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Pd-Catalyzed Carbonylation of Diazo Compounds at Atmospheric Pressure: A Catalytic Approach to Ketenes

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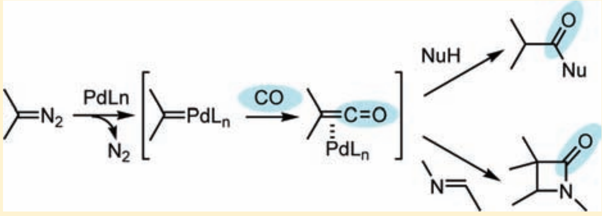
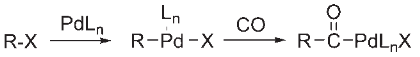
S *Supporting Information*

ABSTRACT: The carbonylation of carbenes through catalytic cycles is highly desirable due to the importance of ketene-mediated reactions in organic synthesis. In this investigation, a highly efficient and mild catalytic approach toward ketene intermediates has been developed based on Pd-catalyzed carbonylation of diazo compounds with CO. When α-diazocarbonyl compounds or *N*-tosylhydrazone salts are heated in the presence of a palladium catalyst under atmospheric pressure of CO, ketene intermediates are formed *in situ*, where they undergo further reactions with various nucleophiles such as alcohols, amines, or imines. The Pd-catalyzed tandem carbonylation−Staudinger cycloaddition gives β-lactam derivatives in good yields with excellent *trans* diastereoselectivity. The results from DFT calculation on the reaction mechanism suggest that Pd is involved in the [2 + 2] cycloaddition process and affects the diastereoselectivity of the β-lactam products by assisting isomerization of the addition intermediate. On the other hand, the acylketenes generated from the Pd-catalyzed carbonylation of α-diazoketones react with imines in a formal [4 + 2] cycloaddition manner to afford 1,3-dioxin-4-one derivatives. This straightforward carbonylation provides a new approach toward highly efficient catalytic generation of ketene species under mild conditions.

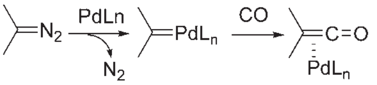


INTRODUCTION

Transition metal-catalyzed carbonylation *via* migratory CO insertion is a vital, elementary process in organometallic chemistry. In particular, Pd-catalyzed carbonylation offers a powerful method to introduce C═O group into organic molecules (eq 1), which is now well-established as one of the most important ways to synthesize a wide variety of compounds bearing carbonyl functionality.[1] In comparison with the CO insertion into M−C bonds, which leads to the formation of acyl−metal species, the carbonylation of metal carbenes would afford metal-complexed ketene intermediate (eq 2). However, this type of transformations is less developed.[2−8] Carbonylation of metal carbene with CO has been mainly focused on stoichiometric transformations, among which the stoichiometric CO insertion of Fischer carbene complexes under photolytic or thermolytic conditions is probably the most prevalent one.[2] The ketenes thus generated have found useful applications in synthetic transformations such as benzannulation reactions (Dötz reaction), and [2 + 2] ketene−imine or ketene−alkene cycloadditions. Since Dötz initially reported the synthesis of naphthoquinone frameworks by the cycloaddition of phenyl-Fischer carbene complexes to alkynes with direct CO insertion,[3a] the reactions of α,β-unsaturated carbene complexes with CO and alkynes leading to the construction of fused cyclic or polysubstituted aryl compounds have attracted great attention in the synthetic organic community.[3] In addition, β-lactam synthesis is another important application of Fischer carbene carbonylation processes, as demonstrated by Hegedus et al.[2a,c] Although those carbene carbonylations are highly reliable and versatile, the stoichiometric use of the transition metal in the preparation of Fischer carbene complexes limits their application in organic synthesis to some extent.



$$\mathrm{R{-}X} \xrightarrow{\mathrm{PdL_n}} \mathrm{R{-}\overset{L_n}{Pd}{-}X} \xrightarrow{\mathrm{CO}} \mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}PdL_nX} \qquad (1)$$



(2)

Carbonylation of metal carbenes with CO in a catalytic reaction has been only sporadically documented, and in most cases the efficiency of reaction is not high, and rigorous conditions such as high pressure of CO and high reaction temperature are needed.[5−8] For example, transition metal-catalyzed carbonylation of dihaloalkanes with CO have been investigated by Miyashita[5] and Osborn.[6] $Rh_2(OAc)_4$-catalyzed carbonylation of ethyl diazoacetate (EDA) has also been reported with high

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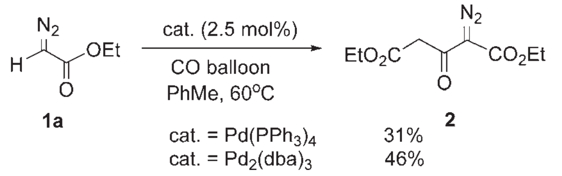
pressure of CO (70 bar).[7] Ungváry and co-workers have systematically studied $Co_2(CO)_8$-catalyzed carbonylation of EDA with CO.[8] They found that ketenes could be formed under a 50 bar pressure of CO, and they reacted further with alcohols to give 1,3-dicarbonyl compounds.[8a] They also demonstrated that β-lactam synthesis was possible by employing imines in the reaction.[8i] These seminal reports indicate that carbonylation of diazo compounds with CO under transition metal-catalyzed conditions is possible. However, while highly significant, these studies are limited in scope (only ethyl diazoacetate is employed as diazo substrate in most cases) and by harsh reaction conditions including high pressure of CO and high reaction temperature, which would hamper their wide applications in preparative organic chemistry.

On the other hand, ketenes are highly useful reactive intermediates in organic chemistry. In particular, they have been extensively used in β-lactam synthesis.[2a,c,9] Ketenes are normally generated in stoichiometric manner by treatment of acyl halides with base.[10,11] Therefore, it would be highly desirable to develop efficient catalytic metal carbene carbonylation process under mild reaction conditions.

Pd complexes are versatile catalysts in various transition metal-catalyzed transformations, particularly in the cross-coupling reactions, which have been developed into indispensable tools in modern synthetic organic chemistry.[12] However, in sharp contrast to those extensive studies, Pd—carbenes in catalytic transformations have so far received much less attention.[13,14] Studies in the past few years have suggested Pd—carbene species can be generated as vital intermediates in Pd-catalyzed reactions of diazo compounds.[15] Those intermediates, which mostly undergo migratory insertions, demonstrate unique properties and thus provide new possibilities for transformations based on Pd catalysis.[14] Very recently, we have reported Pd-catalyzed sequential carbonylation/acyl insertion of diazo compounds.[14m] To further explore the potential of Pd-carbene transformations in organic synthesis, we carried out a study of Pd-catalyzed carbonylation of diazo compounds. It was expected that ketene intermediates may be generated under mild conditions and employed in reactions with nucleophiles to afford esters and amides, or with imines to provide β-lactams. Herein we report an efficient Pd-catalyzed carbonylation of α-diazocarbonyl compounds and *N*-tosylhydrazones as well as tandem reactions with nucleophiles and imines. The results demonstrate that Pd-catalyzed carbonylation of diazo compounds is general and can be carried out under atmospheric pressure of CO.

RESULTS

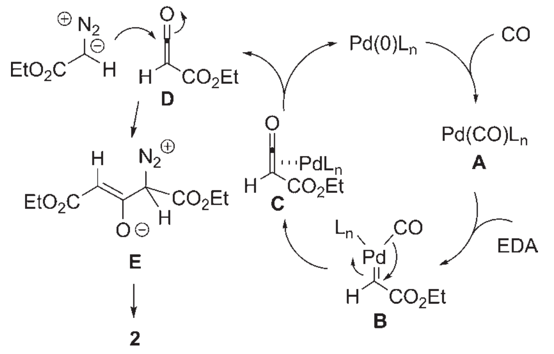
At the outset, the reaction of ethyl diazoacetate (EDA) was catalyzed with $Pd(PPh_3)_4$ under an atmosphere of CO in toluene at 60 °C. Unexpectedly, diethyl 2-diazo-3-oxoglutarate **2** was isolated as a major product in 31% yield (eq 3). When using $Pd_2(dba)_3$ [tris(dibenzylideneacetone)dipalladium(0)] as catalyst, the yield could be slightly improved to 46%. We have noted that the same diazo product was also obtained in Ungváry's study of $Co_2(CO)_8$-catalyzed carbonylation of EDA with CO.[8a]



(3)

The formation of diazo compound **2** can be rationalized by the reaction mechanism shown in Scheme 1. We assume that

Scheme 1. Mechanistic Rationale for the Formation of 2



CO-complexed Pd species **A** is the active catalyst in the system. Decomposition of the diazo compound induced by the Pd catalyst generates a Pd—carbene **B**, which undergoes carbonylation to give ketene intermediates **C** or **D**. The ketene is then attacked by EDA, which functions as a simple nucleophile in this step,[16] affording intermediate **E**. Intermediate **E** undergoes proton transfer to give the final product **2**.

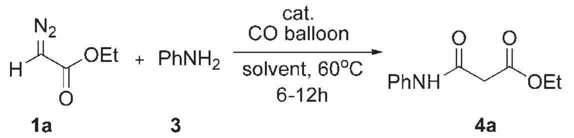
This initial result suggests that Pd-catalyzed carbonylation is a highly efficient process which may serve as a useful method to access ketene species. On the basis of the mechanism shown in Scheme 1, we hypothesized that, if a stronger nucleophile was introduced into this reaction system, the ketene intermediate **D** might be trapped before it can react with EDA. To our delight, this was indeed the case. When the reaction was carried out in the presence of aniline **3**, ethyl 2(phenylcarbamoyl)acetate **4a** was isolated in 50% yield (Table 1, entry 1). Further optimization of the reaction conditions revealed that this reaction proceeded most efficiently in the nonpolar solvent PhMe, whereas reactions in solvents of high polarities such as THF, dioxane, MeCN, and DMF afforded poor yields (entries 2—6). As for the Pd catalysts, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ both gave moderate yields (entries 7, 8), while Pd catalysts containing other phosphine ligands were found not to be effective in this reaction (entries 11—14). However, the yield could be slightly improved by $Pd_2(dba)_3$ (entry 9). The use of inorganic bases K_2CO_3 or K_3PO_4 further improved the yields (entries 15, 16).

To demonstrate the generality of this reaction, a series of α-diazocarbonyl compounds was subjected to the optimized reaction conditions. As shown in Table 2, in all cases the corresponding 1,3-dicarbonyl products were obtained in moderate to good yields. The reaction also worked well with α-diazoketones (entries 5 and 6). It is worth noting that the reactions with both α-aryl and α-alkyl diazocarbonyl compounds proceeded smoothly, affording the corresponding amides in moderate yields (entries 7—9).

We further investigated the reaction scope by employing nucleophiles other than anilines (Table 3). The experiments show that the ketene generated by the Pd-catalyzed carbonylation can be trapped by wide range of nucleophiles. The reaction occurred smoothly with substituted aromatic amines (entries 1—5). Primary and secondary aliphatic amines were also suitable nucleophiles (entries 6—8). Besides, the extension of this reaction to phenol and alcohols also gave the expected results (entries 9—11).

The Pd-catalyzed carbonylation of α-diazoketones produces acylketene species. Acylketenes have been demonstrated as

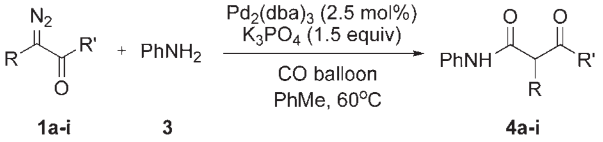
Table 1. Conditions of Pd-Catalyzed Reaction of CO with EDA **1a** and Aniline **3**[a]



entry	cat. (mol %)	solvent	time (h)	yield (%)[b]
1	$Pd(PPh_3)_4$(5)	PhMe	7	50
2	$Pd(PPh_3)_4$(5)	THF	7	32
3	$Pd(PPh_3)_4$(5)	Dioxane	7	45
4	$Pd(PPh_3)_4$(5)	DCE	6	27
5	$Pd(PPh_3)_4$ (5)	MeCN	12	<10
6	$Pd(PPh_3)_4$(5)	DMF	12	<10
7	$PdCl_2(PPh_3)_2$(5)	PhMe	7	33
8	$Pd(OAc)_2$ (5)	PhMe	7	63
9	$Pd_2(dba)_3$ [c](2.5)	PhMe	7	74
10	Pd/C (5)	PhMe	9	44
11	$Pd(OAc)_2$(5)/dppb [d](5)	PhMe	7	48
12	$Pd_2(dba)_3$(2.5)/PBu_3(10)	PhMe	7	63
13	$Pd_2(dba)_3$(2.5)/dppf [e](6)	PhMe	7	68
14	$Pd(OAc)_2$(5)/ $P(OEt)_3$(10)	PhMe	7	67
15	$Pd_2(dba)_3$(2.5)/K_2CO_3(150)	PhMe	6	83
16	**$Pd_2(dba)_3$(2.5)/K_3PO_4 (150)**	**PhMe**	**6**	**87**
17[f]	$Pd_2(dba)_3$(2.5)	PhMe	6	83

[a] Reaction was carried out with 1.0 equiv of **1a** and 1.5 equiv of **3**. [b] Isolated yield with silica gel column. [c] $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0). [d] dppb = 1,2-bis(diphenylphosphino)ethane. [e] dppf = 1,1′-bis(diphenylphosphino)ferrocene. [f] Reaction was carried out with 1.0 equiv of **1a** and 3.0 equiv of **3**.

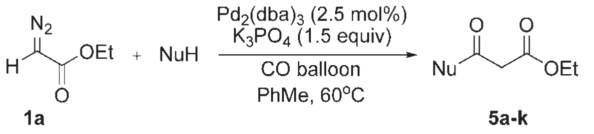
Table 2. $Pd_2(dba)_3$-Catalyzed Reactions of CO with α-Diazocarbonyl Compounds **1a-i** and Aniline **3**[a]



entry	diazo compound **1**	time (h)	yield (**4**, %)[b]
1	**1a**, R = H, R′ = OEt	6	**4a**, 87
2	**1b**, R = H, R′ = O^{i}Pr	7	**4b**, 81
3	**1c**, R = H, R′ = O^{t}Bu	10	**4c**, 66
4	**1d**, R = H, R′ = OBn	6	**4d**, 70
5[c]	**1e**, R = H, R′ = CH_3	6	**4e**, 67
6[c]	**1f**, R = H, R′ = Ph	6	**4f**, 88
7	**1g**, R = Ph, R′ = OMe	18	**4g**, 51
8	**1h**, R = $(CH_2)_3$Ph, R′ = OEt	18	**4h**, 62
9	**1i**, R = CH_3, R′ = Ph	19	**4i**, 57

[a] Reaction conditions: a solution of $Pd_2(dba)_3$ (0.0125 mmol), K_3PO_4 (0.75 mmol), **1a**−**i** (0.5 mmol), and **3** (1.5 mmol) in toluene (4 mL) was stirred at 60 °C under atmospheric pressure of CO (balloon). [b] Isolated yield by silica gel column chromatography. [c] Reaction was carried out in the absence of K_3PO_4.

Table 3. $Pd_2(dba)_3$-Catalyzed Reactions of CO with EDA **1a** and Different Nucleophiles[a]



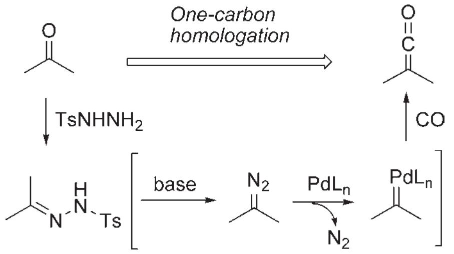
entry	NuH	time (h)	yield (**5**, %)[b]
1	p-$MeOC_6H_4NH_2$	6	**5a**, 82
2	p-$NO_2C_6H_4NH_2$	6	**5b**, 72
3	3,4-$Cl_2C_6H_3NH_2$	6	**5c**, 76
4	2-naphthylamine	6	**5d**, 61
5	Ph_2NH	6	**5e**, 72
6	$BnNH_2$	6	**5f**, 83
7	n-$BuNH_2$	11	**5g**, 67
8	morpholine	12	**5h**, 54
9	PhOH	7	**5i**, 50
10	$PhCH{=}CHCH_2OH$	6	**5j**, 70
11	$Ph(CH_2)_3OH$	6	**5k**, 81

[a] Reaction conditions: **1a** (1 equiv), NuH (1.5 equiv). [b] Isolated yield by silica gel column chromatography.

versatile intermediates in organic synthesis. Their unique reactivity and selectivity have been extensively studied both experimentally and theoretically.[17] However, the methods for the generation of these reactive species have been limited.[17j] Thus, the Pd-catalyzed carbonylation of α-diazoketones provides a novel approach to these species.

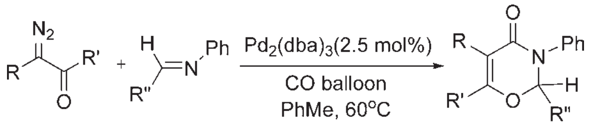
To further investigate the reaction of the ketenes generated by Pd-catalyzed carbonylation of α-diazoketones, we proceeded to introduce imine into the reaction system. It is well documented that acylketene has the tendency to participate as the four-center partner in formal [4 + 2] cycloadditions, instead of engaging in formal [2 + 2] cycloaddition typical of normal ketenes.[17b,f,h,i] The formal [4 + 2] cycloaddition reaction of acylketenes with imines has been documented in the literature.[17b] We found that the acylketenes generated by the Pd-catalyzed carbonylation of diazoketones also reacted with imines in a similar manner to afford 1,3-dioxin-4-one derivatives in good yields (Table 4).

To further expand this ketene generation methodology, the subsequent study was focused on the Pd-catalyzed reaction with *N*-tosylhydrazones.[14d,e,k,n] *N*-Tosylhydrazones are widely used as precursors for *in situ*-generation of nonstabilized diazo compounds.[18] Since *N*-tosylhydrazones can be easily prepared from ketones and aldehydes, this transformation represents a two-step conversion of an oxo group into a ketene group. Moreover, we expect that the ketene thus generated will be useful in *β*-lactam synthesis by the formal [2 + 2] cycloaddition with an imine.



Hence, the reaction of the *N*-tosylhydrazone sodium salt **8a** and anline **3** was catalyzed with $Pd_2(dba)_3$ under an atmosphere of CO in toluene at 60 °C. To our delight, benzeneacetamide **9a** was isolated in 64% yield (Table 5, entry 1). Further optimization of the reaction conditions revealed that the yield could be slightly improved by adding PTC (Aliquat 336, tri*n*-octylmethylammonium chloride) (entry 2). Both polar and nonpolar solvents were suitable for this reaction (entries 2−6), and again toluene was the best solvent. As for the Pd catalysts, $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ both gave low yields (entries 7, 8), while Pd catalysts containing phosphine ligands were found to be ineffective in this reaction (entries 9−13). The use of inorganic bases K_2CO_3 or K_3PO_4 could also improve the yields (entries 14, 15). The sodium salt **8a** could also be formed *in situ* using NaH as the base, with nearly the same yield (entry 16).

Table 4. $Pd_2(dba)_3$-Catalyzed Carbonylation of α-Diazocarbonyl Compounds with imines[a]



1f,j,k,l **6a,b** **7a-f**

entry	**1**, R =, R′ =	imine (**6**, R″ =)	time (h)	yield (**7**, %)[b]
1	**1f**, R = H, R′ = Ph	**6a**, R″ = Ph	18	**7a**, 65
2	**1i**, R = CH_3, R′ = Ph	**6a**, R″ = Ph	8	**7b**, 93
3	**1j**, R = CH_3, R′ = CH_3	**6a**, R″ = Ph	9	**7c**, 87
4[c]	**1k**, R = Ph, R′ = CH_3	**6a**, R″ = Ph	8	**7d**, 75
5	**1l**, R = R′ = $-(CH_2)_4-$	**6a**, R″ = Ph	8	**7e**, 74
6	**1i**, R = CH_3, R′ = Ph	**6b**, R″ = CO_2Et	9	**7f**, 85

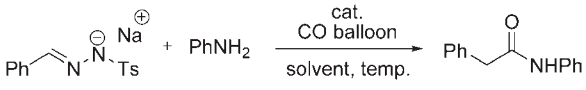
[a] Reaction conditions: **1f-j, l, i** (1.5 equiv), **6a,b** (1 equiv). [b] Isolated yield. [c] Reaction was carried out with 3.0 equiv of **1k** and 1.0 equiv of **6a**.

Next, a series of *N*-tosylhydrazones was subjected to the optimized reaction condition. As shown in Table 6, in all cases the corresponding acetamide products were obtained in moderate to high yields. The reaction also worked well with disubstituted *N*-tosylhydrazones, although the reaction time took longer in these cases (entries 11 and 12). Notably, α,*β*-unsaturated *N*-tosylhydrazones can undergo this reaction in moderate yields (entries 13, 14). The scope of using different nucleophiles was also examined. Primary and secondary amines as well as phenol and primary alcohols were all suitable for this reaction (entries 17−20).

Furthermore, because the formation of *N*-tosylhydrazones is a very easy process, it was conceivable that this carbonylation could be carried out directly from aldehydes or ketones in a one-pot fashion.[14e] A preliminary study indicates that such a one-pot process is indeed possible. By simply heating the carbonyl compounds **10** with tosylhydrazine and performing the subsequent Pd-catalyzed carbonylation without isolating the intermediate *N*-tosylhydrazone, the corresponding one-carbon homologation products could be isolated (Scheme 2). Further optimization of the reaction condition is still required.

Since the most prominent application of ketene is the construction of *β*-lactam skeletons through formal [2 + 2] cycloaddition with imines,[9,10] we explored the possibility of *β*−lactam synthesis with the Pd-catalyzed carbonylation of *N*-tosylhydrazones. Compared with the acylketenes generated by Pd-catalyzed carbonylation of α−diazoketones, which undergo formal [4 + 2] cycloaddition with imines, ketenes generated from *N*-tosylhydrazones are expected to undergo formal [2 + 2] cycloaddition with imines. To our satisfaction, the reaction with imines occurred smoothly under slightly modified conditions (with *N*-tosylhydrazone salt as substrate, DCE as solvent, and in

Table 5. Conditions of Pd-Catalyzed Reaction of CO with *N*-Tosylhydrazone Sodium Salt 8a and Aniline 3[a]

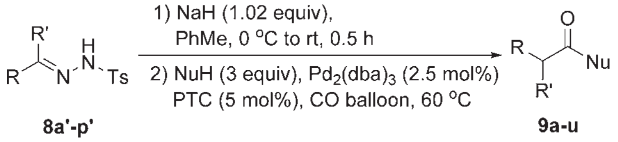


8a **3** **9a**

entry	cat. (mol %)	solvent	time (h)	yield (%)[b]
1	$Pd_2(dba)_3$ (2.5)	PhMe	24	64
2	$Pd_2(dba)_3$(2.5)/PTC [c](5)	PhMe	24	75
3	$Pd_2(dba)_3$(2.5)/PTC(5)	THF	24	59
4	$Pd_2(dba)_3$(2.5)/PTC(5)	Dioxane	24	64
5	$Pd_2(dba)_3$(2.5)/PTC(5)	DCE	24	62
6	$Pd_2(dba)_3$(2.5)/PTC(5)	MeCN	24	55
7	$Pd(OAc)_2$(5)/PTC(5)	PhMe	24	12
8	$Pd(PPh_3)_2Cl_2$(5)/PTC(5)	PhMe	25	<5
9	$Pd(PPh_3)_4$(5)/PTC(5)	PhMe	25	17
10	$Pd(OAc)_2$(5)/dppb (5)/PTC (5)	PhMe	24	9
11	$Pd_2(dba)_3$(2.5)/dppf (5) /PTC(5)	PhMe	24	33
12	$Pd_2(dba)_3$(2.5)/PCy_3[d] (5)/PTC (5)	PhMe	24	40
13	$Pd_2(dba)_3$(2.5)/P(*n*-Bu)$_3$(5)/PTC(5)	PhMe	24	26
14	$Pd_2(dba)_3$(2.5)/PTC(5)/K_3PO_4(3 equiv)	PhMe	23	78
15	$Pd_2(dba)_3$(2.5)/PTC(5)/K_2CO_3(3 equiv)	PhMe	22	81
16	**$Pd_2(dba)_3$(2.5)/PTC(5)/K_2CO_3(3 equiv)**[e]	**PhMe**	**26**	**84**

[a] Reaction was carried out with 1.0 equiv of **8a** and 3.0 equiv of **3** at 60 °C. [b] Isolated yield by silica gel column chromatography. [c] PTC = Aliquat 336, tri-*n*-octylmethylammonium chloride. [d] PCy_3 = tricyclohexylphosphine. [e] Sodium salt **8a** was formed *in situ* from benzaldehyde tosylhydrazone **8a′** using NaH as the base.

Table 6. $Pd_2(dba)_3$-Catalyzed Reactions of CO with *N*-Tosylhydrazones 8a′−p′ and Different Nucleophiles[a]



entry	R =, R′ =	NuH	time (h)	yield (%)[b]
1	**8a′**, R = Ph, R′ = H	$PhNH_2$	24	**9a**, 84
2	**8b′**, R = *p*-MeC_6H_4, R′ = H	$PhNH_2$	23	**9b**, 92
3	**8c′**, R = *o*-MeC_6H_4, R′ = H	$PhNH_2$	23	**9c**, 82
4	**8d′**, R = *p*-ClC_6H_4, R′ = H	$PhNH_2$	23	**9d**, 85
5	**8e′**, R = *p*-$MeOC_6H_4$, R′ = H	$PhNH_2$	24	**9e**, 81
6	**8f′**, R = *p*-$MeO_2CC_6H_4$, R′ = H	$PhNH_2$	23	**9f**, 32
7	**8g′**, R = 2,4-$(Cl)_2C_6H_3$, R′ = H	$PhNH_2$	26	**9g**, 71
8	**8h′**, R = 3,5-$(MeO)_2C_6H_3$, R′ = H	$PhNH_2$	24	**9h**, 59
9	**8i′**, R = 2-naph, R′ = H	$PhNH_2$	23	**9i**, 80
10	**8j′**, R = 2-furyl, R′ = H	$PhNH_2$	25	**9j**, 73
11	**8k′**, R = Ph, R′ = Ph	$PhNH_2$	96	**9k**, 56
12	**8l′**, R = Ph, R′ = Me	$PhNH_2$	96	**9l**, 77
13	**8m′**, R = (*E*)-PhCH═CH, R′ = H	$PhNH_2$	23	**9m**, 54
14	**8n′**, R = (*E*)-MeCH═CH, R′ = H	$PhNH_2$	23	**9n**, 55
15	**8o′**, R = $Ph(CH_2)_2$, R′ = H	$PhNH_2$	23	**9o**, 41
16	**8p′**, R = ^{t}Bu, R′ = H	$PhNH_2$	23	**9p**, 44
17	**8a′**, R = Ph, R′ = H	$^n BuNH_2$	22	**9q**, 84
18	**8a′**, R = Ph, R′ = H	morpholine	22	**9r**, 88
19	**8a′**, R = Ph, R′ = H	MeOH	24	**9s**, 78
20	**8a′**, R = Ph, R′ = H	PhOH	23	**9t**, 72
21	**8a′**, R = Ph, R′ = H	$PhCH═CHCH_2OH$	23	**9u**, 65

[a] Reaction conditions: a solution of $Pd_2(dba)_3$ (0.0075 mmol), K_2CO_3 (0.9 mmol), **8a′**−**p′** (0.3 mmol), Aliquat 336 (0.015 mmol, 0.5 M solution in toluene), and aniline **3** (0.9 mmol) in toluene (10 mL) was vigorously stirred at 60 °C under atmospheric pressure of CO (balloon). [b] Isolated yield by silica gel column chromatography.

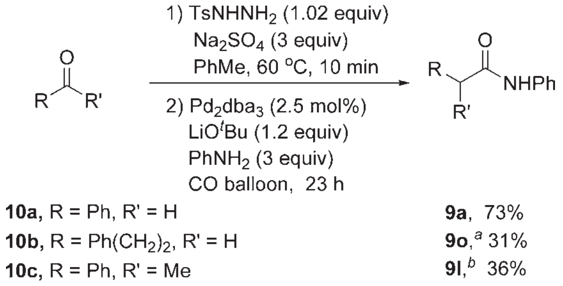
the absence of PTC).[19] A series of *N*-tosylhydrazone salts **8a**−**j** was subjected to these reaction conditions with *N*-methyl- or *N*-benzylbenzaldimines **11a** and **11b** (Table 7). In all cases, the corresponding *β*-lactam product was obtained in moderate to good yield. Remarkably, for most of the substrates, the reactions afforded *trans* products with excellent diastereoselectivity, except in cases where an *N*-benzyl substituted imine was used or when the *N*-tosylhydrazone salt contains a strong electron-donating substituent (entries 2 and 5). In the case of reaction of **8a** with **11a**, it was observed that the *trans* to *cis* ratio (>95:5) was not affected by changing solvent or by adding additives.

Finally, because structural diversity on the ketene moiety may lead to *β*-lactam derivatives with novel biological activities, the Pd-catalyzed carbonylation was further carried out with a series of α,*β*-unsaturated *N*-tosylhydrazones **13a**−**g**. As summarized in Scheme 3, the corresponding α,*β*-unsaturated *β*-lactam derivatives **14a**−**i** were obtained in high yields with excellent *trans* diastereoselectivity in most cases. The structure of **14e** was confirmed by X-ray crystallographic analysis (Figure 1).

■ MECHANISTIC CONSIDERATIONS

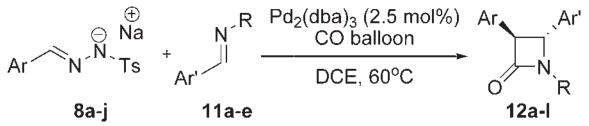
Proposed Mechanism. Although ketene−imine [2 + 2] cycloaddition has been widely used for the synthesis of *β*−lactam derivatives, its reaction mechanism, in particular the problem of diastereoselectivity, has been remained controversial and is still under extensive theoretical and experimental studies until very recently.[20] In the case of free ketene−imine [2 + 2] cycloaddition, the generally accepted stepwise mechanism involves: (a) nucleophilic attack of the imine nitrogen to the ketene to form a zwitterionic intermediate. The steric factors are considered to play the key role in this step; (b) conrotatory ring closure to afford the *β*−lactam product. Both steric factors and "torquoelectronic effect" are suggested to play the role in this step.

Scheme 2. One-Pot Palladium-Catalyzed Homologation of Aldehydes and Ketones



[a] Reaction is carried out at 100 °C. [b] Reaction time is 96 h.

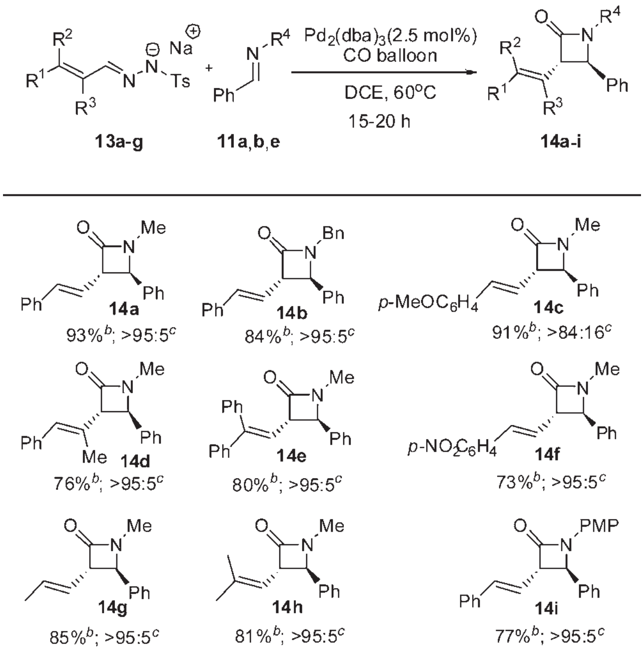
Table 7. $Pd_2(dba)_3$-Catalyzed Reactions of CO with *N*-Tosylhydrazone Salts **8a−j** and Imines **11a−e**[a]



entry	8a−j, Ar	11, R, Ar′	time (h)	12, yield(%)[b] (*trans*: *cis*)[c]
1	**8a**, Ph	**11a**, Me, Ph	14	**12a**, 80 (>95:5)
2	**8a**, Ph	**11b**, Bn, Ph	16	**12b**, 63 (55:45)
3	**8b**, *p*-MeC_6H_4	**11a**, Me, Ph	20	**12c**, 97 (>95:5)
4	**8d**, *p*-ClC_6H_4	**11a**, Me, Ph	16	**12d**, 96 (>95:5)
5	**8e**, *p*-$MeOC_6H_4$	**11a**, Me, Ph	18	**12e**, 92 (40:60)
6	**8f**, *p*-$MeO_2CC_6H_4$	**11a**, Me, Ph	24	**12f**, 81 (>95:5)
7	**8g**, 2,4-$(Cl)_2C_6H_3$	**11a**, Me, Ph	18	**12g**, 47 (>95:5)
8	**8i**, 2-naph	**11a**, Me, Ph	14	**12h**, 98 (>95:5)
9	**8j**, 2-furyl	**11a**, Me, Ph	16	**12i**, 22 (>95:5)
10	**8a**, Ph	**11c**, Me, *p*-$MeOC_6H_4$	19	**12j**, 87 (71:29)
11	**8a**, Ph	**11d**, Me, *p*-$O_2NC_6H_4$	19	**12k**, 96 (14:86)
12	**8a**, Ph	**11e**, PMP, Ph	22	**12l**, 76 (>95:5)

[a] Reaction conditions: a solution of $Pd_2(dba)_3$ (0.0165 mmol), *N*-tosylhydrazone sodium salt **8a−j** (0.66 mmol), and imine **11a−e** (0.3 mmol) in anhydrous DCE (10 mL) was stirred at 60 °C under atmospheric pressure of CO (balloon). [b] Isolated yield by silica gel column chromatography. [c] Ratio of the two diastereomers was determined by ^1H NMR (400 MHz) of the crude reaction mixture.

Scheme 3. $Pd_2(dba)_3$-Catalyzed Reactions of CO with α,*β*-Unsaturated *N*-Tosylhydrazone Salts **13a−g** and Imines **11a, b,e**[a]



[a] Reaction was carried out with 1.8 equiv of **13a−g** and 1.0 equiv of **11a, b, e** under otherwise identical conditions as described in Table 7. [b] Isolated yield with by silica gel column chromatography. [c] *trans*:*cis* ratio determined by ^1H NMR (400 MHz) of the crude product.

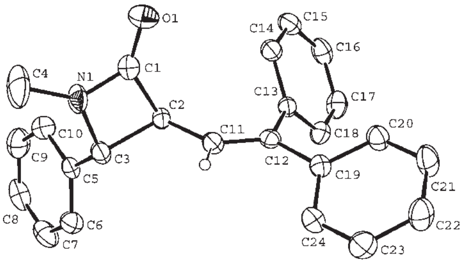


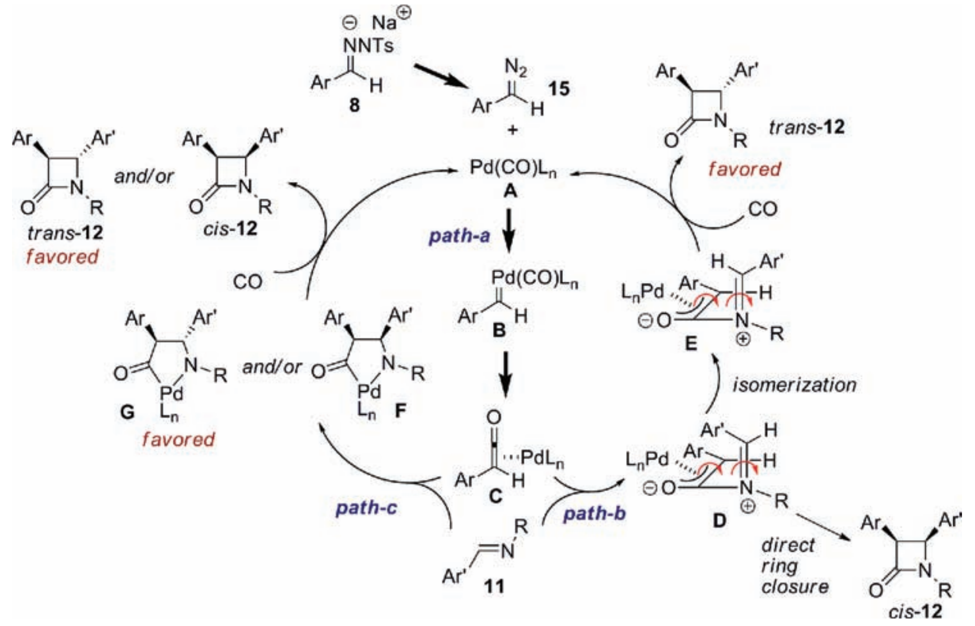
Figure 1. X-ray structure of **14e**.

Previous studies have shown that the stereochemical outcome of the Staudinger reaction depends on many factors, which include the substituents of both ketene and imine, the method used in the generation of the ketene species, reaction solvent and temperature, and also the order of addition of the reactants. It has been suggested that the stereochemical outcome may be attributed to the isomerization of the starting imine[20l] or zwitterionic intermediate.[20h] In addition, in the case of the [2 + 2] cycloaddition of ketenes derived from the irradiation of Fischer carbene complexes, the transition metal is suggested to be involved in the whole reaction process of the *β*-lactam formation, and the transition metal is shown to significantly affect the diastereoselectivity of formal [2 + 2] reaction with imine.[20f,m]

The striking feature of the current Pd-catalyzed *β*-lactam formation is that in most cases, the products of *trans* configuration are formed predominantly with high selectivity. Formal [2 + 2] cycloaddition of ketene and imine under Pd-catalyzed reaction conditions has been previously documented in the literature,[21] and the limited examples so far reported has also shown that *trans* *β*-lactam products predominate in most cases.[21c−e] Torii and coworkers demonstrated that Pd-catalyzed carbonylation of allyl phosphates under CO in the presence of imines afforded either *cis* or *trans* *β*-lactams, depending on the nature of imine.[21c] Pd-complexed ketene was supposed to be the key intermediate by the authors.

Based on the previous mechanistic studies on the related [2 + 2] cycloaddition reactions,[20] the possible reaction pathways were

Scheme 4. Proposed Mechanism for [2 + 2] Cycloaddition of Pd−Ketene Complex



proposed for our reaction (Scheme 4, ***path-a***,***b*** and ***c***). In ***path-a*** (from **15**+**A** to **C**), dinitrogen extrusion of the diazo affords the Pd carbene complex **B**.[13,14] Subsequent CO migratory insertion leads to the Pd-ketene complex **C**. From Pd-ketene complex **C**, we propose two possible reaction pathways to rationalize the observed high *trans* selectivity (***path-b*** and ***path-c***). For ***path-b***, the nucleophilic attack of the (*E*)-imine to the ketene affords the Pd-complexed zwitterionic intermediate **D**. Direct conrotatory ring closure of **D** leads to *cis*-**12** and regenerates Pd catalyst. Alternatively, conrotatory ring closure from the isomerized intermediate **E** affords the *trans*-**12**. The high *trans* selectivity can be rationalized by assuming a fast isomerization process relative to the direct ring closure.

On the other hand, in Torii's Pd-catalyzed [2 + 2] cycloaddition of ketenes *trans* β−lactams were also obtained as major products for the similar imines as those used in our study.[21c] They suggested a pathway involving stereoselective formation of five-membered azapalladacycle. On the basis of Torii's report, we propose an alternative mechanism for our Pd-catalyzed reaction by invoking a similar azapalladacycle intermediate (Scheme 4, ***path-c***). First, the reaction of imine with Pd−ketene intermediate **C** leads to the formation of isomeric five-membered azapalladacycles **G** and **F**. The formation of *trans* azapalladacycle **G** should be favored over *cis* isomer **F** both kinetically and thermodynamically. Reductive elimination from **G** affords the *trans* β-lactam as a major product. However, this pathway is excluded by DFT calculations.[22]

Computational Studies. To further understand the reaction mechanism shown in Scheme 4, density functional theory (DFT)[23] studies with GAUSSIAN03 program[24] have been performed. In this study the geometries were fully optimized at B3LYP/6-31G* level in gas phase,[25] and the solvent effects were estimated using IEFPCM[26] model (UAHF radii) in DCE (ε = 10.36). The B3LYP method has been previously used in the theoretical investigations of this type of reactions.[20e,f,l−n] Harmonic vibration frequency calculations confirmed that the optimized structures are either minima (having no imaginary vibration) or transition states (having one imaginary vibration). B3LYP/6-311+G** single-point calculations were performed to obtain more accurate energies. The relative free energies (ΔG_{sol}) were obtained by adding the B3LYP/6-311+G** single-point energies and the thermal free energy corrections as well as the solvent effect corrections (including both electrostatic and nonelectrostatic donations). Atomic charges were calculated with NBO natural bonding analysis for some selected structures.[27] The typical substrates **8a** and **11a** were used as the model for calculation. Because it is known that the dba ligand coordinates to palladium with its C═C double bond unit,[28] the dba ligand was simplified to ethene in the calculation models to accelerate the computation. To confirm the validity of this simplification, further test calculations using selected complete dba models were performed. The results are similar to those of the corresponding simplified models.[22]

Path-a: The Formation of the Pd−Ketene Complex. The mechanism to account for the formation of Pd-complexed ketene intermediate is shown in Figure 2. Since CO has strong coordination ability toward Pd, we suppose that CO-complexed Pd(0) species **A** is the effective catalyst in the system. There are two sites for the coordination of the diazo group to the Pd center, the terminal nitrogen and the carbon.[15b] The calculation results show that palladium prefers to coordinate to the terminal nitrogen atom of diazo group (**A**+**15N**) than the corresponding carbon atom (**A**+**15C**) by 4.9 kcal/mol. From the complex **A**+**15C**, dinitrogen extrusion occurs *via* transition state **TS-AB** over a barrier of 18.5 kcal/mol. In the transition state **TS-AB**, the C−N distance is elongated from 1.328 to 1.753 Å, and the C−Pd distance is decreased from 2.466 to 2.125 Å. In the Pd carbene complex **B**, the C−Pd distance is 1.970 Å. This value is very close to the corresponding C−Pd distance observed in the X-ray structure of a stable Pd(II)−carbene complex.[13b]

Subsequently, CO migratory insertion occurs *via* the transition state **TS-BC** over a barrier of 14.5 kcal/mol, leading to the

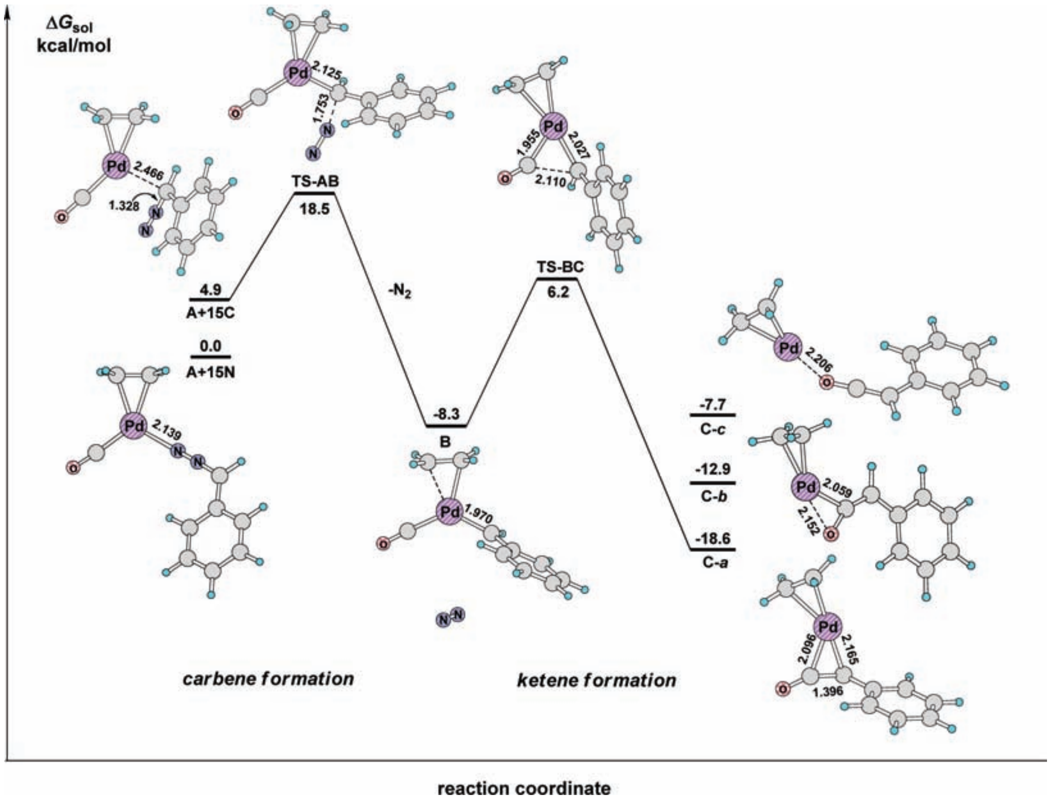


Figure 2. Calculated reaction pathways for the Pd-complexed carbene and ketene formation. The distances are in angstroms. Calculated at B3LYP/6-311+G**//6-31G* level.

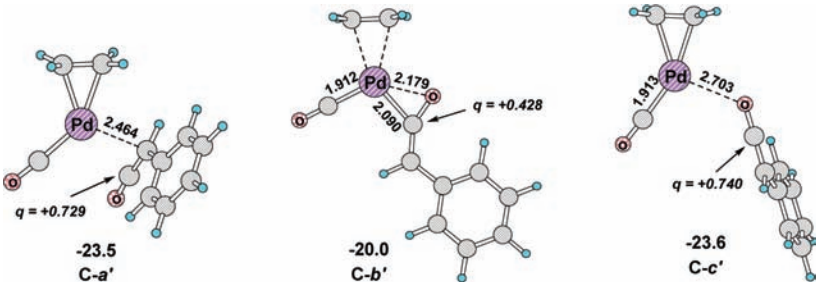


Figure 3. Optimized structures of **C-*a*′**, **C-*b*′** and **C-*c*′** (at B3LYP/6-311+G**//6-31G* level). The relative free energies ΔG_{sol} are in kcal/mol, the distances are in angstroms. The NBO charges are given in italic.

η^2−(C,C) Pd-ketene complex **C-*a***, which is supposed to be in equilibrium with the corresponding η^2−(C,O) Pd−ketene complex **C-*b***.[29,30] In **TS-BC**, the C=Pd distance is elongated to 2.027 Å and the C−C distance is decreased to 2.110 Å. The calculated free energies show that **C-*a*** is 5.7 kcal/mol more stable than **C-*b***, qualitatively consistent with the theoretical studies by Gong et al. on a series of bis(phosphine) palladium ketene complexes in which η^2−(C,C) mode is preferred over η^2−(C, O) mode by 10−15 kcal/mol.[29c] The η^1−(O) Pd−ketene complex **C-*c*** is 10.9 kcal/mol less stable than **C-*a***.

On the other hand, the vacancy on the Pd center in **C-*a***, **C-*b*** and **C-*c*** may accommodate another CO as a ligand to form **C-*a*′**, **C-*b*′** and **C-*c*′**, and the calculated relative free energies show that this process is thermodynamically favorable (Figure 3). The binding energies of CO to **C-*a***, **C-*b*** and **C-*c*** are 4.9, 7.1, and 15.9 kcal/mol, respectively. In these complexes the η^1−(O) Pd-ketene complex **C-*c*′** become the most stable one. In addition, the large NBO charge (+0.740) on the central carbon atom of ketene indicates that the oxygen coordinated ketene in **C-*c*′** is more electrophilic. Therefore, the complex of **C-*c*′** with the imine is used as the reactant complex (**R**) in the DFT calculation of the subsequent Staudinger reaction. This result is comparable with the nucleophilic reaction of imine with the metal-ketene complex generated from irradiation of Fischer carbene complexes.[20m]

Path-b: The Mechanism for the Formation of β-Lactam. Next, DFT calculation was performed on the formal [2 + 2] cycloaddition process. As shown in Figure 4, in the reactant complex **R**, the nitrogen of the imine can attack the ketene from two possible directions: *endo* or *exo* relative to the phenyl group of the ketene.[20] The *exo*-attack transition state **TS-*exo*** is 4.5 kcal/mol more favorable than the *endo*-attack transition state **TS-*endo*** for steric reasons. These transition states lead to two zwitterionic intermediates **D** and **D′**. Subsequently, the conrotatory ring closure occurs *via* the transition states **TS-3In4In** (with the

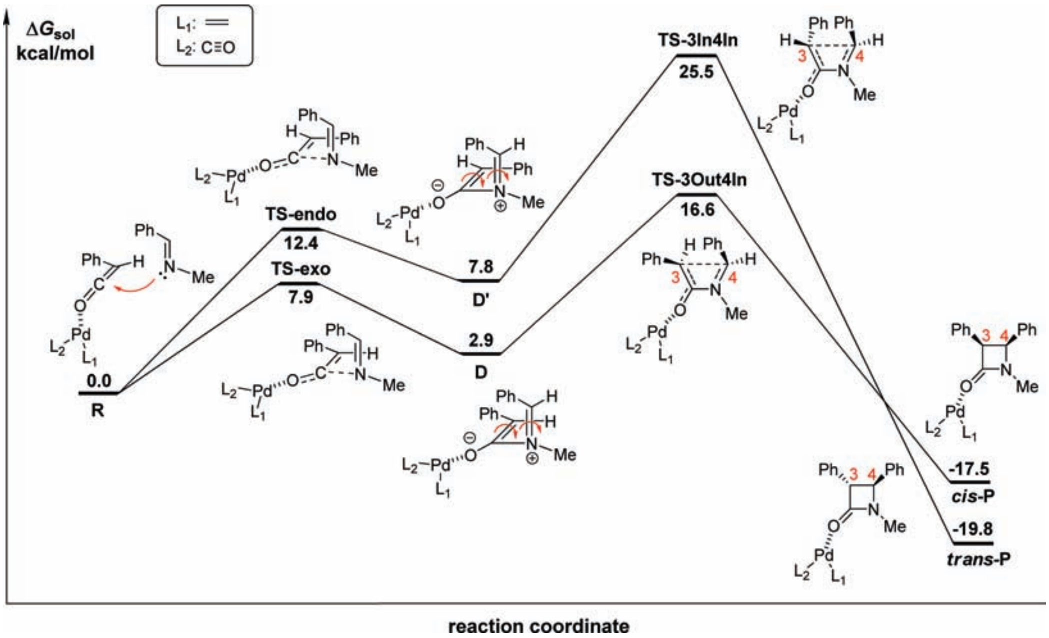


Figure 4. Calculated reaction pathway for the Staudinger reaction (***path-b***, direct ring closure). Calculated at B3LYP/6-311+G**//6-31G* level.

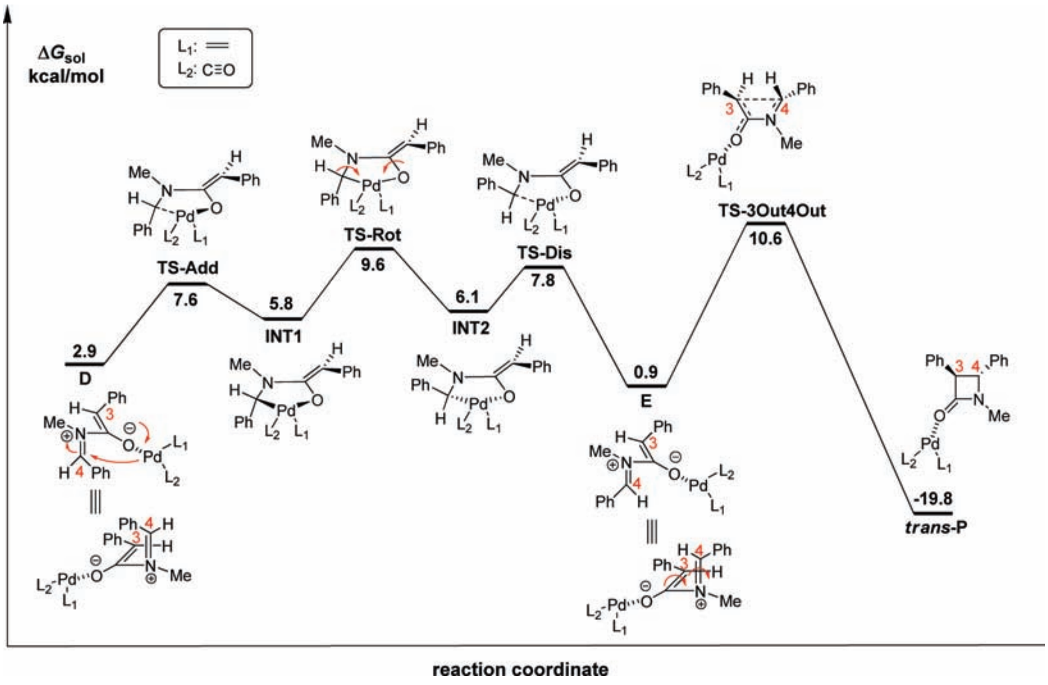


Figure 5. Calculated reaction pathway for the Pd-assisted isomerization of the zwitterionic intermediate **D** through an addition/dissociation pathway (at B3LYP/6-311+G**//6-31G* level).

phenyl groups both inward) or **TS-3Out4In** (the phenyl group of imine is inward, and that of ketene is outward). In both cases, the ring closure step is the rate-determining step, with overall energy barriers of 25.5 and 16.6 kcal/mol, respectively.

According to the DFT calculation results, **TS-3Out4In** is more favorable than **TS-3In4In** (16.6 kcal/mol vs 25.5 kcal/mol). However, **TS-3Out4In** leads to the *cis* β-lactam product, which is inconsistent with our experimental results. Therefore, other pathways to produce *trans* β-lactam must be considered, and the energy of the rate determining step of such pathways should be lower than that of **TS-3Out4In** (16.6 kcal/mol).[22]

Interestingly, further DFT calculations show that the Pd catalyst can assist the isomerization of the zwitterionic intermediate **D** to **E** through an addition/dissociation pathway (Figures 5 and 6).[20] In the imine moiety of the intermediate **D**, the phenyl group is in *E*-conformation with the methyl group, the dihedral angle C5−C4−N−C6 is 176.9°, and the bond length of the C4═N double bond is 1.309 Å. The addition of the palladium to the C4 atom of the imine C4═N double bond over

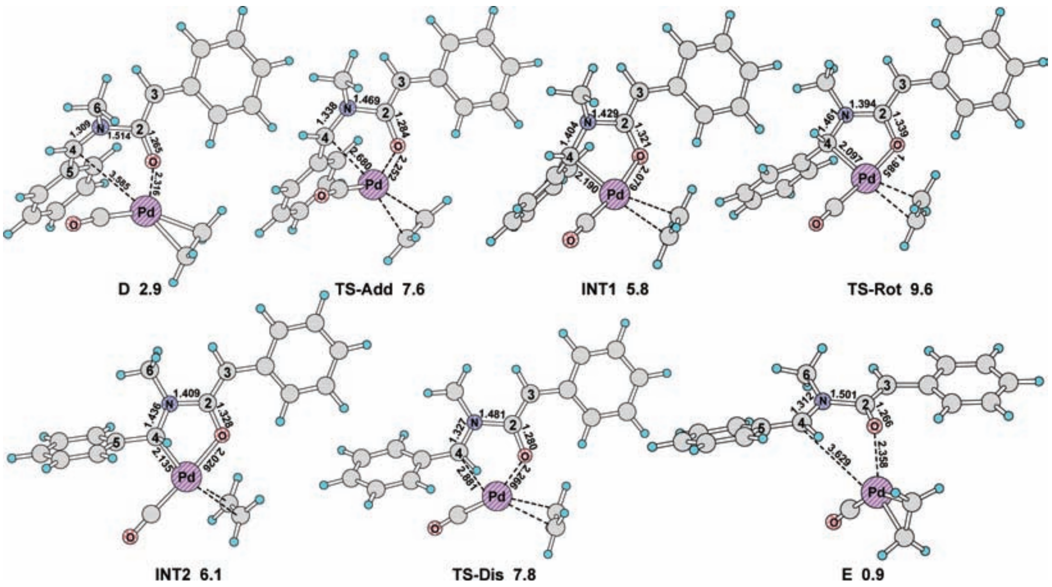


Figure 6. Fully optimized structures for the Pd-assisted isomerization process of the zwitterionic intermediate **D**. The relative free energies ΔG_{sol} are in kcal/mol. Calculated at B3LYP/6-311+G**//6-31G* level.

a small barrier of 4.7 kcal/mol (**TS-Add**) leads to a five-membered ring intermediate **INT1**, in which the palladium is above the ring plane, and the C4−N bond is elongated to 1.404 Å. Comparing with the length of the N−C single bong in **R** (1.452 Å), C4−N in **INT1** can be considered as a single bond. The rotation of the N−C4 and C2−O bonds *via* transition state **TS-Rot** over a barrier of 3.8 kcal/mol leads to the intermediate **INT2**. In **TS-Rot** the five-membered ring become nearly coplanar, with the dihedral angle Pd−C4−N−C2 of −7.7°. In **INT2**, the palladium is under the ring plane, with the dihedral angle C5−C4−N−C6 of 38.4°. The phenyl group is now in *gauche* conformation with the methyl group. The dissociation of the Pd−C4 bond *via* **TS-Dis** over a small barrier (1.7 kcal/mol) generates the zwitterionic intermediate **E**, in which the dihedral angle C5−C4−N−C6 is 8.5°. The configuration of the iminium moiety now turns to *Z*-configuration. Intermediate **E** is 2.0 kcal/mol more stable than **D**.

From intermediate **E**, the conrotatory ring closure could occur *via* a much low energy transition state **TS-3Out4Out** (10.6 kcal/mol) and leads to the *trans* β-lactam product, which is in consistent with the experimental observations. Likewise, the zwitterionic intermediate **D′** may also isomerize and form the *cis* product. However, this pathway is excluded by the higher energy of the transition state **TS-3In4Out** (18.0 kcal/mol).

The relative stabilities of the conrotatory ring closure transition states shown in this study are in agreement with the torquoselectivity effects, according to which electronic donating groups prefer rotate outward.[31,32] The transition state with both phenyl groups inward (**TS-3In4In**) is the most unstable one, in which the filled π orbitals of the phenyl groups have destabilization effect with the newly forming C3−C4 σ orbital. Conversely, the transition state with both phenyl groups outward is the most stable one (**TS-3Out4Out**).

Since there has been no experimental evidence for the participation of the metal moiety in the whole reaction process, the reaction pathway shown in Figure 4 were recalculated using models without the palladium moiety.[22] Similar results were obtained except for slightly higher barriers, indicating that the palladium moiety only has small effect on the nucleophilic attack and the conrotatory ring closure steps. However, the participation of the metal moiety may play an important role in the zwitterionic intermediate isomerization process.[33]

■ CONCLUSION

In conclusion, we have reported the first efficient Pd-catalyzed carbonylation of α-diazo carbonyl compounds or *N*-tosylhydrazones with CO.[12h,34] This carbonylation process proceeds at atmospheric CO pressure and moderately high temperatures, and these reaction conditions have been employed for a wide range of diazo substrates, *N*-tosylhydrazones and nucleophiles. Moreover, particular precatalyst/ligand combination is not required. It provides a practical and efficient way for the homologation of ketones or aldehydes, and also provides a diastereoselective method for the transformation of aldehydes to β-lactam derivatives in two steps. Computational studies have provided useful insights into the mechanism of the Pd−ketene complex formation and the diastereoselective formal [2 + 2] cycloaddition. In particular, the DFT calculation suggests that Pd assists the isomerization of the C═N bond of the initially formed zwitterionic intermediate, which may responsible for the predominant formation of *trans* β-lactam in most of the cases. From the synthetic point of view, this straightforward carbonylation represents an alternative method for the generation of ketene species in general. Some substituted ketenes, such as acylketenes which are difficult to access by conventional means, can be generated by this method from easily available precursors. The results shown in this study also demonstrate that the ketene species generated under such catalytic conditions can be used for the subsequent transformations without interference by the carbonylation step and the overall reaction can be carried out in one-pot fashion. With these advantages, it can be expected that this method of catalytic ketene generation will find wide applications in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray crystallographic data for **14e**, DFT calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

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