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Palladium-Catalyzed Desulfurative Amide Formation from Thioureas and Arylboronic Acids

Jianke Su,^[a] Wendong Li,^[a] Xin Li,^[a] Jian Xu^[a] and Qiuling Song*^[a]

ABSTRACT: The development of the reactivity on carbene complexes would lead to the creation of novel synthetic strategies. We discovered herein the Pd-catalyzed desulfurative amide formation involved Suzuki–Miyaura coupling reaction, notably the Pd complex was generated in situ from thioureas, Ag salt and Pd catalyst. Silver salt was essential for the construction of this type of carbenes from available and stable thioureas and well participated in the catalytic cycle. We report a method for the synthesis of arylamides from arylboronic acids, which greatly enriched the application of thiourea chemistry and expanded the application of the Suzuki–Miyaura coupling.

Introduction

Amide bonds are one of the most important functional motifs in chemistry and biology, they are not only the key chemical connections of proteins but also the basis for some of the most versatile and widely used synthetic polymers.¹ Because of their prevalence and stability, amides are attractive reagents for chemical transformations and can be converted into versatile valuable products.² Therefore, the development of the efficient synthesis of amides is an ongoing research hotspot in chemistry and biology.³ Traditionally, amides are synthesized via the condensation between amines and carboxylic acids or amine acylation with acid derivatives, such as acyl chlorides, anhydrides, or active esters, using various coupling reagents.^{3,4} However, the production of large quantities of waste is the major concern using stoichiometric activating agents⁵. Therefore, the development of green and novel catalytic methods for amide synthesis is in great demand.

Organoboronic acids are widely used in various coupling reactions under the catalysis of palladium.⁶ However, the use of arylboronic acids in the synthesis of arylamides has been rarely reported. In the past few decades, Buchwald,⁷ Jiao,⁸ and others⁹ have made great achievements on transition-metal-catalyzed carbonylation of aryl halides and related compounds with carbon monoxide (CO) and amines (Scheme 1a). More recently, palladium/copper-catalyzed oxidative coupling of arylboronic acids with isocyanides to amides was achieved by Lei's group¹⁰ (Scheme 1b), but the current methods reached their inherent limits,¹¹ such as the production of large quantities of waste is the major concern using stoichiometric activating agents, unfriendly CO or isonitrile need to be used. Therefore, it is necessary to develop new efficient and general methods for amide synthesis.

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Scheme 1. Different approaches for the synthesis of amides from organoboronic acids

Along with our continuous interest on thiocarbonyl chemistry,12 we found that stable and easily-obtained thioureas could be used as the ADC (acyclic diaminocarbene) precursors and ADC-metal complexes could be formed in situ in the presence of silver salts. Moreover, it could perfectly immerse to the catalytic system in coupling with aryl boronic acids (Scheme 1c). There are several unprecedented merits in this transformation: 1) no need to use the activator commonly used in the past,13 such as EDC (1-ethyl-3-(3dimethylaminopropyl)carbodiimide), and T3P (n-propylphosphonic acid anhydride), etc; 2) the complexes were compatible with both substrate (boronic acids) and oxidant (Ag salt) although carbenes are active species which are reported to be intolerable to either NuH or oxidant; 3) form ADC-meta complexes in situ, the ADC-metal complexes were the real catalyst species in the tranformations. Herein, we disclose a Suzuki-Miyaura coupling of thioureas via a palladium diaminocarbene intermediate, affording various aryl amides upon further hydrolysis (Scheme 1C). Compared with the previous research on thiourea, the application of thiourea in synthesis was further expanded.¹⁴ This reaction provides the rare case of thiourea arylation via formal C-N bond cleavage reaction¹⁵.

Results and Discussion

By using di(piperidin-1-yl)methanethione (**1a**) and phenyl boronic acid (**2a**) as the model substrates, we first investigated the effect of key parameters (Pd catalysts, entries 1-5; temperature, entries 6-8). Silver salt was essential for the success of this reaction. As our description above, it could play the role of achieving ADC via desulfurization¹⁶ which was only accomplished by metal K¹⁷ or oxalyl chloride,¹⁸ by the formation of Ag₂S. Additionally, Ag salt is the typical oxidants for regeneration of Pd^{II} from Pd⁰ to furnish the

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whole catalytic cycle. Such dual identities make it indispensable in this reaction (entry 20). No reaction occurred if other common oxidants were used such as BQ and copper salts (entries 9-11). Further screening of common silver salts showed that Ag_2CO_3 exhibited best activity. To facilitate transmetallation of phenyl boronic acid, a series of additional bases were also studied and Na₂CO₃ was the optimal one (entries 13-17). Amount of Pd catalyst as well as the silver salt loading and base usage highly affected the efficiency of this transformation. When submitting them along with 10 mol% of Pd(PPh₃)₂Cl₂ in trifluoroethanol (TFE, without dehydration) under air atmosphere with 1.5 equiv of Ag_2CO_3 , a 93% yield of the amide phenyl(piperidin-1-yl)methanone (**3a**) could be obtained (entry 19). **Table 1:** Optimization of the reaction conditions^a



entry	catalyst	t (°C)	oxidant	solvent	base	yield (%) ^b
			(x equiv)	(1.5 mL)	(y equiv)	
1	Pd(OAc) ₂	90	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	15
2	Pd(MeCN) ₂ Cl ₂	90	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	23
3	Pd(TFA)2	90	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	39
4	PdCl ₂ (dppf) ₂	90	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	36
5	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	60
6	PdCl ₂ (PPh ₃) ₂	70	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	16
7	PdCl ₂ (PPh ₃) ₂	80	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	21
8	PdCl ₂ (PPh ₃) ₂	100	$Ag_2CO_3(3)$	t-AmylOH	NaHCO ₃ (2)	42
9	PdCl ₂ (PPh ₃) ₂	90	AgOAc (3)	t-AmylOH	NaHCO ₃ (2)	18
10	PdCl ₂ (PPh ₃) ₂	90	BQ (3)	t-AmylOH	NaHCO ₃ (2)	0
11	PdCl ₂ (PPh ₃) ₂	90	Cu(OAc) ₂ (3)	t-AmylOH	NaHCO ₃ (2)	0
12	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(3)$	t-BuOH	NaHCO ₃ (2)	36
13	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(3)$	TFE	NaHCO ₃ (2)	53
14	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(3)$	TFE	K ₂ CO ₃ (2)	23
15	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(3)$	TFE	$Na_2CO_3(2)$	68
16	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(3)$	TFE	Na ₂ CO ₃ (1)	79
17	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(3)$	TFE	$Na_2CO_3(0.5)$	80
18	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(2)$	TFE	Na ₂ CO ₃ (0.5)	83
19	PdCl ₂ (PPh ₃) ₂	90	Ag ₂ CO ₃ (1.5)	TFE	Na ₂ CO ₃ (0.5)	93
20	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(0)$	TFE	$Na_2CO_3(0.5)$	0
21	PdCl ₂ (PPh ₃) ₂	90	$Ag_2CO_3(1.5)$	TFE	Na ₂ CO ₃ (0.5)	71

^a Reaction conditions: 0.2 mmol of **1a**, 0.4 mmol of **2a**, 0.02 mol of Pd catalyst, x equiv of oxidant, y equiv of base and 1.5 mL of solvent , the reaction is carried out under air atmosphere; ^b Isolated yield; ^c0.01 mmol PdCl₂(PPh₃)₂.

The optimal parameters obtained were applied toward the reaction of the thiourea 1a with a number of boronic acids (Scheme 2), giving product 3a in 93% yield. When alkyl substituents were on the phenyl ring, desired amide products were obtained in high yields (3b-3c). And 4-Ph substituent also can give the product 3d in 67% yield. Electron-donating substituents led to a relatively negative effect for this reaction (3g-3h), while halogen and other strong electron-deficient group substituted phenyl boronic acids generally demonstrated high activities (3f, 3i-3u). It is noteworthy, yet very unusual in palladium chemistry, that bromo-substituted boronic acids were tolerated well under our conditions (3j), and this provides an extremely important choice for cross-coupling reactions and makes the further structural elaboration feasible. To our delight, substrates with functional groups such as the aldehyde group was intact in such oxidative conditions (3q and 3r). Polyphenyl and vinyl boronic acids were also compatible in this transformation (3e and 3v). However, alkyl boronic acids failed to achieve desired products in this coupling reaction, probably because of the low rates for reductive elimination of groups bound to metal by sp³-hybridized carbons.



The nucleophiles in this Suzuki-Miyaura-type reaction could also be extended to aryl boronate esters (Scheme 3). When propane-1,3- diol arylboronates **4a**, **4b** and **4c** were subjected to the reaction with thiourea **1a**, good yields of corresponding benzamides were obtained except that acetyl on the para position. Pinacol phenylboronate **4d** could also smoothly lead to the formation of amide **3a** in 83% yield.

Scheme 3. Substrate scope of boronic esters



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Next, we examined the manifestation of various structures of thioureas in this reaction (Scheme 4). When a symmetric thiourea (1b-1f) was used, sole product was obtained. High yields of benzamides were achieved whatever the thiourea substrate was derived from a tertiary aliphatic amine or an aromatic one (3w-3aa). Release of an amine from thiourea that owns high boiling point could be detected by GC-MS (See SI). Thiocarbonyldiimidazole (1g), which possesses the fine leaving group, was unreactive under the standard conditions (3bb), indicating this reaction unlikely proceeds through the typical nucleophilic addition-elimination mechanism. Asymmetric thiourea would lead to a couple of possible products. According to the discrimination in iminium salt formation step, a regioselectivity can be observed (1h-1j). The results obtained showed that the thioureas bearing more electron-rich amine-moiety tend to donate its electron pair to form iminium salt, further hydrolysis of which transferred to an amine, thus driving the reductive elimination of ADC complex. The electron-deficient part was apt to reserve in the amide product with the selectivity between 2:1 and 4:1, approximately (3cc-3ff). Thioureas bearing primary or secondary amino moiety lead to unknown mixtures, according to the detection by GC-MS.

Scheme 4. Substrate scope of thioureas^a





dual roles in this transformation: it acts as a reagent for desulfuration to form ADC-metal complexes, at the same time, it also serves as an oxidant to oxidize Pd(0) to Pd(II) to furnish the catalytic cycle. When urea 1a' was exposed to the standard conditions, there was no reaction occurred, suggesting the unique structure of thioureas for the success of the transformation (eq. 1). In order to understand the origins of oxygen in the product, ¹⁸O labeling experiment were performed with H₂¹⁸O under standard conditions, the ¹⁸O-labeled product 3a-18O was obtained (eq. 2), which demonstrated that oxygen atom in carbonyl group of the final product was from water. The low ¹⁸O incorporation might stem from the residual water which was contained in reagents, catalysts or glassware. Direct reaction of thiourea 1a with equivalent amount of PdCl₂(PPh₃)₂ was subsequently conducted. After filtration of inorganic solids and addition of ether solvent, yellow crystal 5 was precipitated and separated (eq. 3). All these operations were conducted under air atmosphere. Complex 5 catalyzed the Suzuki-Miyaura reaction under standard condition in the presence of Ag₂CO₃ delivering 3a in high yield, suggesting the plausible intermediacy of it in the catalytic cycle (eq. 4). Not surpringly, in the absence of Ag₂CO₃, there was no product 3a detected. These results further demonstrated the key role of Ag salt in the transformation. The reaction between stoichiometric amount of complex 5 and arylboronic acid 2a were performed subsequently under standard conditions, rendering 3a in 81% yield (eq. 5), which further confirmed that complex 5 might be the key intermediate in our transformation.

Scheme 5. Control experiments



Conclusions

In summary, we have developed the Pd-catalyzed Suzuki–Miyaura coupling of thioureas with the formal C-N bond activation to afford aryl amides. Silver salts assisted the formation of Pd-ADC complex in a facile and direct manner, which is believed to undergo reductive elimination to result in the C-C coupling. This reaction is mild under air atmosphere and tolerant of a variety of functional groups with high yields, and can be expanded to thioureas to achieve aryl amides. It proved that thioureas can be harnessed as

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a useful synthon for C-C bond construction, which provides alternative and complementary methods for C-N bonds activation in amides for the amides synthesis. Further studies on expansion of this reaction to other substrates to achieve new coupling reactions as well as the development of this carbene chemistry are underway in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

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Keywords: amide formation • arylboronic acids • desulfurative • Suzuki–Miyaura coupling • thioureas

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From thiourea to amide. We disclosed a desulfurative reaction which provides the rare case of thiourea arylation from arylboronic acids via formal C-N bond cleavage, which greatly enriched the application of thiourea chemistry and expanded the application of the Suzuki–Miyaura cross couplings.



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