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Palladium-Catalyzed Amidation of *N*-Tosylhydrazones with Isocyanides

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As two formally divalent organic species, both carbenes[1] and isocyanides[2] have attracted great attention in the synthetic community owing to their high reactivity. The direct reaction between carbenes and isocyanides is expected to produce ketenimines, which are highly useful intermediates in synthetic chemistry[3–9] and conventionally prepared by substitution of ketenes,[4] dehydrohalogenation of imidoyl halides,[5] transformation of nitriles with a Brønsted base,[6] or copper-catalyzed azide–alkyne cycloaddition reactions.[7] However, the previously reported methods for the formation of ketenimines from carbenes and isocyanides are very limited and mainly focus on the reaction of Fischer carbene complexes with isocyanides.[8,9] Some other specially stabilized carbenes like N-heterocyclic carbenes or β-lactam carbenes are also reported to react with isocyanides to form ketenimines or other rearrangement products.[10] Since the preparation of Fischer carbenes requires several steps and uses stoichiometric amounts of metal reagents, it is highly desirable to develop a transition-metal-catalyzed method for this kind of transformation. To the best of our knowledge, no Pd-catalyzed approach has been reported for the formation of ketenimines from carbenes and isocyanides.

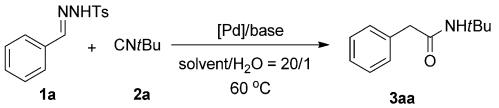
N-Tosylhydrazones, which are easily prepared from carbonyl compounds, have found extensive applications in organic synthesis.[11–13] They can be converted into diazo compounds under basic conditions, which can further produce metal–carbenes in situ by reacting with transition metals.[12,13] Recently, Wang et al.[13a] reported an efficient Pd-catalyzed carbonylation of carbenes with carbon monoxide. The Pd–carbenes were generated in situ from α-diazocarbonyl compounds or *N*-tosylhydrazones under mild conditions.

We conceived that isocyanides, as isoelectronic isomers of carbon monoxide, might react similarly with Pd–carbenes to form ketenimines, which can then be transformed into amides in the presence of water (Scheme 1). Herein, we would like to disclose our research results on the Pd-catalyzed aminocarbonylation reaction of in situ generated carbenes from *N*-tosylhydrazones with isocyanides.

Scheme 1. Pd-catalyzed aminocarbonylation of in situ generated carbenes with isocyanides.

The investigation was initiated by exploring the Pd-catalyzed reaction of benzaldehyde tosylhydrazone (**1a**) with *tert*-butyl isocyanide (**2a,** Table 1). When 2 mol% of Pd-$(PPh_3)_4$ was used as the catalyst, no desired amide product was detected with or without DIPEA or DBU at 60°C in CH_3CN (Table 1, entries 1–3). However, the amide product **3aa** was isolated when using inorganic bases, such as K_2CO_3, K_3PO_4, CsF, or Cs_2CO_3, and Cs_2CO_3 seemed to be the best choice (Table 1, entries 4–7). Further screening of solvents and Pd sources revealed that the reaction also proceeded

Table 1. Screening conditions for the Pd-catalyzed amidation of benzaldehyde tosylhydrazone with *tert*-butyl isocyanide.[a]



1a 2a 3aa

Entry	Catalyst	Base	Solvent	Yield [%][b]
1	$[Pd(PPh_3)_4]$	–	CH_3CN	n.d.[c]
2	$[Pd(PPh_3)_4]$	DIPEA	CH_3CN	n.d.[c]
3	$[Pd(PPh_3)_4]$	DBU	CH_3CN	n.d.[c]
4	$[Pd(PPh_3)_4]$	K_2CO_3	CH_3CN	22
5	$[Pd(PPh_3)_4]$	K_3PO_4	CH_3CN	40
6	$[Pd(PPh_3)_4]$	CsF	CH_3CN	51
7	**$[Pd(PPh_3)_4]$**	**Cs_2CO_3**	**CH_3CN**	**95**
8	$[Pd(PPh_3)_4]$	Cs_2CO_3	CH_3CN	<5[d]
9	$[Pd(PPh_3)_4]$	Cs_2CO_3	CH_3CN	40[e]
10	–	Cs_2CO_3	CH_3CN	n.d.[c]
11	$[Pd(PPh_3)_4]$	Cs_2CO_3	dioxane	87
12	$[Pd(PPh_3)_4]$	Cs_2CO_3	THF	22
13	$[Pd(PPh_3)_4]$	Cs_2CO_3	toluene	78
14	$[Pd(PPh_3)_4]$	Cs_2CO_3	DMF	58
15	$[Pd_2(dba)_3]$	Cs_2CO_3	CH_3CN	85
16	$[Pd(OAc)_2]$	Cs_2CO_3	CH_3CN	87
17	$[Pd(PPh_3)_2Cl_2]$	Cs_2CO_3	CH_3CN	94
18	$[Pd(dppf)_2Cl_2]$	Cs_2CO_3	CH_3CN	92

[a] Reagents and reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (0.55 mmol, 1.1 equiv), Pd catalyst (2 mol%), base, (1.0 mmol, 2.0 equiv), solvent (1 mL), 10 h. [b] Isolated yield, [c] No desired product was detected. [d] 0.25 mol% Pd catalyst was used. [e] 35°C.

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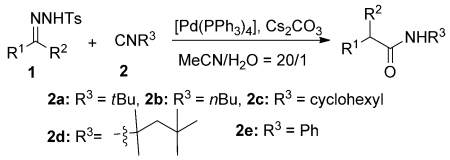
smoothly in 1,4-dioxane or toluene, and both Pd^0 and Pd^{II} catalysts delivered the desired product in high yields, while no desired product was detected without the addition of a Pd catalyst (Table 1, entries 9–18). Furthermore, to examine the influence of water, we tested the reaction in CH_3CN with a water content ranging from 1 to 50%, and all the reactions delivered the desired product in more than 85% yield. In pure water (100%), however, the reaction system was very complex. Finally, we used CH_3CN with a water content of about 5% as the solvent for our reaction.

With the optimized conditions in hand, we then explored the substrate scope of the aminocarbonylation. At first, a series of *N*-tosylhydrazones derived from aryl aldehydes and *tert*-butyl isocyanide (**2a**) were tested (Table 2). Electron-donating groups, such as a methyl or methoxy group, on the aryl ring of *N*-tosylhydrazones were well tolerated and the corresponding products were obtained in excellent yields (Table 2, entries 1–6). When electron-withdrawing groups, such as a trifluoromethyl or methoxycarbonyl group, were attached to the aryl ring, only moderate yields were obtained (Table 2, entries 8–10). We speculated that the electron-withdrawing groups destabilize the Pd–carbene intermediate and thus, it easily decomposes, which is unfavorable for the formation of ketenimine intermediates. For the reaction of *N*-tosylhydrazones derived from aryl ketones with *tert*-butyl isocyanide (**2a**), a higher reaction temperature was needed to generate the corresponding products. Excellent yields were obtained when the reactions were performed in CH_3CN under reflux (Table 2, entries 11–19). Furthermore, *N*-tosylhydrazones were tested with other isocyanides and the desired amide products were obtained in moderate to good yields (Table 2, entries 20–26), even with the steric bulky isocyanide **2d**. However, when aryl isocyanide **1e** was used, the reaction system became very complex and no desired product was detected (Table 2, entry 27).

To further explore the substrate scope, we tested a series of *N*-tosylhydrazones deriving from alkyl aldehydes/ketones in our reaction system. Only a small amount of the corresponding products was detected in CH_3CN under reflux (data not shown). We speculated that the alkyl groups may have a weaker stabilization effect on the Pd–carbene species as compared to the aryl groups. As a result, the Pd–carbene species is more unstable and decomposes more easily. However, better results were obtained when the reactions were heated under reflux in less polar 1,4-dioxane and the corresponding products were generated in moderate yields (Table 3).

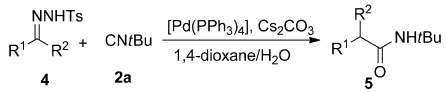
Table 2. Substrate scope of the reaction of *N*-tosylhydrazones **1** with isocyanides **2** leading to the formation of amides **3**.[a]

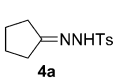
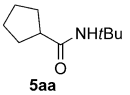
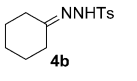
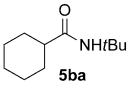
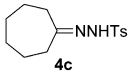
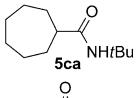
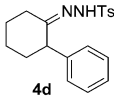
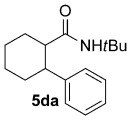
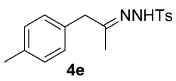
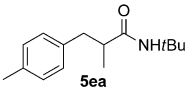
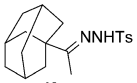
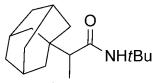


Entry	**1** (R^1, R^2)	**2**	**3**	Yield [%][b]
1	**1b** (H, *p*-tolyl)	**2a**	**3ba**	82
2	**1c** (H, *m*-tolyl)	**2a**	**3ca**	86
3	**1d** (*o*-tolyl, H)	**2a**	**3da**	90
4	**1e** (4-methoxyphenyl, H)	**2a**	**3ea**	94
5	**1f** (3-methoxyphenyl, H)	**2a**	**3fa**	86
6	**1g** (4-chlorophenyl, H)	**2a**	**3ga**	91
7	**1h** (3-thiophenyl, H)	**2a**	**3ha**	50
8	**1i** (4-trifluoromethylphenyl, H)	**2a**	**3ia**	75
9	**1j** (4-methoxycarbonylphenyl, H)	**2a**	**3ja**	57
10	**1k** (3-trifluoromethylphenyl, H)	**2a**	**3ka**	48
11	**1l** (Ph, Me)	**2a**	**3la**	78[c]
12	**1m** (Ph, Et)	**2a**	**3ma**	85[c]
14	**1n** (Ph, *n*Pr)	**2a**	**3na**	83[c]
15	**1o** (Ph, Bn)	**2a**	**3oa**	91[c]
16	**1p** (Ph, Ph)	**2a**	**3pa**	80[c]
17	**1q** (4-chlorophenyl, Me)	**2a**	**3qa**	90[c]
18	**1r** (4-methoxyphenyl, Me)	**2a**	**3ra**	74[c]
19	**1s** (*p*-tolyl, Me)	**2a**	**3sa**	61[c] (93)[d]
20	**1a**	**2b**	**3ab**	82
21	**1a**	**2c**	**3ac**	89
22	**1a**	**2d**	**3ad**	78
23	**1g**	**2d**	**3gd**	85
24	**1o**	**2d**	**3od**	65
25	**1p**	**2c**	**3pc**	70
26	**1q**	**2d**	**3qd**	66
27	**1a**	**2e**	**3ae**	–[e]

[a] Reagents and reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2** (0.55 mmol, 1.1 equiv), $[Pd(PPh_3)_4]$ catalyst (2 mol%), Cs_2CO_3, (1.0 mmol, 2.0 equiv), CH_3CN (1 mL), 60°C, 10 h. [b] Isolated yield. [c] CH_3CN, under reflux. [d] 1,4-Dioxane, under reflux. [e] No desired product was detected.

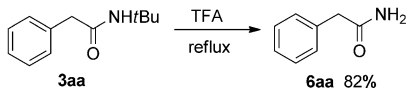
Table 3. Substrate scope of the reaction of *N*-tosylhydrazones **4** derived from alkyl aldehydes/ketones with isocyanide **2a** leading to the formation of amides **5**.[a]



Entry	Substrate	Product	Yield [%][b]
1	 **4a**	 **5aa**	43
2	 **4b**	 **5ba**	45
3	 **4c**	 **5ca**	75
4	 **4d**	 **5da**	53
5	 **4e**	 **5ea**	62
6	 **4f**	 **5fa**	71

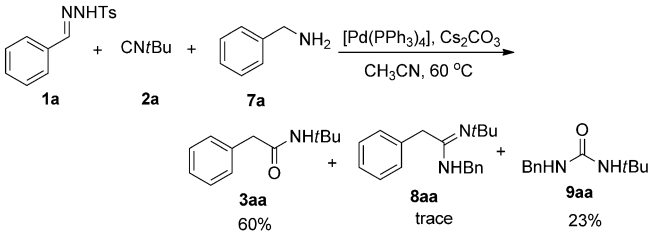
[a] Reagents and reaction conditions: **2a** (0.55 mmol, 1.1equiv), **4** (0.5 mmol, 1.0 equiv), $[Pd(PPh_3)_4]$ catalyst (2 mol%), Cs_2CO_3, (1.0 mmol, 2.0 equiv), 1,4-dioxane (1 mL), under relux, 10 h. [b] Isolated yield.

The synthesized *N-tert*-butyl amide products can easily be transformed into simple amides according to a method reported in the literature.[14] For example, when *N-tert*-butyl-2-phenylacetamide (**3aa**) was heated to reflux in trifluoroacetic acid, the desired 2-phenylacetamide product (**6aa**) was obtained in more than 80% yield (Scheme 2).



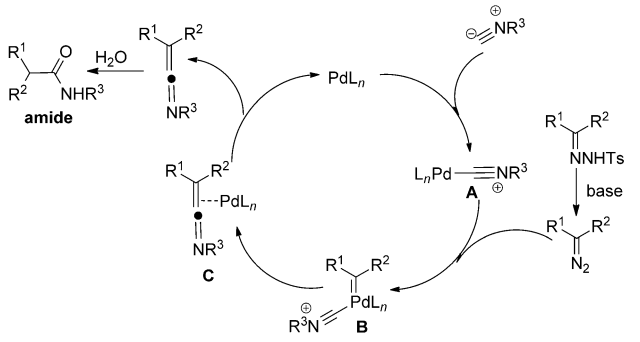
Scheme 2. Transformation of *N-tert*-butyl amides into simple amides.

To further explore the reaction possibilities of our system, benzylamine (**7a**) was used to trap the ketenimine intermediate. However, the reaction system was very complex and only a trace amount of the desired product **8aa** was detected (Scheme 3). The isolated products included amide **3aa** and a urea derivative **9aa**, which was formed through the direct reaction of benzylamine with isocyanide **2a**.



Scheme 3. Trapping the ketenimine intermediate with benzyl amine failed.

Based on literature reports[2,13a] and our experimental observations, a plausible mechanism was proposed (Scheme 4). The isocyanide-complexed Pd species **A** is first formed and acts as an active catalyst in our system. The *N*-tosylhydrazone is detosylated under basic conditions and the newly formed diazo compound reacts with the Pd catalyst to form Pd–carbene **B**, which undergoes migratory insertion to form the ketenimine intermediate **C**. The latter then reacts with water to give the final amide product.



Scheme 4. A plausible mechanism for the aminocarbonylation of *N*-tosylhydrazones.

In summary, a novel Pd-catalyzed approach for the aminocarbonylation of *N*-tosylhydrazones with isocyanides via ketenimine intermediates has been developed that avoids the use of stoichiometric organometallic reagents. It represents a general one-carbon extension transformation of carbonyl compounds into amides through the Pd-catalyzed aminocarbonylation of in situ generated Pd–carbenes with isocyanides. Further studies on the applications of this methodology are currently underway.

Experimental Section

Typical procedure for the Pd-catalyzed amidation of *N*-tosylhydrazones with isocyanides: *tert*-Butyl isocyanide (**2a**, 0.55 mmol) was added to a mixture of cesium carbonate (325 mg, 1.0 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol,), and benzaldehyde tosylhydrazone (**1a**, 137 mg, 0.5 mmol) in CH_3CN (5 mL) and the mixture was stirred at 60 °C for 10 h under argon. Monitoring by TLC showed that the reaction was complete. Water (5 mL) was added and the aqueous phase was extracted with ethyl acetate (5 mL × 3). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate, 5:1) to afford final product **3aa**.

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Keywords: amidation · isocyanides · ketenimines · synthetic methods · tosylhydrazones

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