]Reaction conditions: phenyldiazoacetate **1a** (0.3 mmol), **2b**−**g** (1.2 equiv), Pd(OAc)$_2$ (10 mol %), 4 Å MS (30.0 mg) in 1,4-dioxane (6.0 mL) at 60 °C under Ar for 12 h; isolated yields. [b]PEPPSI-SIPR (5 mol %) was used as the catalyst, and the reaction was performed at 80 °C.

yield. These poor yields might result from the lower reactivity of aryl isocyanides, thus making the dimerization of diazo compounds faster than the reaction with aryl isocyanides.

Being inspired by the success of the cross-coupling of isocyanides with stabilized diazo compounds, we then turned our attention to nonstabilized donor-type diazo reagents to access ketenimines without an EWG substituent, which are difficult to isolate and used as intermediates in reactions.[8] Upon extensive evaluation of reaction conditions, the desired ketenimine **6o** was isolated in 86% yield by the treatment of *N*-triftosylhydrazones **5o** with *t*-BuNC **2a** in the presence of Pd(OAc)$_2$, Cs$_2$CO$_3$, and 4 Å MS at 60 °C.[19] Under these modified conditions, *t*-BuNC (**2a**) was readily coupled with *N*-triftosylhydrazones possessing electron-donating (Me and OMe) and electron-withdrawing (Cl, F, and CO$_2$Me) substituents on various positions of the phenyl ring, providing the corresponding ketenimines **6a**−**6g** in 59−86% yield (Scheme 3). Substrates featuring biphenyl (**5h**), naphthyl (**5i**), 2-benzofurenyl (**5j**), and 2-thienyl (**5k**) substituents also delivered the expected ketenimines **6h**−**6k** in moderate to good yields (49−82%). The influence of the R^2 substituent on the coupling reaction was investigated. For example, *N*-triftosylhydrazones with ethyl and cyclohexyl substituents (**5l** and **5m**) gave products **6l** and **6m** in 85 and 71% yields, respectively. The *N*-triftosylhydrazone derived from α-ketoester **5n** was also tolerated and gave the corresponding product **6n** in 84% yield, thus avoiding the use of a syringe pump for slow addition of diazo esters. We then turned our attention toward variously substituted symmetrical *N*-triftosylhydrazones. Benzophenone derivative **5o** coupled with different isocyanides, such as *t*-BuNC (**2a**), *n*-butyl isocyanide

Scheme 3. Palladium(II)-Catalyzed Cross-Coupling of *N*-Triftosylhydrazones with Isocyanides[a]

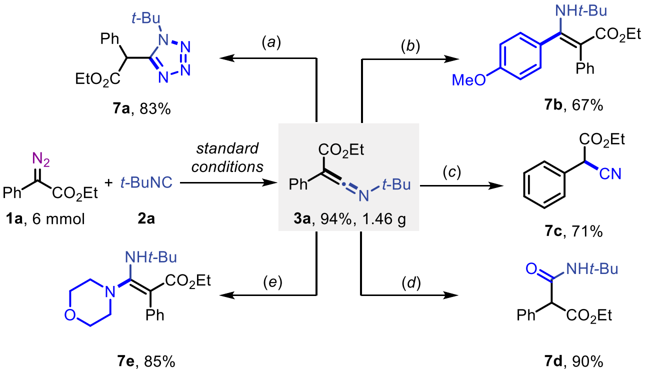


[a]Reaction conditions: *N*-triftosylhydrazone **5** (0.3 mmol) and Cs$_2$CO$_3$ (0.45 mmol) in 1,4-dioxane (5.0 mL) were stirred at room temperature for 1 h, then **2** (1.2 equiv), Pd(OAc)$_2$ (10 mol %), and 4 Å MS (30.0 mg) were added, after which the mixture was stirred at 60 °C for 12 h; isolated yields. [b]The reaction was performed at 40 °C.

(**2h**), and cyclohexyl isocyanide (**2c**), affords the expected products **6o**−**6q** in 82−86% yield. Sterically hindered isocyanides **2b** and **2d** were also coupled efficiently with **5o** to yield ketenimines **6r** and **6s** in 89 and 83% yields, respectively, and the fluorenone-derived substrate **5t** resulted in **6t** in 83% yield. This cross-coupling reaction is not limited to ketone-derived *N*-triftosylhydrazones only; aldehyde-derived *N*-triftosylhydrazones (**5u**−**5y**) could also be cross-coupled with **2a** at 40 °C to provide disubstituted ketenimines **6u**−**6y** in moderate to good yields (51−80%), confirming the versatility of this cross-coupling reaction.

As a demonstration of scalability of this cross-coupling method, we performed the reaction under the optimized conditions with 6 mmol **1a** and **2a**, obtaining the cross-coupling ketenimine product **3a** in 94% isolated yield (Scheme 4). Product **3a** could be transformed into a variety of derivatives, to attest to the synthetic versatility of keteinimines: to unprotected benzyl tetrazole **7a** by tandem hydroazidation/[3+2] cycloaddition with $TMSN_3$ (Scheme 4a); to *β*-enamino ester **7b** by the addition of *p*-methoxyphenylmagnesium bromide (Scheme 4b); to ethyl 2-cyano-2-phenylacetate **7c** by cleavage of the ketenimine N−C bond in the presence of $BF_3{\cdot}Et_2O$ (Scheme 4c); and to amide **7d** by hydrolysis (Scheme 4d).[15] Interestingly, palladium-catalyzed hydroamination of ketenimine **3a** with morpholine exclusively produced ene-1,1-diamine **7e** rather than the expected amidine (Scheme 4e).[8h]

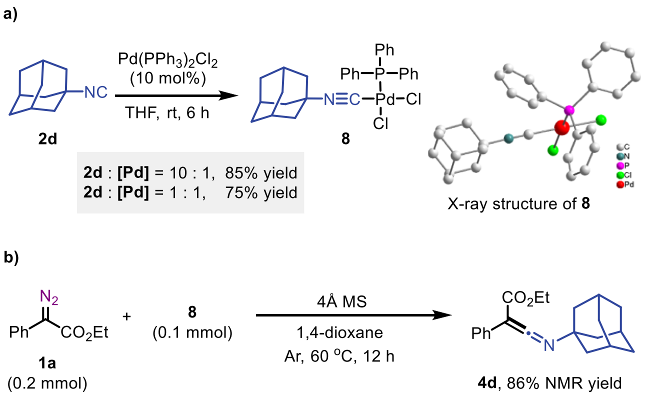
Scheme 4. Gram-Scale Reaction and Further Synthetic Transformations[a]



[a]Reagents and conditions: (a) $TMSN_3$ (2.0 equiv), toluene, 50 °C, overnight; (b) 4-OMePhMgBr (2.0 equiv), THF, 0 °C, Ar, 24 h; (c) $BF_3{\cdot}Et_2O$ (1.0 equiv), CH_2Cl_2, 0 °C to rt, Ar, 12 h; (d) 1 M HCl/dimethylformamide, 30 °C, 2 h; and (e) morpholine (1.2 equiv), $Pd(OAc)_2$ (5 mol %), and PPh_3 (15 mol %) in THF, 100 °C, 3 h.

Our initial screening results showed that this coupling reaction was effective with both Pd(0) and Pd(II) catalysts (entries 5−8, Table 1). In previously described Pd(II)-catalyzed isocyanide insertion reactions, palladium was assumed to change from the Pd(II) to Pd(0) oxidation state during the catalytic cycle, albeit no substantive evidence was presented to support this assertion.[14,15,18] To elucidate the reaction mechanism, we carried out a control reaction between isocyanide **2c** (1 mmol) and $Pd(PPh_3)_2Cl_2$ (10 mol %) in THF at room temperature for 6 h, which afforded the bench-stable Pd(II)−isocyanide complex **8** in 85% yield. The single-crystal X-ray structure of complex **8** (CCDC no. 1812945; for details, see the Supporting Information) clearly indicates that the Pd(II) center remains tetracoordinated in a square planar geometry, in which one isocyanide group is strongly coordinated to the Pd(II) center as a result of ligand exchange with one of the triphenylphosphine ligands (Scheme 5a).

Scheme 5. Experiments for Mechanistic Investigations; (a) Isolation of Pd(II) Complex 8; (b) Reaction of Isolated Pd(II) Complex 8 with 1a.



Subsequently, the isolated palladium complex **8** was treated with **1a** in dioxane at 60 °C for 12 h, affording the target product **4d** in 86% NMR yield (Scheme 5b). These results suggest that when a Pd(II) precatalyst is used, the oxidation state of palladium does not change during the course of the catalytic process, which is in contrast to the previously described Pd(II)-catalyzed isocyanide insertion reactions.[6d,14,15,18]

A proposed mechanism for the Pd(II)-catalyzed isocyanide insertion reaction was supported by DFT calculations at the M06/6-311+G(d,p)-SDD(Pd) level of theory. The Pd(II)−isocyanide complex **8** was chosen as the starting point for the free energy profiles for the cross-coupling process with phenyldiazoacetate **1a** (Figure 2; for details, see the Supporting Information). Because of the spatial extension of the Ph_3P and isocyanide ligands, which fill the axial Pd d_{z^2} orbital, coordination of ligands via the empty axial p_z orbital is blocked, thus a dissociation mechanism is favored over an association mechanism.[20] By virtue of a strong *trans* effect of the PPh_3 ligand,[21] the ligand exchange energy of the chloride ligand opposed to PPh_3 is the lowest among all ligands in **8**, as shown by the relative free energy of **Int1-1** compared with **Int1-2** and **Int1-3**. Here, the ligand exchange refers to the first dynamic dissociation of the chlorine ligand of **8** and then coordination with phenyldiazoacetate **1a** to form the diazo complex **Int1-1**. The ensuing dissociation of N_2 to form the Pd(II)−carbene complex **Int3** occurs via **TS1**, with $\Delta\Delta G^{\ddagger}$ = 9.3 kcal/mol, followed by the migratory insertion of Pd(II)−carbene via a three-membered ring transition state **TS2**, $\Delta\Delta G^{\ddagger}$ = 16.7 kcal/mol, releasing $Pd(PPh_3)Cl_2$ and the product **4d**. The migratory insertion of Pd(II)−carbene is the rate-determining step for the overall reaction, as it presents an energy barrier ($\Delta\Delta G^{\ddagger}$) of 16.7 kcal/mol, easily surmountable at the temperature (60 °C) established for this experimental procedure of this reaction. The oxidation state of Pd(II) remains unchanged during the course of the catalytic process.

3. CONCLUSIONS

A simple and practical method for the synthesis of ketenimines via a palladium-catalyzed cross-coupling reaction of diazo

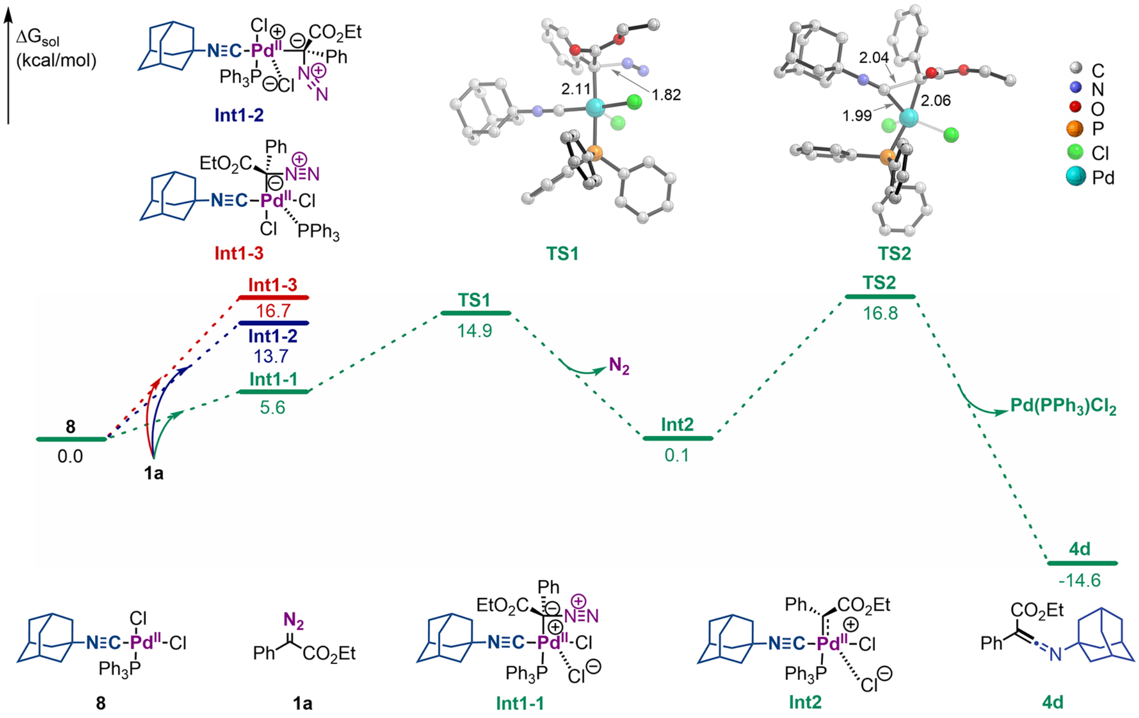


Figure 2. Gibbs-free energy profile (in kcal/mol) for the cross-coupling of phenyldiazoacetate **1a** with Pd(II)−isocyanide complex **8** calculated at SMD//M06/6-311+G(d,p)-SDD(Pd) level in 1,4-dioxane. AdNC: 2-adamantyl isocyanide. Distances are given in angstroms.

compounds with isocyanides was established under mild conditions. The operationally simple protocol is compatible with substrates ranging from stabilized diazo compounds to *N*-triftosylhydrazones as nonstabilized diazo surrogates and affords ketenimines in good to excellent yield. This synthetic methodology provides a valuable alternative to the existing methods that rely on scarcely available substrates. The combination of experimental results and DFT calculations provided evidence that the in situ-generated Pd(II)−isocyanide complex is a key reactive intermediate in the catalytic cycle. According to the proposed reaction mechanism, the palladium center preserves its oxidation state of Pd(II), differently from previously reported Pd-catalyzed cross-coupling reactions. Further investigations toward an enantioselective variant to access axially chiral ketenimines are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c02867.

> Details on reagents and experimental procedures, optimization of the reaction conditions, characterization data, synthetic transformations, mechanistic studies, computational studies, X-ray crystallographic data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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