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论文题目：Unexpected Chemistry in the Synthesis of A Key Drug Intermediate under Buchwald-Hartwig Amination Conditions

Unexpected Chemistry in the Synthesis of A Key Drug Intermediate under Buchwald-Hartwig Amination Conditions

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ABSTRACT

The manuscript described that an unexpected compound was formed in the reaction of an aryl halide bearing an aldehyde group with an amine under Buchwald-Hartwig Amination conditions. A tentative mechanism was proposed. It also suggests that cesium carbonate may play an important role in the formation of a carboxylate as a key intermediate. This research may provide insights in catalytic system design and a novel synthetic approach of amide via Cannizzaro-type reaction.

KEYWORDS

Unexpected chemistry, Buchwald-Hartwig Amination, Mechanism study, Cesium Carbonate, Dehalogenation

CONTENT

ABBREVIATIONS

Abbreviation	Name
CDI	1,1'-Carbonyldiimidazole
DCE	1,2-Dichloroethane
DMA	Dimethylacetamide
HPLC	High-performance liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
^{1}H NMR	^{1}H Nuclear magnetic resonance
IS	Internal standard
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

1. INTRODUCTION

1.1.Accidental discoveries in chemistry

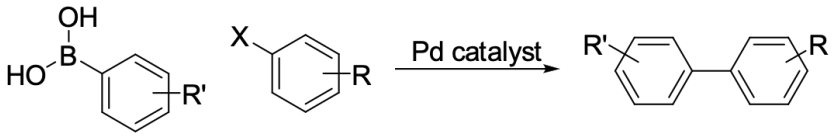
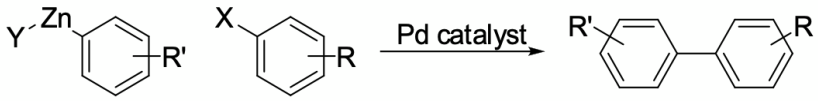
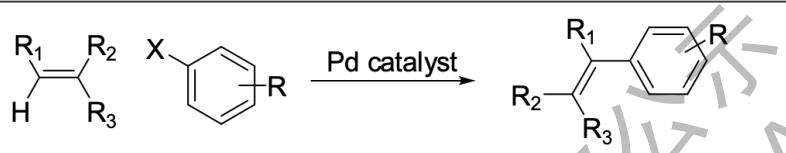
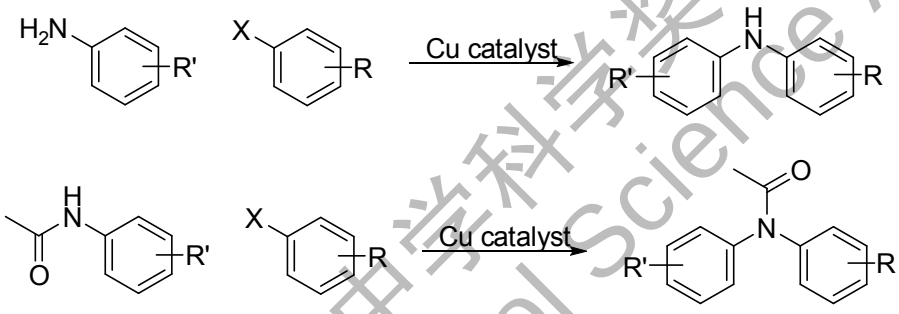
Chemistry is the branch of science dealing with the study of matter, its properties, and the changes in composition of substance and energy during various process. Sounds boring and complicated? Maybe. But chemistry plays a crucial role in all aspects of our daily life, including but not limited to medicines, foods, textiles and even ourselves. Generations of scientists and numerous resources and efforts have been involved in its innovation, development and application, which has driven our society and technology forward dramatically. Besides, a number of game-changing reactions and chemicals were discovered accidentally. The first synthetic dye was obtained when William Perkins tried to create an artificial quinine with tree bark and coal tar in 1856.[1] Polyethylene, the most produced plastic with a market size at $ 114.79 billion in 2021, was surprisingly produced in a reaction of ethylene and benzaldehyde in 1933.[2,3] So far, penicillin, considered as the most well-known and impactful finding, was achieved unexpectedly by Fleming after his two-week summer vacation. Recently, a study by scientist Xiangrui Kong and his group showed that a surface-promoted sulfate-reducing ammonium oxidation could take place spontaneously, where extra energy is usually required to overcome a barrier. The unexpected chemistry was published in Science, and may become very useful in sewage treatment and other industrial application, providing a new and cost-effective method beating biocatalysts and other expensive techniques.[5] Therefore, reactions with interesting results but failed to follow the known rules or intended designs should not be easily ignored. A further investigation is worthy of time and effort, and sometimes may be rewarded with major breakthroughs.

1.2.Palladium catalyzed coupling reactions

Synthetic chemistry plays a vital role in human society. New compounds are designed and prepared to improve living standards, to accelerate technology innovations, and to stimulate economic growth.

However, sometimes synthesis can be very challenging, thus scientists devote themselves to develop novel processes which are safer, more energy-efficient and more environment-friendly. Transition metal catalyzed coupling is one of the best examples of such. Coupling reactions have been widely employed in synthesis of pharmaceutical molecules, conjugated polymers, natural products and other complex compounds. The invention and commercialization of cross coupling are of great value, and have become an intensive interest for academic and industrial chemists. Suzuki, Negishi, and Heck shared the 2010 Nobel Prize in Chemistry for their breakthroughs in palladium-catalyzed formation of carbon-carbon bonds.[6-8] Meanwhile, carbon-nitrogen bond formation by cross coupling is also studied comprehensively and considered classical in organic chemistry. In 1901 Ullman discovered the amination mediated by copper under harsh reaction conditions, expanding the scope to include a variety of nucleophiles. In 1983 Mikita published the first example of a palladium catalyzed aryl-amine coupling under mild conditions with clean results. However, the reaction scope is limited and the amines used are toxic and sensitive. Therefore, the work did not get referenced until Hartwig took a closer look at it. In 1994, Hartwig reported an improved protocol for the coupling of aryl bromides and aminostanaes. Three months later, Buchwald submitted his independent but overlapping work to expand the scope of the reaction by generating tin amines *in situ*, yet the use of tin reagents is still required. Later in 1995, a tin-free Pd-catalyzed coupling of aryl bromides with amines reported from both labs, is now know as the Buchwald-Hartwig Amination.[7,8] The general methodology and its restless evolutions provide efficient tools to synthesize drug-like small molecules and novel materials in high productivity, low energy consumption and good atom economy under mild and environment-friendly conditions.

Table 1

Suzuki Coupling	
Negishi Coupling	
Heck Coupling	
Ullmann Coupling	
Buchwald-Harwig Coupling	

The general accepted reaction mechanism of Buchwald-Harwig Coupling has been demonstrated to proceed three stages as below: an active Pd (0) is inserted into the aryl-halide bond via an oxidative addition, followed by transmetallation with amine and base, in which the amino group of the amine is transferred to the palladium complex and replaces the halide group. Finally, formation of a new σ bond between the aryl group and the amino group, which are released from the palladium complex, gives the coupling product and regenerates the catalyst. [8](**Figure 1**)

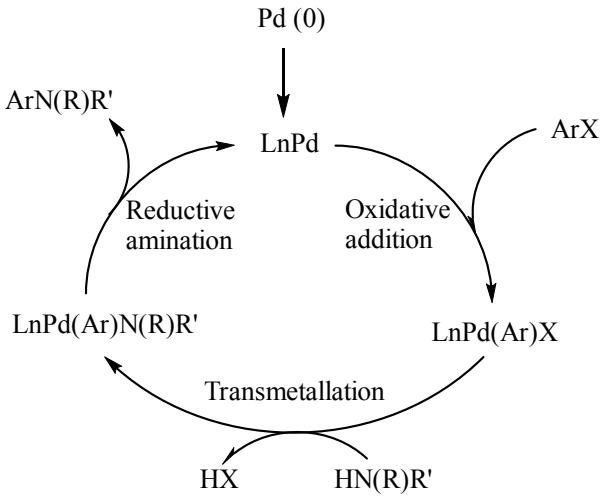


Figure 1

1.3.An unexpected reaction

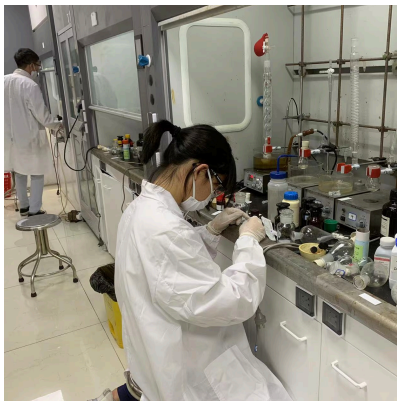
t-butyl 1-(6-formylpyridin-3-yl) pyridine-4-carboxylate (**1**) is one of the most important pharmaceutical intermediates. Ideally, it could be synthesized via Buchwald-Hartwig Amination by a one-step reaction. However, in my synthesis of **1** under the classical conditions, a significant amount of t-butyl 1-(pyridine-2-carbonyl) piperidine-4-carboxylate (**2**) was yielded unexpectedly. **1** was readily obtained through a three-step synthesis. But why was **2** produced instead of **1**? Why did the striking chemistry happen?

In the study, we found that a key intermediate t-butyl 1-(5-bromopyridine-2-carbonyl) piperidine-4-carboxylate (**2a**) may be partially responsible for the formation of **2**. By looking into the factors that dominate the formation of **2a** and the transformation of **2a** to **2**, a tentative mechanism of this unexpected chemistry was proposed.

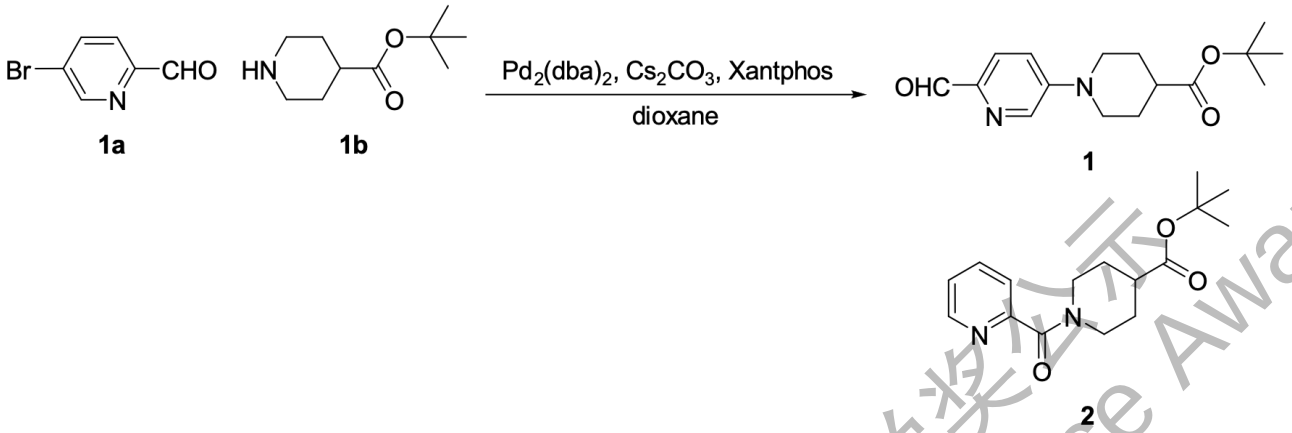
2. RESULTS AND DISCUSSION

2.1.The structural elucidation

Compound **1** is a key intermediate in drug synthesis, which is supposed to be obtained conveniently by reacting aromatic halide **1a** with amine **1b** via a Pd mediated C-N coupling protocol (**Scheme 1**). After heating the reaction mixture of **1a** and **1b** with $Pd_2(dab)_3$, Xanphos, and Cs_2CO_3 in dioxane at 100°C for 20 hours, a major product with a molecular weight of 290 was detected by LC-MS, exactly the same as **1**. The reaction was relatively clean, and the product was isolated with a yield of 44.4%. However, when proton NMR was applied to confirm the structure, it was found that: **1)** the characteristic signal of aldehyde (^{1}H NMR: δ 9 - 10 ppm) was absent; **2)** the signals (^{1}H NMR: δ 8.60, 7.82, 7.61, 7.36 ppm) showed four asymmetrical aromatic

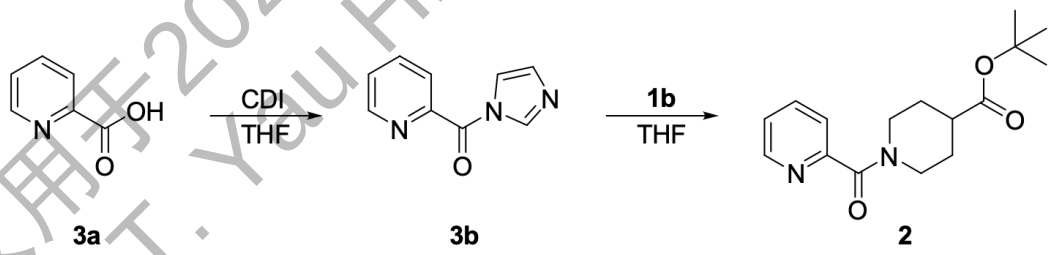


protons present other than three aromatic hydrogens as in **1**. Obviously, the product of the reaction was not the target molecule **1**, but what would be *the mystery compound*?



Scheme 1

After studying the NMR data carefully, **2** was surmised to be the possible product of the reaction. Thus, We chose to probe the identity of "*the mystery compound*" by comparing it with **2**, which was synthesized as shown in **Scheme 2.** Aromatic acid **3a** was treated with CDI to generate **3b** *in situ* quickly, then **1b** was added and stirred at room temperature for 20 hours. Compound **2** was isolated, and its ^{1}H NMR and LC-MS were essentially identical with the spectra of "*the mystery compound*". The straightforward results promptly confirmed the assumption.

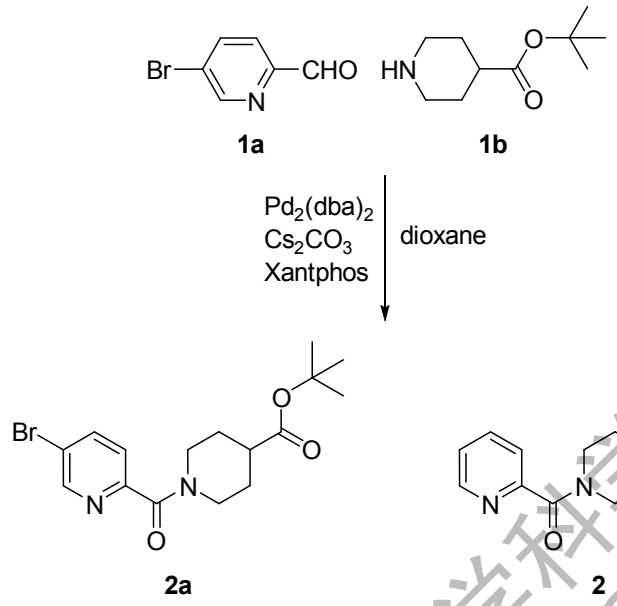


Scheme 2

2.2.A tentative mechanism

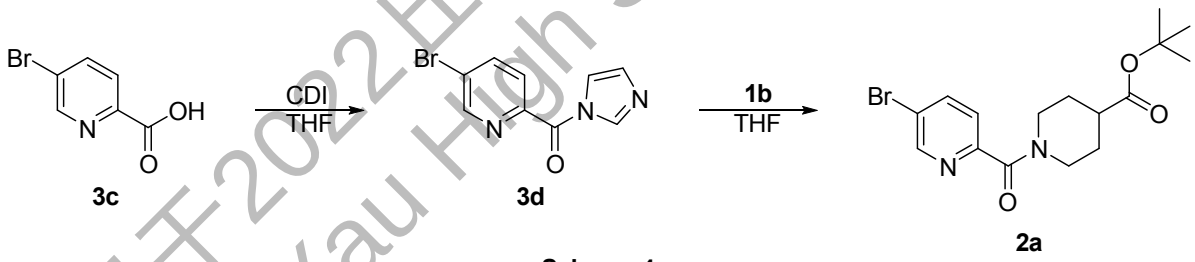
Prompted by the bizarre but intriguing formation of **2** in the Pd-catalyzed reaction, we investigated the reaction (**Scheme 3**) by monitoring the progress closely with LC-MS. It was observed that after 6 hours of vigorous stirring of **1a** with **1b** under the same conditions as mentioned above, a significant amount of **2** was formed along with a minor amount of **2a**. After 20

hours, **2a** disappeared completely, while **2** was the major product found by LC-MS. This finding indicates that **2a** may be initially formed, then converted to **2** subsequently.



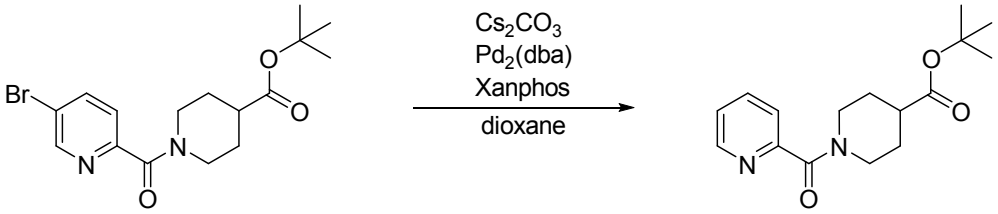
Scheme 3

To verify the presumption, **2a** was prepared independently as shown in **Scheme 4**. The procedure was similar to the synthesis of **2**.



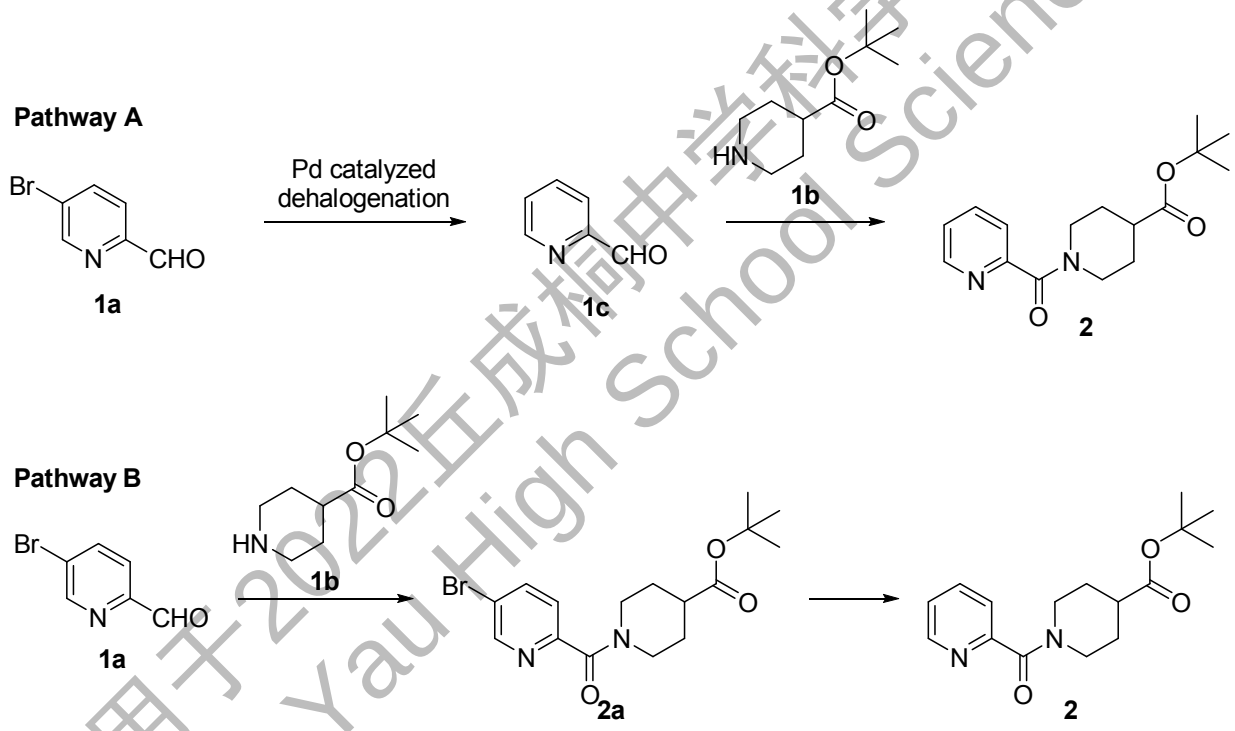
Scheme 4

With **2a** in hand, we carried out an experiment to explore the transformation of **2a** to **2.** By heating **2a** in the $Pd_2(dab)_3$, xanphos, and Cs_2CO_3 under 100°C for 20 hours, it was observed that the ratio of **2a**:**2** was around 1:1 on LC-MS, along with some unidentified products. Although the conversion was not complete, it indicated that part of **2** was produced by **2a**.



Scheme 5

The formation of **2** could be surmised in two different pathways. In both, the well documented Pd catalyzed dehalogenation[9,10] and the formation of amides from aldehydes were accounted for the formation of **2**, but in different orders. In **Pathway A**, aldehyde **1a** goes through dehalogenation first, then reacts with amine **1b** to form **2**. Another pathway is that **1a** and **1b** reacts to offer **2a**, which goes through dehalogenation in a second stage. Base on the formation of **2a** and its conversion to **2** in the experiment executed as above, Pathway B is one of the possible pathways of the chemistry. Though **1c** was not observe in the reaction mixture, Pathway A should not be ruled out.

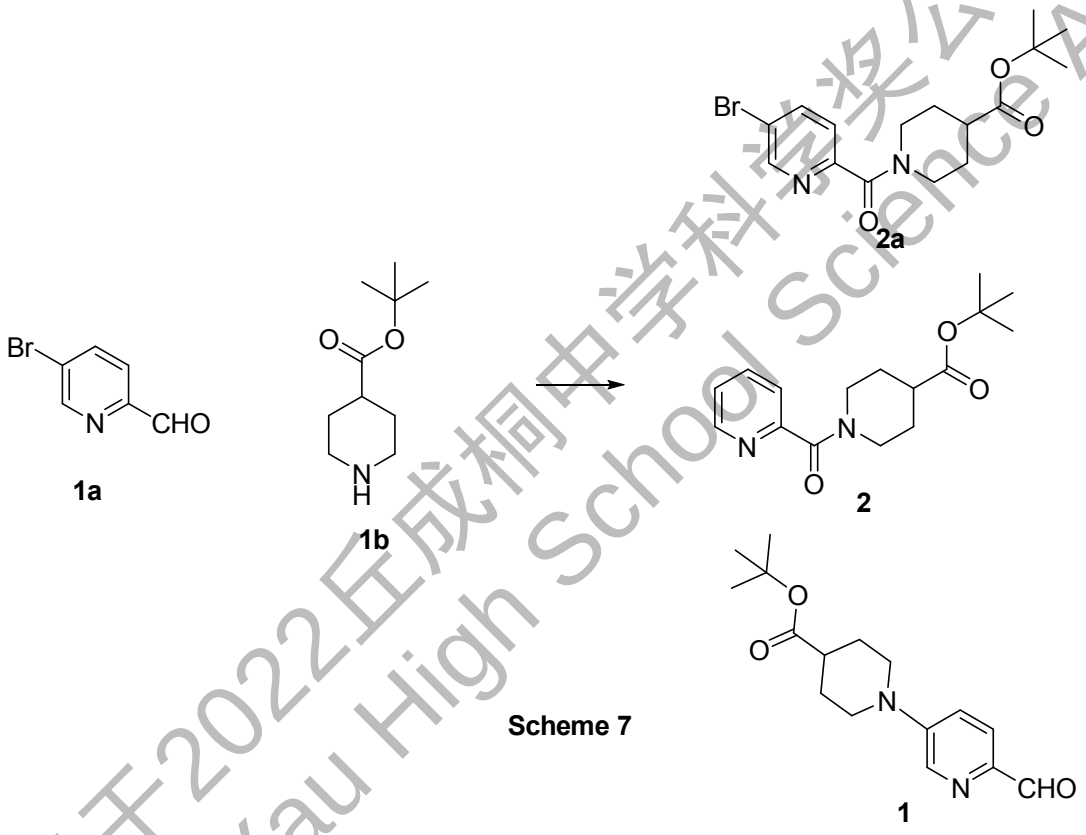


Scheme 6

In both pathways, the production of amides (**2** and **2a)** from aldehydes (**1c** and **1a)** is the key step. The factors dominating the formation of the amides were worthy of further investigation, hoping to enlighten the mechanism in depth. Here, the conversation of **1a** to **2a** was utilized the as a model.

The catalyst, the ligand, the base and various combinations were surveyed independently. 0.1 ml of 1M diphenyl ether dioxane solution as an IS was added to each trial. An IS is a substance that

does not react in a reaction, but can provide a distinguishing signal in LC-MS. Issues such as instrument drift, experimental procedure or injection volume, affect the signals of IS and analyte to the same degree, so the ratio between them remains constant, reflecting the analyte concentration independent of other conditions. Therefore, by keeping track of the ratio of the area or height of the analyte and IS instead of absolute peak area or height of the analyte, the precision of quantitative analysis is better guaranteed.



Scheme 7

Table 2

Entry	Compound	Retention Time
1	**1a**	1.30 min
2	**1**	1.82 min
3	**2**	1.60 min
4	**2a**	1.85 min

Meanwhile, samples of **1a, 1**, **2 and 2a** were prepared and injected into HPLC independently. The retention times were collected as references to interpret the reaction results monitored by HPLC.

The results were summarized in **Table 3**. In Entry 1, by employing the same conditions as in **Scheme 3**, aldehyde **1a** was fully consumed, and the reaction was relatively clean. A trace amount of **1** was observed, and the ratio of **2**:**1** was around 80:1. This is in agreement with previous observation. In Entry 2, aldehyde **1a** was barely left, and most of it was decomposed to unidentified byproducts, but the formation of **2** and **2a** in a 1:1.4 ratio was detected. In the absence of the base, the combination of $Pd_2(dba)_3$ and Xanphos did not convert much of **1a** (Entry 3). Same in Entry 7

Table 3

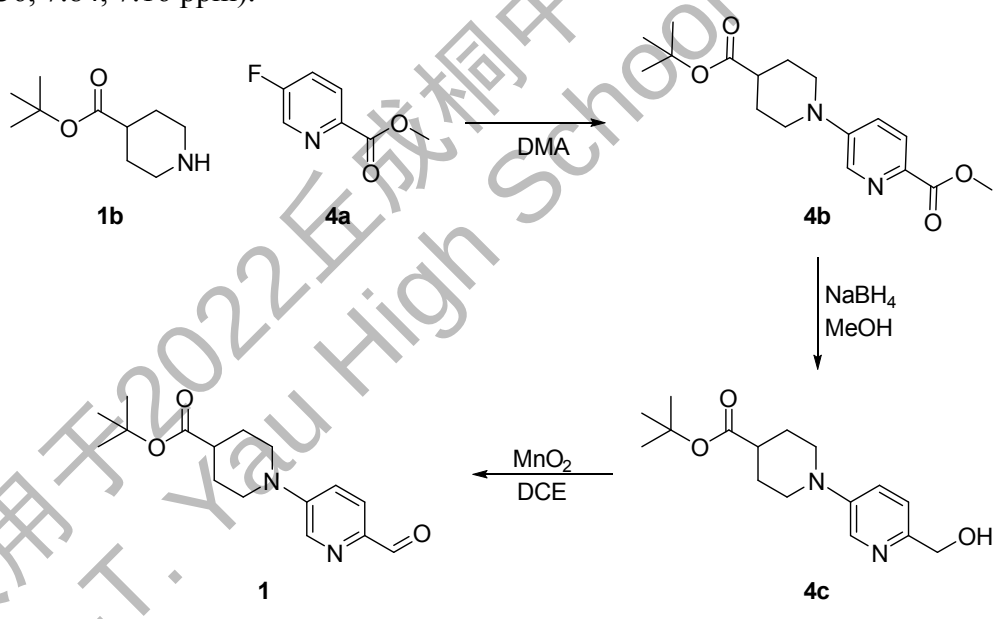
Entry	Reagent	Temperature & Time	Result
1	Cs_2CO_3 (2.0 eq), $Pd_2(dba)_3$ (0.1 eq), Xanphos (0.1 eq)	100°C, 20 hours	Full conversion of **1a**; **2**:**1** = 80:1
2	Cs_2CO_3 (2.0 eq), $Pd_2(dba)_3$ (0.1 eq)	100°C, 20 hours	Full conversion of **1a**, a little bit messy; **2a**:**2** = 1:1.4
3	$Pd_2(dba)_3$ (0.1 eq), Xanphos (0.1 eq)	100°C, 20 hours	**2a**:**1a** = 1:23
4	Cs_2CO_3 (2.0 eq), Xanphos (0.1 eq)	100°C, 20 hours	**2a**:**1a** = 1:3
5	Cs_2CO_3 (2.0 eq)	100°C, 20 hours	**2a**:**1a** = 1:1
6	$Pd_2(dba)_3$ (0.1 eq)	100°C, 20 hours	Messy
7	Xanphos (0.1 eq)	100°C, 20 hours	**1a** with trace amount of **2a**
8	None	100°C, 20 hours	**1a** with trace amount of **2a**

and 8, trace amount of **2a** was observed while most of **1a** remained intact in the reaction. In Entry 6, sole $Pd(OAc)_2$ caused the decomposition of **1a** and the reaction turned messy. In Entry 4, with the use of Cs_2CO_3 and Xanphos, around 25% **1a** was converted to **2a**. It is interesting that solely Cs_2CO_3 showed much better activity, and about half of **1a** was converted to **2a** (Entry 5).

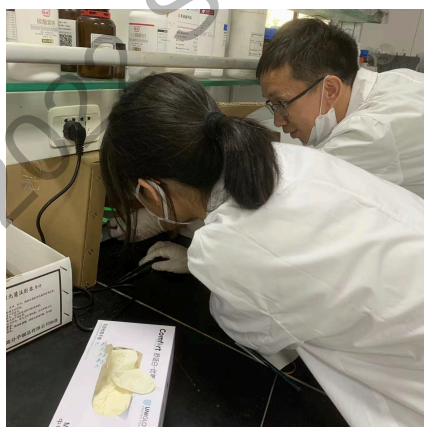
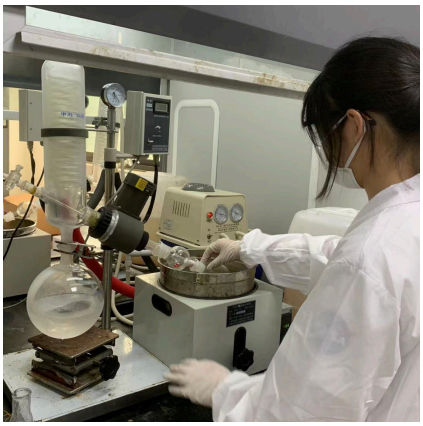
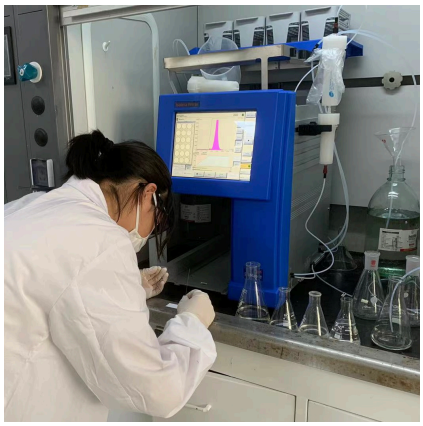
Previously, the formation of amides from aldehydes by Cannizzaro-type reaction requires $LaCl_3$ as a catalyst and LDA or n-BuLi as bases.[11,12] In the study, it is the first time such a reaction to be conducted without the application of strong and extremely moisture-sensitive bases.

*2.3.Synthesis of target molecule **1***

Since the desired compound **1** could not be synthesize with aromatic halide **1a** and amine **1b** via a one-step synthesis, we undertook a traditional 3-step route to synthesize **1** (**Scheme 8**). Starting from methyl 5-fluoropicolinate (**4a**), a methyl ester **4b** was obtained by simple substitution reaction. **4b** was reduced to afford alcohol **4c** without affecting the t-butyl carboxylate moiety. Aldehyde **1** was obtained by active MnO_2 oxidation of **4c**. The NMR of the product showed the characteristic proton of aldehyde (^{1}H NMR: δ 9.90 ppm, singlet) and three aromatic protons (^{1}H NMR: δ 8.36, 7.84, 7.16 ppm).



Scheme 8

3. EXPERIMENTAL SECTION

*3.1. "The mystery compound"(**Scheme 1**)*

Under nitrogen protection, **1a** (1.85 g, 10 mmol, 1.0 eq), **1b** (2.30 g, 12 mmol, 1,2 eq), $Pd_2(dba)_3$ (916 mg, 1.0 mmol, 0.1 eq), Xanphos (578 mg, 1.0 mmol, 0.1 eq), Cs_2CO_3 (6.50 g, 20 mmol, 2.0 eq), and 20 ml of dioxane were added to a 50 ml flask. The mixture was stirred at 100°C for 20 hours until LC-MS showed the aldehyde was fully consumed. The solution was partitioned between distilled water (25 ml) and ethyl acetate (25 ml), and the aqueous phase was washed with ethyl acetate (2 × 10 ml) . The organic phases were combined, washed with diluted hydrochloride solution (10 ml) and diluted sodium bicarbonate solution (10 ml), dried with sodium sulfate, and concentrated under reduced pressure. Column chromatography (ChemFlash, gradient 20 to 50% ethyl acetate in hexane) yielded "*the mystery compound*" (1.28 g, 44.4%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): 8.60 (d, J = 4 Hz, 1H), 7.82 (m, 1H), 7.61 (m, J =7.6 Hz, 1H), 7.36 (m, 1H), 4,53 (m, 1H), 3.88 (m, 1H), 3.06~3.17 (m, 2H), 2.52 (m, 1H), 1.99~2.04 (m, 1H), 1.71~1.83 (m, 3H), 1,44 (s, 9H); MS: 291 [M+1].

*3.2. Independent synthesis of **2** (**Scheme 2**)*

To a 25 ml round-bottomed flask, pyridine-2-carboxylic acid (369 mg, 3.0 mmol, 1.0 eq), CDI (734 mg, 4.5 mmol, 1.5 eq) and 5 ml of THF were added. The solution was stirred at room temperature for 30 minutes and monitored with LC-MS. Bubbles were formed in the process. When the reaction completed, t-butyl piperidine-4-carboxylate (834mg, 4.5 mmol, 1.5 eq) was carefully added. The mixture was stirred at room temperature for 20 hours until LC-MS showed the carboxylic acid was fully consumed. The solution was partitioned between distilled water (5 ml) and ethyl acetate (5 ml), and the aqueous phase was washed with ethyl acetate (2 × 5 ml). The organic phases were combined, washed with diluted hydrochloride solution (5 ml) and diluted sodium bicarbonate solution (5 ml), dried with sodium sulfate, and concentrated under reduced

pressure. Column chromatography (ChemFlash, gradient 20 to 70% ethyl acetate in hexane) yielded the compound 5 (341 mg, 35.5%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 8.60 (d, J = 4 Hz, 1H), 7.82 (m, 1H), 7.61 (m, J =7.6 Hz, 1H), 7.36 (m, 1H), 4,53 (m, 1H), 3.88 (m, 1H), 3.06~3.17 (m, 2H), 2.52 (m, 1H), 1.99~2.04 (m, 1H), 1.71~1.83 (m, 3H), 1,44 (s, 9H); MS: 291 [M+1]. The ^{1}H NMR and LC-MS of **2** were identical with "*the mystery compound*".

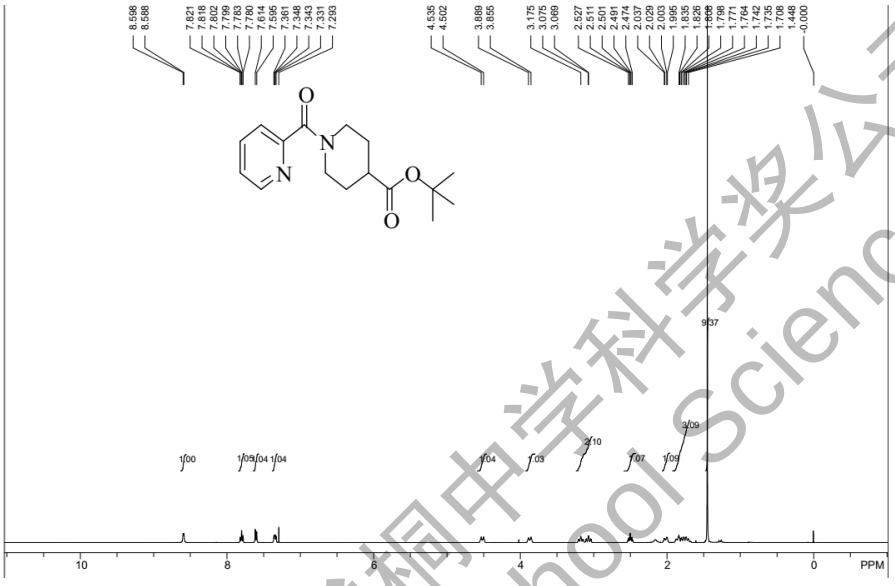


Figure 2: ^{1}H NMR of **2**

*3.3. Transformation of **2a** to **2***

3.3.1.Synthesis of 1-(5-bromopyridine-2-carbonyl)piperidine-4-carboxylate (**2a**)

To a 25 ml round-bottomed flask, 5-bromopicolinic acid (603 mg, 3.0 mmol, 1.0 eq), CDI (734 mg, 4.5 mmol, 1.5 eq) and 5 ml of THF were added. The solution was stirred at room temperature for 30 minutes and monitored with LC-MS. Bubbles formed in the process. When the reaction was done, t-butyl piperidine-4-carboxylate (834mg, 4.5 mmol, 1.5 eq) was carefully added. The mixture was stirred at room temperature for 20 hours until LC-MS showed the carboxylic acid was fully consumed. The solution was partitioned between distilled water (5 ml) and ethyl acetate (5 ml), and the aqueous phase was washed with ethyl acetate (2 × 5 ml). The organic phases were combined, washed with diluted hydrochloride solution (5 ml) and diluted sodium bicarbonate solution (5 ml), dried with sodium sulfate, and concentrated under reduced pressure. Column

chromatography (ChemFlash, gradient 20 to 70% ethyl acetate in hexane) yielded the compound **2a** (736 mg, 67.7%) as yellow solids. ^{1}H NMR (400 MHz, $CDCl_3$): 8.64 (d, 1.6 Hz), 7.92-7.94 (m, 1H), 7.53-7.55 (d, 1H, J = 8 Hz), 4.47-4.50 (m, 1H), 3.88-3.91 (m, 1H), 3.02-3.21 (m, 2H), 2.52 (m, 1H), 1.70- 2.03 (m, 4H), 1.45 (s, 9H) ; MS: 369, 371 [M+1].

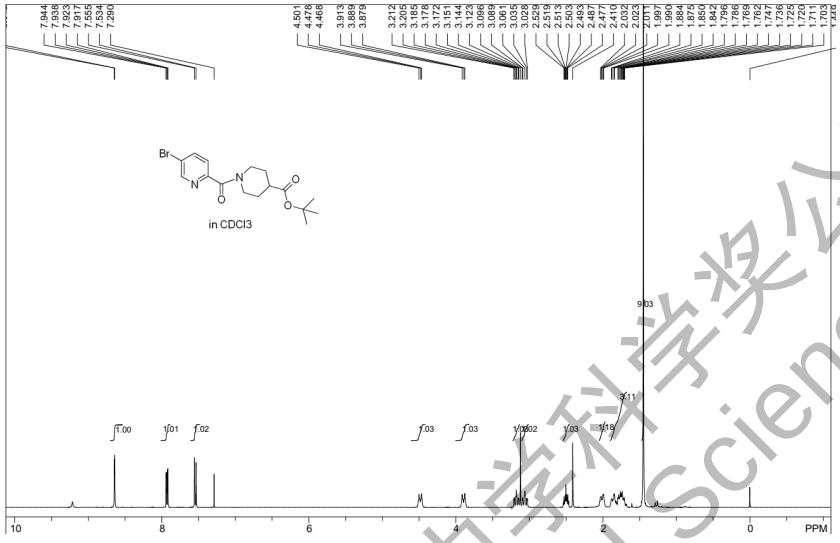


Figure 3: ^{1}H NMR of **2a**

3.3.2.Conversion of **2a** to **2**

Under N_2 protection, **2a** (368 mg, 1 mmol, 1.0 eq), $Pd_2(dba)_3$ (92 mg, 0.1 mmol, 0.1 eq), Xanphos (60 mg, 0.1 mmol, 0.1 eq), Cs_2CO_3 (650 mg, 2 mmol, 2.0 eq) were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

*3.4. Formation of **2a** (**Scheme 5**)*

3.4.1.Preparation of internal standard (IS) stock solution

Diphenyl ether (1.70 g, 10 mmol) was added in 10 ml of dioxane, and stirred for 5 minutes.

3.4.2.Reaction of 1a and 1b under different condition

Entry 1: Under N_2 protection, **1a** (185 mg, 1 mmol, 1.0 eq), **1b** (230 mg, 1.2 mmol, 1.2 eq), $Pd_2(dba)_3$ (92 mg, 0.1 mmol, 0.1 eq), Xanphos (60 mg, 0.1 mmol, 0.1 eq), Cs_2CO_3 (650 mg, 2 mmol, 2.0 eq) and 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial

was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

Entry 2: Under N_2 protection, **1a** (185 mg, 1 mmol, 1.0 eq), **1b** (230 mg, 1.2 mmol, 1.2 eq), $Pd_2(dba)_3$ (92 mg, 0.1 mmol, 0.1 eq), Cs_2CO_3 (650 mg, 2 mmol, 2.0 eq) and 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

Entry 3: Under N_2 protection, 1a (185 mg, 1 mmol, 1.0 eq), 1b (230 mg, 1.2 mmol, 1.2 eq), $Pd_2(dba)_3$ (92 mg, 0.1 mmol, 0.1 eq), Xanphos (60 mg, 0.1 mmol, 0.1 eq) and 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

Entry 4: Under N_2 protection, 1a (185 mg, 1 mmol, 1.0 eq), 1b (230 mg, 1.2 mmol, 1.2 eq), , Xanphos (60 mg, 0.1 mmol, 0.1 eq), Cs_2CO_3 (650 mg, 2 mmol, 2.0 eq) and 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

Entry 5: Under N_2 protection, 1a (185 mg, 1 mmol, 1.0 eq), 1b (230 mg, 1.2 mmol, 1.2 eq), Cs_2CO_3 (650 mg, 2 mmol, 2.0 eq) and 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

Entry 6: Under N_2 protection, **1a** (185 mg, 1 mmol, 1.0 eq), **1b** (230 mg, 1.2 mmol, 1.2 eq), $Pd_2(dba)_3$ (92 mg, 0.1 mmol, 0.1 eq), 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

Entry 7: Under N_2 protection, **1a** (185 mg, 1 mmol, 1.0 eq), **1b** (230 mg, 1.2 mmol, 1.2 eq), Xanphos (60 mg, 0.1 mmol, 0.1 eq), and 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed

by LC-MS

Entry 8: Under N_2 protection, **1a** (185 mg, 1 mmol, 1.0 eq), **1b** (230 mg, 1.2 mmol, 1.2 eq), and 0.1 ml of IS solution were mixed in 3 ml of dioxane in a vial. This sealed vial was stirred at 100°C for 20 hours, and a small amount of sample were assayed by LC-MS.

*3.5. Synthesis of **1** (**Scheme 8**)*

3.5.1.Methyl 5-{4-[(t-butoxy)carbonyl]piperidin-1-yl}pyridine-2-carboxylate (**4b**)

To a 25 ml round-bottomed flask, methyl 5-fluorophyridine-2-carboxylate (465 mg, 3.0 mmol, 1.0 eq), t-butyl piperidine-4-carboxylate (832 mg, 4.5 mmol, 1.5 eq) and 5 ml of DMA were added. The solution was allowed to warm up to 120°C, stirred for 20 hours until LC-MS showed methyl 5-fluorophyridine-2-carboxylate was fully consumed. The reaction was partitioned between distilled water (5 ml) and ethyl acetate (5 ml), and the aqueous phase was washed with ethyl acetate (2 × 5 ml) . The organic phases were combined, washed with diluted sodium bicarbonate solution (5 ml) and diluted hydrochloride solution (5 ml), dried with sodium sulfate, and concentrated under reduced pressure. Column chromatography (ChemFlash, gradient 20 to 70% ethyl acetate in hexane) yielded **4b** (271.0 mg, 28.2%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.35 (d, J = 2.8 Hz, 1H), 8.00 (d, J=7.2 Hz, 1H), 7.17 (m, 1H), 3.96 (s, 3H), 3.83 (m, 2H), 3.02 (m, 2H), 2.45 (m, 1H), 2.00 (m, 2H), 1.82 (m, 2H), 1.45 (s, 9H); MS: 321 (M+1).

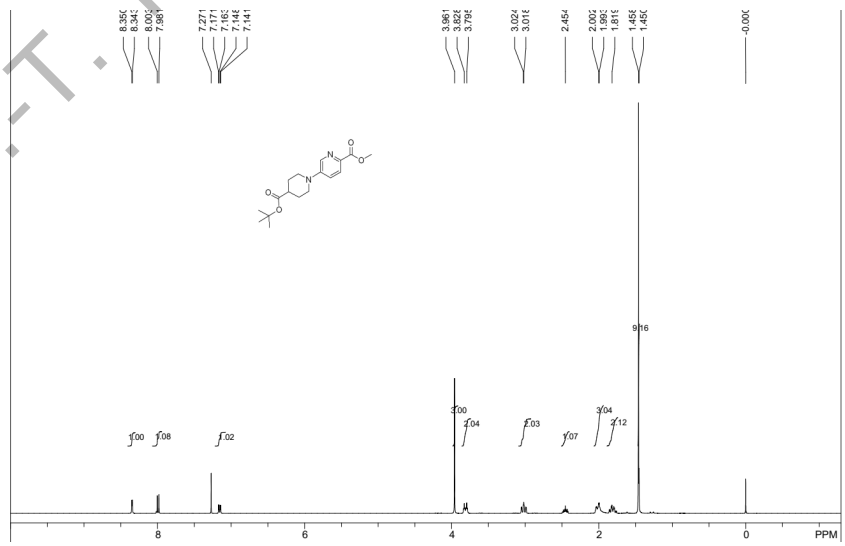


Figure 4: ^{1}H NMR of **4b**

3.5.2.t-butyl 1-[(6-(hydroxylmethyl)piperidin-3-yl]pyridine-4-carboxylate (**4c**)

To a 25 ml round-bottomed flask, 4b (160 mg, 0.5 mmol, 1.0 eq) in 5 ml of methanol, sodium borohydride (95 mg, 2,5 mmol, 2,5 eq) was added portion wisely. The solution was allowed to stirred for 20 hours at room temperature until TLC showed 4b was fully consumed. The reaction was partitioned between distilled water (5 ml) and ethyl acetate (5 ml), and the aqueous phase was washed with ethyl acetate (2 × 5 ml) . The organic phases were combined, washed with diluted sodium bicarbonate solution (5 ml) and diluted hydrochloride solution (5 ml), dried with sodium sulfate, and concentrated under reduced pressure. Column chromatography (ChemFlash, gradient 20 to 100% ethyl acetate in hexane) yielded **4c** (116.8 mg, 80.0%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (m, 1H), 7.25 (m, 1H), 7.15 (m, 1H), 4.67 (s, 2H), 3.64 (m, 2H), 2.87 (m, 3H), 2.40 (m, 1H), 2.03 (m, 2H), 1.88 (m, 2H), 1.45 (s, 9H); MS: 293 (M+1).

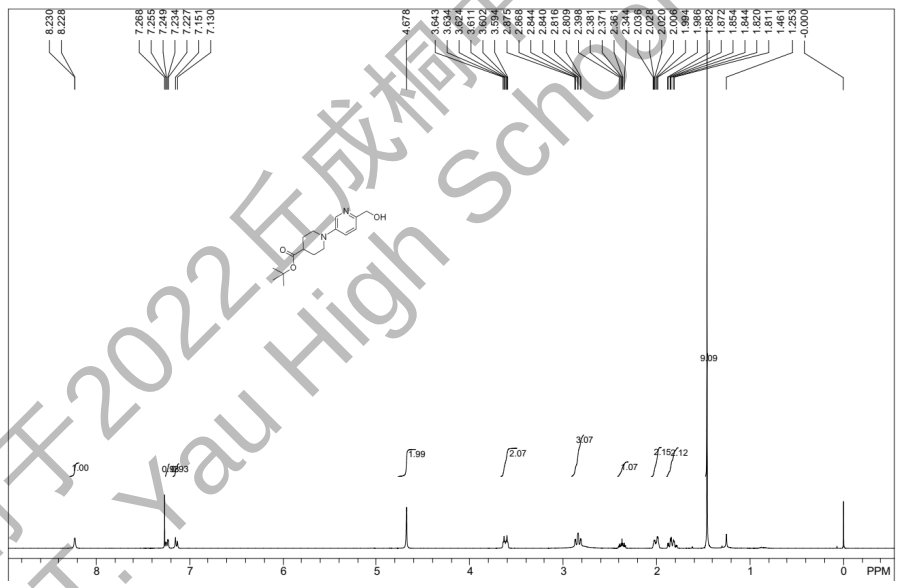


Figure 5: ^{1}H NMR of **4c**

3.5.3.t-butyl 1-(6-formylpyridin-3-yl)pyridine-4-carboxylate (**1**)

To a 25 ml round-bottomed flask, **4c** (58.4 mg, 0.2 mmol, 1.0 eq) in 5 ml of methylene chloride, activated MnO_2 (70 mg, 0.8 mmol, 4.0 eq) was added. The solution was allowed to stirred for 2 hours at room temperature until TLC showed **4c** was fully consumed. The reaction was partitioned between distilled water (5 ml) and ethyl acetate (5 ml), and the aqueous phase was

washed with ethyl acetate (2 × 5 ml) . The organic phases were dried with sodium sulfate, and concentrated under reduced pressure. Column chromatography (ChemFlash, gradient 20 to 100% ethyl acetate in hexane) yielded **1** (116.8 mg, 80.0%) as a white semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): 9.90 (s, 1H), 8.36 (d, J = 2.8 Hz), 7.84-7.86 (d, J = 8 Hz, 1H); 7.16-7.19 (m, 1H), 3.86-3.89 (m, 2H), 3.12 (m, 2H), 2.49 (m, 1H), 2.00- 2.05 (m, 2H), 1.79-1.83 (m, 2H), 1.46 (s, 9H); MS: 291 (M+1).

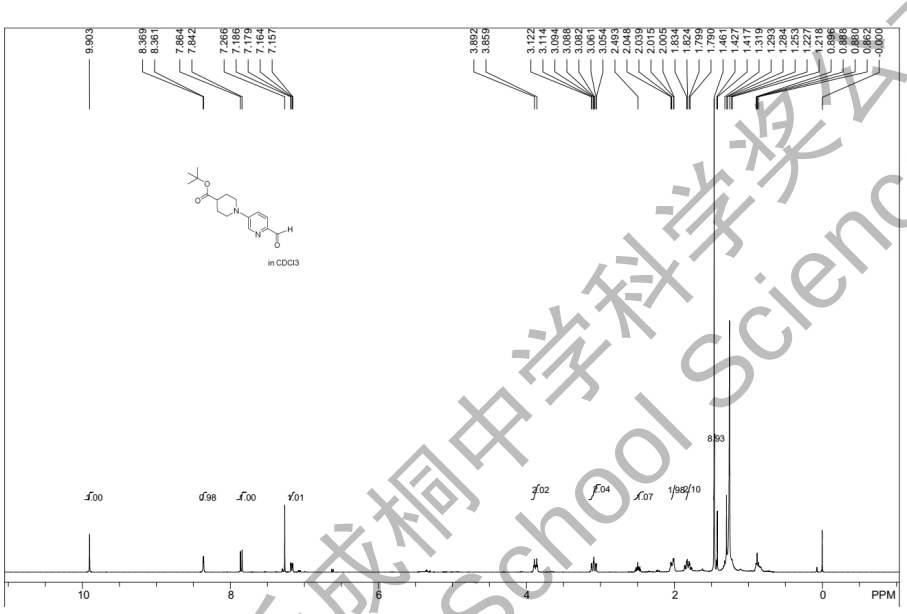


Figure 5: ^{1}H NMR of **1**

4. CONCLUSION

In conclusion, an unexpected chemistry was discovered when an aryl halide bearing an aldehyde group reacted with an amine under classical Buchwald-Hartwig Coupling conditions. After exploring the reaction carefully and systematically, we tentatively propose a mechanism, although other mechanistic possibilities cannot be ruled out at this stage. We also found that cesium carbonate could be used in the synthesis of amide by Cannizaro Reaction via aldehyde and amine which has not been reported before. The find shows a potential of a milder, more cost-effective and environment-friendly approach of peptide synthesis, which usually requires special coupling reagents and strong bases, though future work is necessary.

5. FUTURE WORK

5.1.Catalytic systems of Buchwald-Hartwig Coupling

When digging into the research on Pd-catalyzed C-N coupling of aromatic halide bearing an aldehyde group with secondary amines, two interesting literature reports emerged.

As shown in **Scheme 9**, by the coupling of 4-bromobenzaldehyde (**5a)** and morpholine (**5b)**, benzaldehyde (**5)** was obtained in a promising yield of 99% while a much lower yield of 42% under different reaction conditions, particularly when different reagents were utilized.[13, 14]

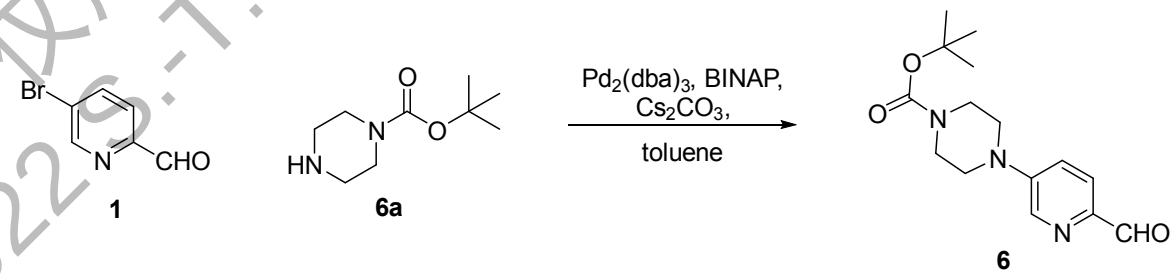
5a **5b** **5**

Scheme 9

Table 4

Entry	Reaction Conditions	Yield
1	**5a (**1.0 eq), **5b** (1.2 eq); NaOtBu (1.4 eq), toluene (1.0 ml), 1 mol% [(μ-$PPh_2CH_2PPh_2$)$Co_2(CO)_4$(μ, η-$Me_2NCH_2C{\equiv}CP(Cy_2)$] /[($\eta^3$-$C_3H_5$)PdCl]$_2$; 80°C, 2 hours.	99%
2	**5a (**1.0 eq), **5b** (2.5 eq); Cs_2CO_3 (2.0 eq), 10% Pd/C (2%), dppf (3%); rt →120°C, 24 hours.	42%

In addition, Patent WO2020160710 showed that the yield of coupling of **1a** and t-butyl piperazine-1-carboxylate (**6a**) was 17% only as shown in **Scheme 10**.[15]



1 **6a** **6**

Scheme 10

Based on the information and our study, we assume that under Buchwald-Hartwig Coupling conditions, substrates carrying an aldehyde group may undergo different pathways when different

catalytic systems were employed, offering significantly distinct results. In order to validate the theory and design more effective and efficient catalytic systems, further lab experiments and theoretical computation are required.

5.2.Formation of amides via Cannizzaro-type reaction

In addition, it is the first time that amides can be produced from aldehydes via Cannizzaro-type reaction without coupling reagents and strong bases. The work demonstrates a potential of a milder, more cost-effective and environment-friendly approach of peptide synthesis. Next steps on the study will focus on: 1) optimizing reaction conditions; 2) expanding substrates to widen the scope of the reaction; 3) conducting a in-depth investigation of the reaction mechanism.

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