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Pd(0)-Catalyzed Four-Component Reaction of Aryl Halide, CO, *N*-Tosylhydrazone, and Amine

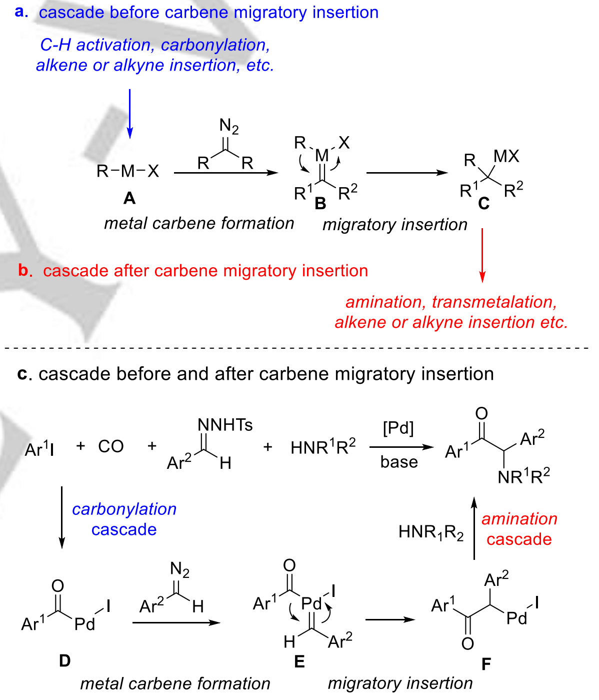
Yiyang Liu,[+] *Zhen Zhang,*[+] *Songnan Zhang, Yan Zhang, Jianbo Wang,* and Zhenhua Zhang**

Abstract: A Pd(0)-catalyzed four-component cascade reaction of aryl halide, CO, *N*-tosylhydrazone, and amine affording α-amino ketone has been developed. This reaction involves a sequential carbonylation, metal carbene migratory insertion and amination. Control experiments and DFT calculations further reveal the reaction sequence and chemoselectivity of individual components in this cascade process.

Multi-component cascade reactions have been identified as a prominent strategy for rapid generation of molecular complexity.[1] Among numerous cascade processes, transition-metal-catalyzed three-component transformation have been well documented over the years.[2] In contrast, transition-metal-catalyzed intermolecular cascade process involving four or more components are still rare and have remained a formidable challenge, obviously due to the difficulty in controlling the subtle balance between reactivity and selectivity of the multiple components involved in the reaction system.[3]

On the other hand, transition-metal-catalyzed cross-coupling with carbene precursors has been recently emerged as a highly efficient strategy for the construction of C-C and C−X (O, N) bonds.[4] These coupling reactions are featured by the involvement of metal carbene formation and subsequent migratory insertion. Three-component cascade reactions involving metal carbene migratory insertions have also been developed. As shown in Scheme 1, the previously reported three-component cascade reactions have two types: 1) with cascade process before the carbene formation and migratory insertion (type **a**); 2) with cascade process following the carbene formation and migratory insertion (type **b**). For the type a reaction, the intermediate **A** can be generated through C-H activation,[5] carbonylation,[6] alkene[7] or alkyne insertions[8] (Scheme 1, **a**). In contrast, for the type b reaction the organometallic species **C** generated from carbene migratory insertion is trapped by amination,[9] transmetalation,[10] alkene[11] or alkyne insertion[12] (Scheme 1, **b**).

We have envisioned a multi-component reaction involving cascades both before and after metal carbene migratory insertion. While it is a challenging issue to control the reaction to follow a premeditated sequence when there exist several reactive components, we have successfully accomplished an intermolecular cascade reaction of aryl halide, CO, *N*-tosylhydrazone, and amine *via* a sequential assembly of these four components to afford α-amino ketones (Scheme 1, **c**). Compared with several recent methods for preparing similar aminoketones,[13] this reaction provides a direct synthetic pathway utilizing simple molecules without any oxidants. We have proposed the reaction follows the sequence as shown in the scheme. The acylpalladium species **D** is first generated, followed by Pd(II) carbene formation and migratory insertion to give an alkylpalladium(II) species **F**, which is trapped by amine. The proposed reaction mechanism has been substantiated by control experiments and DFT calculations.



Scheme 1. Transition-metal-catalyzed cascade processes involving metal carbene migratory insertion.

Our initial study began with the Pd(0)-catalyzed reaction using iodobenzene **1a**, *N*-tosylhydrazone **2a** and morpholine **3a** as the model substrates under a balloon of CO atmosphere (Table 1). To our delight, the desired α-amino ketone **4a** was obtained in 43% yield using Pd(PPh$_3$)$_4$ as the catalyst, LiO*t*Bu as the base in the solvent of PhCF$_3$ (entry 1). This result encouraged us to explore the effects of various parameters. Remarkably, compared with ligands such as PMe$_3$, DPPP, DPPE and DPPF, the bidentate phosphine ligands DPPB showed superior performance (69% yield; entry 8), presumably attributed to their suitable bite angles and electronic property. Elevating the reaction temperature to 80 °C led to a diminished yield of **4a** (entry 9). As for the effects of bases, we found that the product yield could be improved to 78% by employing K$_2$CO$_3$ as the base in dioxane, whereas a decreased yield was observed when

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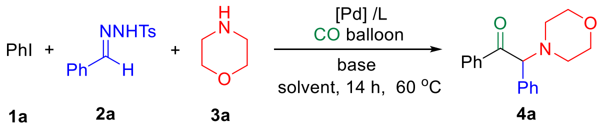
either K_3PO_4 or Cs_2CO_3 was utilized (entries 12, 13). Notably, in the absence of ligand, the target product could also be obtained in 32% yield (entry 14).[14]

Table 1. Optimization of reaction conditions.[a]



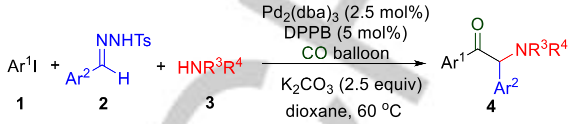
entry	[Pd] (mol%)	ligand (mol%)	solvent	base	yield [%][b]
1	$Pd(PPh_3)_4$ (5.0)	-	$PhCF_3$	LiO^{t}Bu	43
2	$Pd_2(dba)_3$ (2.5)	PMe_3 (15)	$PhCF_3$	LiO^{t}Bu	23
3	$Pd_2(dba)_3$ (2.5)	$P(OEt)_3$ (10)	$PhCF_3$	LiO^{t}Bu	37
4	$Pd_2(dba)_3$ (2.5)	DPPE (5)	$PhCF_3$	LiO^{t}Bu	Trace
5	$Pd_2(dba)_3$ (2.5)	DPPP (5)	$PhCF_3$	LiO^{t}Bu	39
6	$Pd_2(dba)_3$ (2.5)	DPPF (5)	$PhCF_3$	LiO^{t}Bu	33
7	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	$PhCF_3$	LiO^{t}Bu	Trace
8	$Pd_2(dba)_3$ (2.5)	DPPB (5)	$PhCF_3$	LiO^{t}Bu	69
9[c]	$Pd_2(dba)_3$ (2.5)	DPPB (5)	$PhCF_3$	LiO^{t}Bu	49
10	$Pd_2(dba)_3$ (2.5)	DPPB (5)	Dioxane	LiO^{t}Bu	65
11	**$Pd_2(dba)_3$ (2.5)**	**DPPB (5)**	**Dioxane**	**K_2CO_3**	**78**
12	$Pd_2(dba)_3$ (2.5)	DPPB (5)	Dioxane	Cs_2CO_3	Trace
13	$Pd_2(dba)_3$ (2.5)	DPPB (5)	Dioxane	K_3PO_4	63
14	$Pd_2(dba)_3$ (2.5)	-	Dioxane	K_2CO_3	32

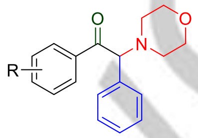
[a] Optimized reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), **3a** (0.4 mmol), base (0.25 mmol), 60 °C for 14 h. [b] All yields refer to the isolated products. [c] Reaction were conducted at 80 °C. dba: dibenzylideneacetone; DPPE: 1,2-bis-(diphenylphosphino)ethane; DPPP: 1,3-bis(diphenylphosphino)propane, DPPF: 1,1'-bis(diphenylphosphino)ferrocene, DPPB: 1,4-bis(diphenylphosphino)butane.

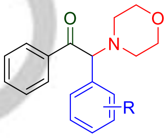
To demonstrate the scope of the reaction, the optimized reaction conditions were then applied to a series of aryl iodides, *N*-tosylhydrazones and amines (Table 2). First, a series of aryl iodides were tested under the standard reaction conditions. *para*-, *meta*- and *ortho*- substituted aryl iodides were shown to be suitable for this reaction (**4b-d**). However, the reaction was found to be affected by the electronic property of the substituents on the aryl iodides. Electron-deficient substituent (**4g**) gives lower yield than electron-rich ones (**4e**, **4f**). Notably, this transformation tolerated halogen substituents (**4h**, **4i**), which are normally reactive in transition-metal-catalyzed cross-coupling reactions. With respect to the scope of *N*-tosylhydrazones, variations of the position of substituent on the benzene ring had no apparent effect on the reaction (**4j-i**). Substrates bearing electron-donating groups (**4p**, **4m**) exhibit higher reactivity than those with electron-withdrawing groups (**4o**). In terms of amine scope, *N*-methylaniline (**4r**) and piperidine (**4s**) both react smoothly, albeit with a slightly reduced yield (60% and 61%). However, only trace amount of **4t** was observed when a primary amine was employed as the coupling partner.

While the four-component reaction has been achieved, a challenging issue still needs to be addressed: how do the four-components react in the specific sequential manner as described in Scheme 1c? Since both CO and carbene are known to undergo α,α-insertion, a question can be asked is which component is more favorable for migratory insertion. Moreover, several competitive pathways along with the addition of amine may occur, which include Buchwald–Hartwig coupling of amine with aryl halide,[15] mono-or dicarbonylation followed by amidation,[16] and direct amination after metal carbene migratory insertion.[9] Therefore, to clarify these mechanism issues, an array of control experiments have been conducted, and DFT calculations have been carried out for further rationalization of the reaction mechanism.

Table 2. Reaction scope.

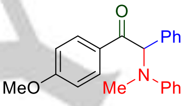




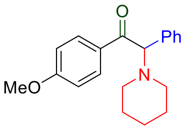


4a, R = H, 78% (14 h)
4b, R = *o*-Me, 65% (16 h)
4c, R = *m*-Me, 68% (17 h)
4d, R = *p*-Me, 69% (17 h)
4e, R = *m*-OMe, 74% (12 h)
4f, R = *p*-OMe, 73% (12 h)
4g, R = *p*-CO_2Me, 43% (18 h)
4h, R = *p*-Cl, 56% (16 h)
4i, R = *p*-Br, 61% (18 h)

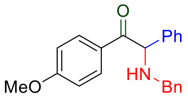
4j, R = *o*-Me, 71% (16 h)
4k, R = *m*-Me, 61% (14 h)
4l, R = *p*-Me, 65% (12 h)
4m, R = *p*-OMe, 73% (12 h)
4n, R = *p*-Cl, 63% (14 h)
4o, R = *p*-CO_2Me, 61%[a] (14 h)
4p, R = *m*,*p*-dimethoxy, 74% (15 h)



4r, 60% (15 h)



4s, 61%[b] (14 h)



4t, *trace*

Reaction conditions are as follows if not otherwise noted: $Pd_2(dba)_3$ (0.005 mmol), DPPB (0.01 mmol), **1** (0.2 mmol), **2** (0.3 mmol), **3** (0.8 mmol) and K_2CO_3 (0.5 mmol) were added in dioxane (10 mL), the mixture was reacted for corresponding hours at 60 °C. Yield of isolated product. [a] With toluene as the solvent. [b] K_2CO_3 was replaced by K_3PO_4.

First, control experiments have been designed in order to gain insights into the reaction (eqs 1-4). As mentioned above, the challenge of realizing a four-component intermolecular reaction lies in the competitive reactions among diverse components. In the current reaction, two facile side-reactions were Buchwald–Hartwig coupling and amination.[15] However, the cross-coupling of amine with aryl halide did not occur under the optimized conditions (eq 1). Besides, in the absence of CO, tertiary amine **6** was not observed under the standard conditions (eq 2). This result implied the direct amination and carbene migratory insertion of arylpalladium are unfavorable processes in this

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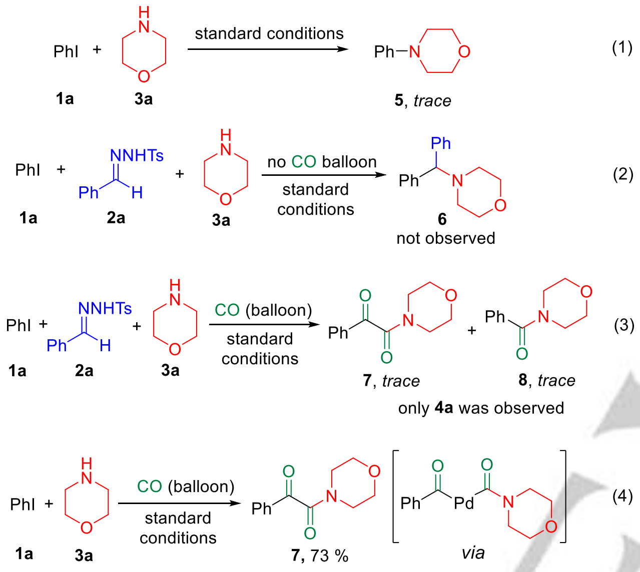
catalytic four-component system. Thus, CO insertion to form an acylpalladium species is reasonably proposed as the initial step for the four-component cascade reaction.

Besides, Pd(0)-catalyzed CO insertion with aryl halide and subsequent amidation have been widely documented in early efforts.[16] Intriguingly, the control experimental showed that a trace amount of **7** or **8** were observed when *N*-tosylhydrazone was present in the reaction system (eq 3). Thus, we speculate a competitive course exists in this multi-component reaction. As we had hypothesized, when removing carbene precursor from the reaction system, the product of dicarbonylation α-ketoamide **7** were obtained in 73% yield *via* a diacyl Pd intermediate (eq 4).[16b]



Scheme 2. Control experiments.

Next, computational study has been carried out. Although the optimized reaction conditions involved a bidentate phosphine ligands (DPPB), the reaction could also proceed in the absence of phosphine ligands to afford the desired product with an acceptable yield.[17] Thus, CO was chosen as the ligand and the diazo substrate was chosen as the carbene precursor for the computation study. All the DFT calculations were performed using Gaussian09 (Revision D.01).[18] Geometry optimizations were carried out with B3LYP[19] level of theory. Lanl2dz[20] basis set was used for Pd, I and K atom and 6-31G(d,p)[21] basis set for other atoms. Gibbs free energy was corrected by frequency calculations using the optimized structures. Single point energies of the optimized geometries were calculated at the level of M06[22] denoting the basis set combination of SDD[23] for Pd and 6-311+G(d,p) for all other atoms. Single point solvation energy corrections in toluene computed by the IEFPCM[24] method were added to the gas-phase free energy. The key intermediates and transition-state structures were prepared with CYLview.[25]

The migratory insertion of CO and carbene have been considered as two typical classes of α,α-insertion. The intriguing question is thus the sequence of the insertions. With DFT calculations, we first examined the order of insertions under the identical reaction conditions. In the catalytic cycle, acyl Pd carbene intermediate **E** is proposed to be involved in the formation of α-amino ketones. For the generation of **E**, the oxidative addition of PhI first occurs to give Pd(II) species **A**, which undergoes migratory insertion of CO to generate acyl Pd(II) intermediate **B** (blue solid lines in Figure 1).[26] In situ generated diazo substrate coordinates to acyl Pd(II) intermediate **B** to generate complex **C**. Intriguingly, before forming acyl Pd(II) carbene, an auxiliary intermediate **D** with much lower energy (-6.31 kcal/mol) is generated in the presence of K_2CO_3 through coordination between O atom in carbonyl of **C** and one K atom in K_2CO_3. Subsequently, facile decomposition of **D** occurs along with N_2 extrusion by spanning a low barrier of 4.64 kcal/mol (**TS2**), resulting in the formation of acyl Pd carbene species **E**. This process is highly exergonic by 22.8 kcal/mol. Moreover, **TS2** possess lower energy than **TS2'** without participation of K_2CO_3. The computed length (1.96 Å) of Pd=C double bond in **E** is similar to that reported for the Pd carbene species.[27]

For the alternative path that involves Pd(II) carbene formation prior to CO insertion, we have carried out similar DFT calculation (red dashed lines in Figure 1). Thus, upon oxidative addition, one CO in **A** is replaced by diazo substrate, leading to complex **F**, which generates phenyl Pd carbene **G** through dinitrogen with an energy barrier of 7.01 kcal/mol (**TS1**). The transition state **TS1** is higher than **TS2** by 12.3 kcal/mol, suggesting that migratory insertion of CO is a facile process, as compared with the dediazotization which need to cross a higher barrier. As for the dediazotization process, the nitrogen extrusion from the K_2CO_3-assisted acyl Pd(II) intermediate **D** is slightly favored than that from phenyl Pd(II) complex **F** (6.98 kcal/mol from **F** to **TS1** *versus* 4.64 kcal/mol from **D** to **TS2**).

The results suggest that the cascade reaction may involve the competition between carbene migratory insertion of acyl Pd(II) and dicarbonylation (the CO migratory insertion). The former shows favored than the latter, which is demonstrated by the control experiments (eq. 3 and eq. 4). Thus, further DFT calculation was carried out in order to gain insights into the details of such insertion competition. With respect to the dicarbonylation, the key Pd(II) acyl amide intermediate similar to **J** have been documented in the literatures.[14] Herein, we focused on the process to generate complex **J** from acyl Pd(II) intermediate **B** (red solid lines in Figure 2). First, a second CO coordinates to Pd(II) center to generate intermediate **H**, which is further converted into complex **I** *via* ligand exchange and the coordination of K_2CO_3 that is similar to that of **D** (Figure 1). The process is found highly endergonic by 13.15 kcal/mol. Subsequently, CO migratory insertion occurs *via* transition-state **TS5** with activation energy of 3.71 kcal/mol, generating intermediate **J**. Finally, α-ketoamide **7** is produced and the Pd(0) species is regenerated through reductive elimination. For this dicarbonylation pathway, the overall energy barrier is 7.65 kcal/mol, which is higher than that of dediazotization process by 8.83 kcal/mol. This scenario may be attributed to the weakened interaction of O in K_2CO_3 with the acidic proton in the diazo fragment to stabilize **TS2** ($H\cdots O$, 1.98 Å). Besides, it is noted that an energy barrier as high as 16.86 kcal/mol from **H** to **TS5** has to be crossed for the generation of key intermediate **J**, which is unfavorable as compared to that for generating **E** from

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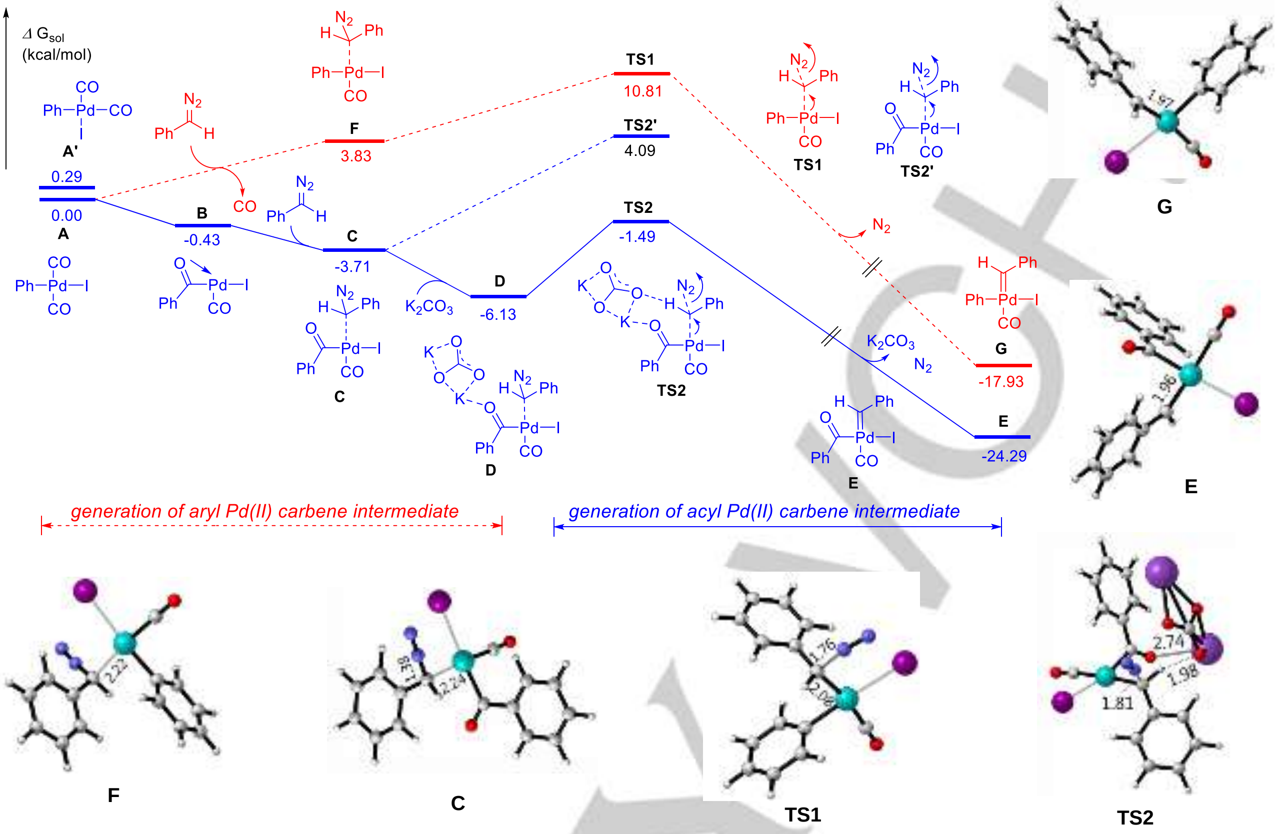

Figure 1. Free-energy profile for the generation of aryl and acyl Pd(II) carbene intermediate.

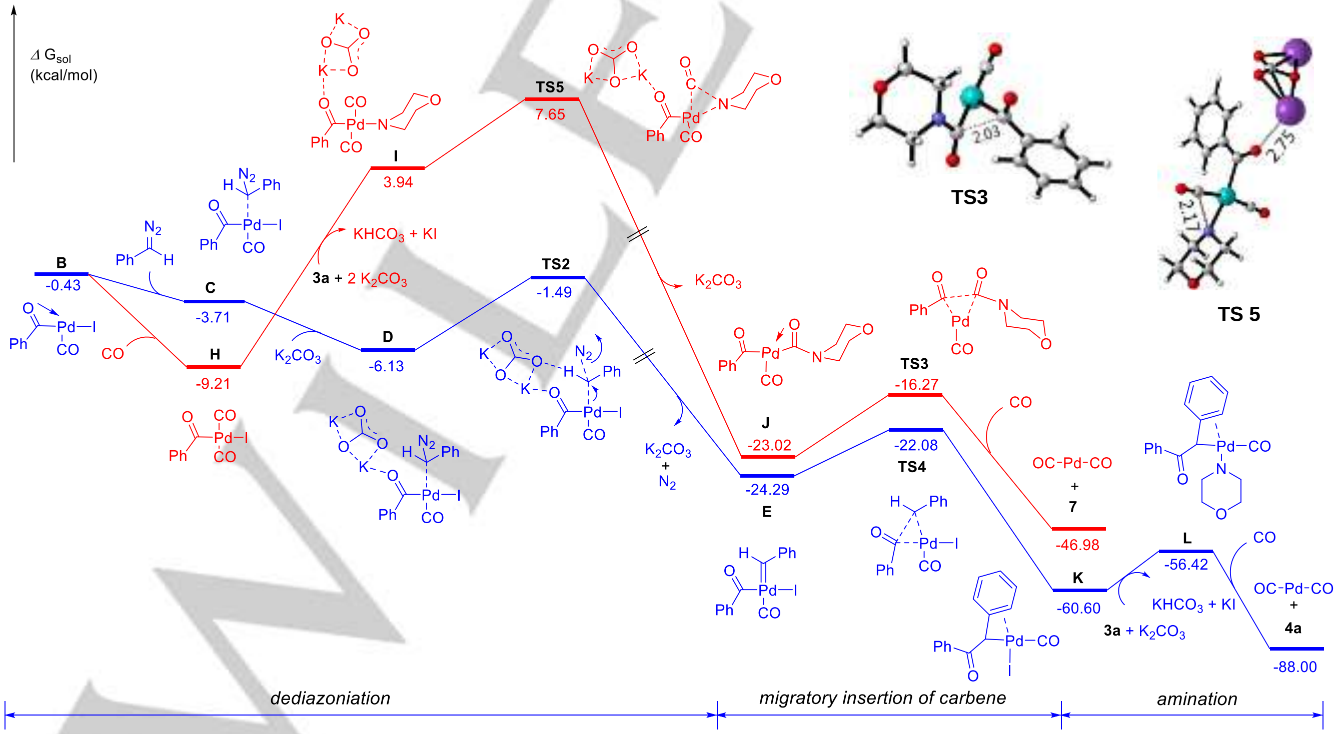

Figure 2. Free-energy profile for the Pd(II)-catalyzed four-component cascade reaction and dicarbonylation process.

D (4.64 kcal/mol). Thus, the computational data rationalize the experimental results that the Pd(II) carbene migratory insertion process is favored over the competitive dicarbonylation.

In conclusion, we have reported a palladium-catalyzed four-component cascade reaction involving carbonylation, Pd(II) carbene migratory insertion and amination, affording α-amino ketones in a straightforward manner. This protocol exquisitely combined metal carbene migratory insertion and two cascade processes in a sequential manner. A series of control experiments have revealed that the reaction follows a sequence of carbonylation, acyl Pd(II) carbene formation, migratory insertion and amination. The control experiments have also shown that from the acyl Pd(II) species, carbene formation and migratory insertion is favored over dicarbonylation. Finally, DFT calculations provide insights into the detailed reaction mechanism and rationalize the chemoselectivity observed for this multi-component reaction.

Acknowledgements

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Keywords: carbene migratory insertion • multi-component reaction • cascade reaction • DFT calculation • carbon monoxide

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[17] In the absence of phosphine ligands, **4a** was obtained in 32% yield with a trace amount of dicarbonylative product **7**. When the phosphine ligand and the carbene precursor were removed simultaneously, **7** was formed in 35 % yield.

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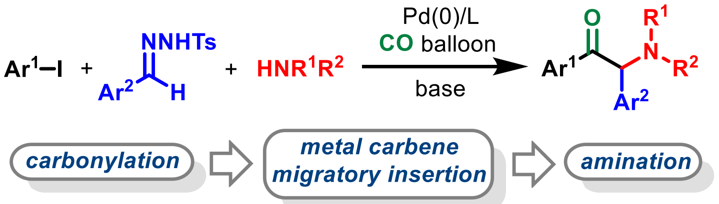

Four-component cascade in sequence: Pd(0)-catalyzed four-component cascade reaction of aryl halide, CO, *N*-tosylhydrazone, and amine follows a sequence of carbonylation, Pd(II) carbene migratory insertion and amination, affording α-amino ketones in a straightforward manner.

Yiyang Liu, Zhen Zhang, Songnan Zhang, Yan Zhang, Jianbo Wang, and Zhenhua Zhang**

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Pd(0)-Catalyzed Four-Component Reaction of Aryl Halide, CO, *N*-Tosylhydrazone, and Amine