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Benzoic Acid-Catalyzed Transamidation Reactions of Carboxamides, Phthalimide, Ureas and Thioamide with Amines

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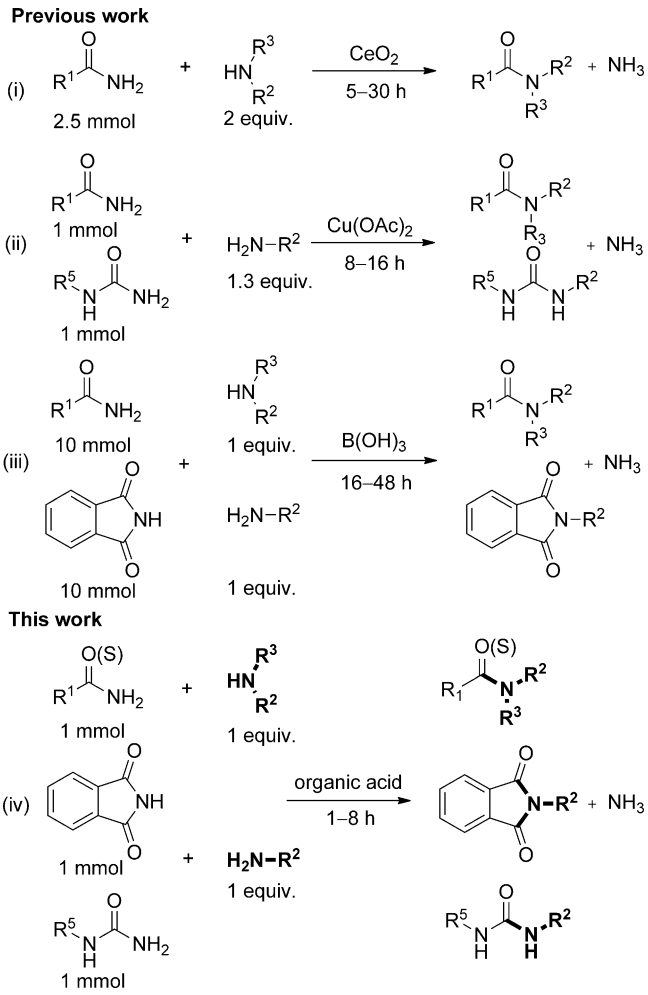
Abstract: An efficient and simple method for the transamidation of carboxamides, phthalimide, ureas and thioamide with amines catalyzed by commercially available benzoic acid under metal-free conditions is described. Furthermore, to the best of our knowledge, this is the first report about the transamidation of an aromatic thioamide with amines.

Keywords: benzoic acid; metal-free conditions; thioamides; transamidation

The amide linkage is one of the most important functional groups in nature because it constitutes the backbone of all natural peptides and proteins.[1] Also, it has been regarded as the most important linkage in the fields of industrial and medicinal chemistry.[2] According to the authoritative statistics reports from the leading pharmaceutical companies, nearly 25% of the drug molecules contain an amide bond unit,[3] which demonstrates its importance in organic synthetic chemistry. Amides, as an important class of compounds, have been widely found in bioactive products,[4] biological[5] and synthetic polymers.[6] Consequently, many methods for the synthesis of amides have been reported, such as the reactions of amines with carboxylic acid derivatives,[7] esters,[8] aldehydes[9] or alcohols,[10] rearrangement of aldoximes,[11] hydration of nitriles,[12] aminocarbonylation processes,[13] hydroamination of alkynes.[14] However, they always suffer from some limitations, such as stoichiometric amounts of activating agents, tedious work-up procedures and low reactivity. Therefore, as one of most straightforward and convenient methods, transamidation has gained more and more attention in this field. Unfortunately, because of the high stability of amided, transamidation usually requires harsh conditions, such as long reaction times, high temperatures (>250 °C) or stoichiometric amounts of activating



Scheme 1. Various methods for the transamidation of amides with amines.

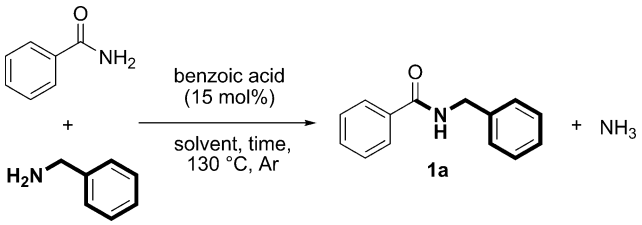
agents to cleave the amide bond.[15] In the last two decades, great efforts have been made in this area in order to develop a simple method that allows the reactions to occur under relatively mild conditions. Bertrand,[16] Beller (Scheme 1, ii),[17] Myers,[18] Akamanchi,[19] Shimizu (Scheme 1, i),[20] Stahl,[21] and Williams[22] have reported a series of metal-catalyzed methods of transamidation. Despite the advances achieved, all of these methods were catalyzed by transition or lanthanide metals, and these bring great difficulties for the separation and purification of the target product, especially in the synthesis of pharmaceutical molecules. Furthermore, these methods also suffer from certain demerits, for example, the use of expensive activation reagents and stoichiometric amounts of catalysts. To solve these problems, Allen,[23] Nguyen (Scheme 1, iii),[24] Adimurthy[25] and Singh[26] have reported a series of metal-free catalyzed methods for transamidation. However, these methods suffer from the shortcoming of long reaction times and limited substrate scope. The transamidation of aliphatic thioamides with amines has been reported by Schlatter.[27]

Herein, we have developed an efficient and simple method for the transamidation of carboxamides, phthalimide, ureas and thioamide with amines catalyzed by commercially available benzoic acid at 130 °C under metal-free conditions. To the best of our knowledge, the transamidation of aromatic thioamides with amines has not yet been reported (Scheme 1, iv).

Our initial studies were focused on screening for an efficient catalyst for the reaction of benzamide with benzylamine. Organic acids like aliphatic monocarboxylic acids, aliphatic diacids, aromatic acids and heterocyclic carboxylic acids were investigated and we found that benzoic acid was the best catalyst.[28] To further optimize the reaction conditions, different solvents, times and temperatures were screened in the presence of benzoic acid. Through a screening of the different solvents, we found that *p*-xylene was the best solvent for this reaction which can afford the desired product with a 98% yield (Table 1, entries 1–12). Then the reaction time was screened and results showed that the yield of the target product was not reduced even when the reaction time was decreased to 8 h (compare entries 11 and 13 with entry 14). The yield of **1a** declined significantly when the reaction temperature was 120 °C (Table 1, entry 16). The reaction was also carried out in air with a low yield of **1a** (Table 1, entry 17).

With the optimized conditions in hand, we then investigated the generality of this protocol. The transamidation of benzamide with benzylic amines including $BnNH_2$, 4-(Cl)$BnNH_2$, 2-(F)$BnNH_2$, 3-(MeO)$BnNH_2$, gave corresponding transamidation products (Table 2, **1a–d**) in excellent yields (92–96%),

Table 1. Optimization of the reaction conditions.[a]



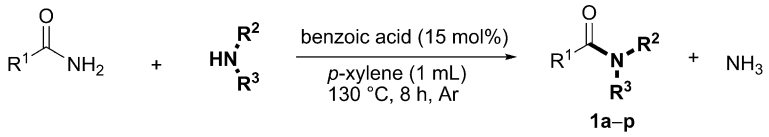
Entry	Solvent	Time [h]	Yield [%][b]
1	H_2O	20	13
2	*t*-BuOH	20	16
3	*n*-$C_6H_{11}OH$	20	10
4	butanone	20	49
5	CH_3CN	20	28
6	DMSO	20	23
7	benzene	20	57
8	PhMe	20	84
9	*o*-xylene	20	60
10	*m*-xylene	20	66
11	*p*-xylene	20	98
12	mesitylene	20	63
13	*p*-xylene	10	97
14	*p*-xylene	8	98
15	*p*-xylene	6	83
16[c]	*p*-xylene	8	84
17[d]	*p*-xylene	8	87

[a] Benzamide (1 mmol), benzylamine (1mmol), catalyst (15 mol%), solvent (1 mL), in a sealed tube.
[b] Determined by GC.
[c] Temperature: 120 °C.
[d] In air.

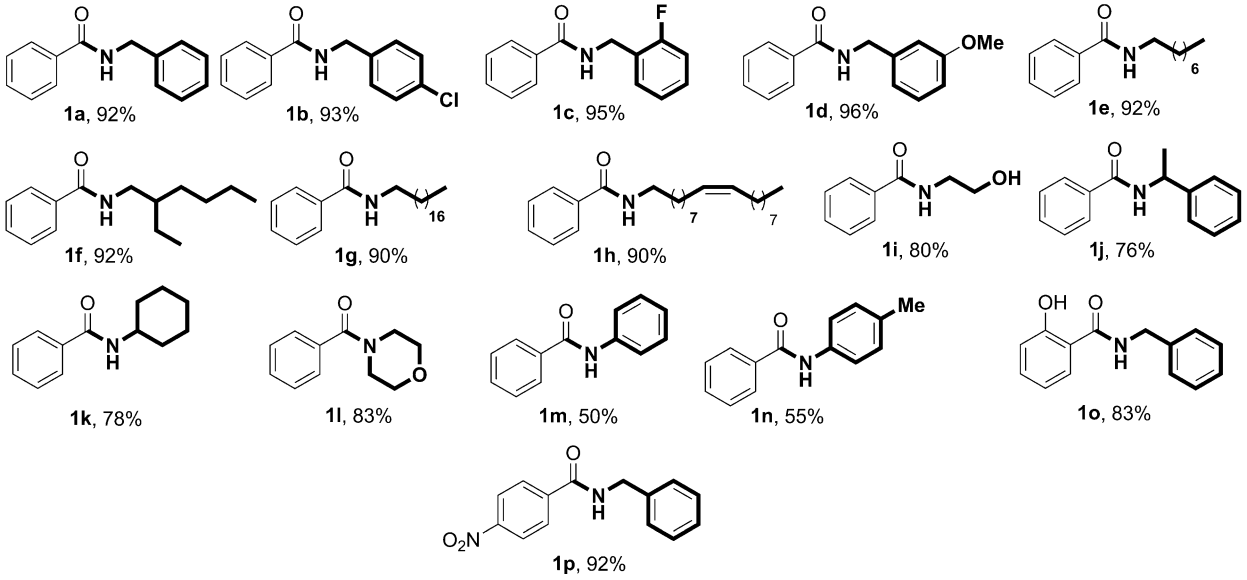
which indicated the substituent on the benzene ring showed no effect on this reaction. And also, on reacting aliphatic primary amines, good to excellent yields (80–92%) were obtained (Table 2, **1e–i**). Cyclic secondary amines could be also reacted effectively under the optimized condition in good yields (Table 2, **1l**). However, the present method was not so effective for aromatic amines, which only afforded moderate yields of corresponding products (Table 2, **1m** and **1n**).

In previous works, the transamidation of heterocyclic amides and heterocyclic amines were reported only rarely. However, in our reaction system, the heterocyclic amines could react well with benzamide to give the corresponding transamidation products (Table 3, **2a–d**) in excellent yields (90–96%). What is more, heterocyclic amides could also react with the benzylamine to form the target products (Table 3, **2e**, **2n** and **2o**) in excellent yields (94–96%). Similarly, the transamidation of nicotinamide with heterocyclic amines also formed the corresponding products (Table 3, **2g–i**) in excellent yields (90–98%). Regrettably, only moderate yields were obtained when nicotinamide was reacted with aromatic amines (Table 3, **2l** and **2m**).

Table 2. The transamidation of benzene aromatic amides with amines.[a]

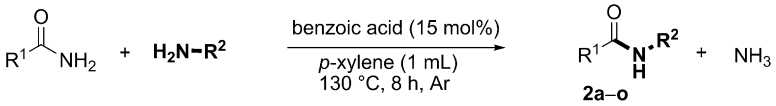


1a–p

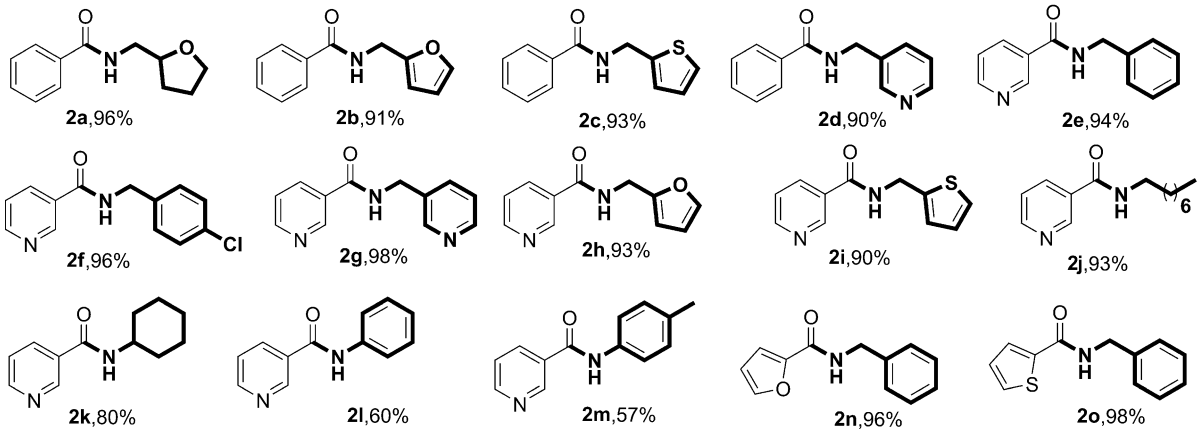


[a] Isolated yields of **1** based on amide are shown.

Table 3. The transamidation of heterocyclic amides with amines.[a]



2a–o

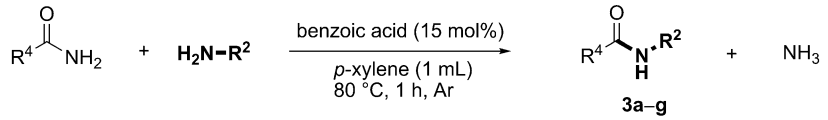


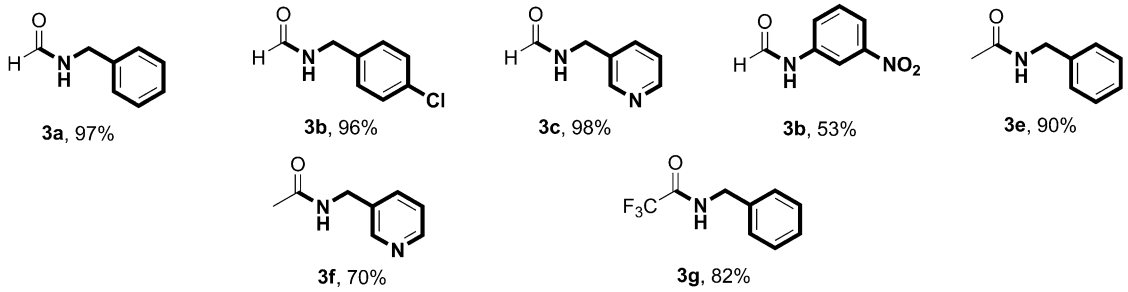
[a] Isolated yields of **2** based on amide are shown.

It is noteworthy to emphasize that the transamidation of aliphatic amides with amines could be realized under milder conditions: at 80 °C for 1 h. Under these conditions, aliphatic amides including formamide, acetamide and trifluoroacetamide reacted with a variety of benzylic, aromatic, and heterocyclic amines to form the corresponding products in moderate to excellent yields (53–98%) (Table 4).

Phthalimide, a common potential precursor of pesticides, dyestuffs, medicinal and many other fine chemicals, is widely used in organic synthesis. Thus we examined the benzoic acid-catalyzed transamida-

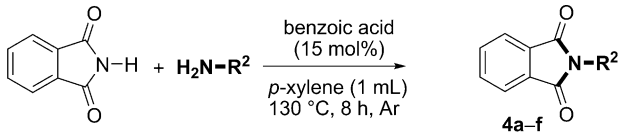
Table 4. The transamidation of aliphatic amides with amines.[a]

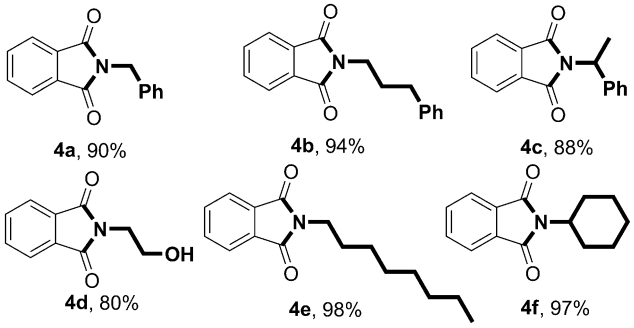




[a] Isolated yields of **3** based on amide are shown.

Table 5. The transamidation of phthalimide with amines.[a]





[a] Isolated yields of **4** based on amide are shown.

tion of phthalimide with various primary amines (Table 5). To our delight, phthalimide showed a high activity in this reaction system. Good to excellent yields (80–98%) were obtained from the reaction of phthalimide with primary amines such as benzylamine, amphetamine, 1-phenylethanamine, ethanolamine, octylamine and cyclohexylamine.

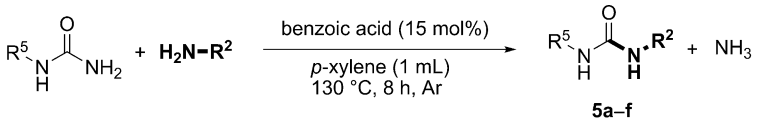
To further extend the scope of the protocol, the benzoic acid-catalyzed transamidations of ureas were examined with various amines. The transamidation of ureas needed copper as catalyst in previous documents.[17] Fortunately, all types of substituted ureas could be reacted with aromatic amines in good to excellent yields with our developed protocol (Table 6). In general, the transamidation of ureas with aniline and benzene-1,2-diamine gave the corresponding target products in excellent yields (Table 6, entries 1 and 2, **5a** and **5b**). Interestingly, the reaction of 1-ethylurea and aniline or 4-toluidine gave diphenyl or 1,3-bis(*p*-tolyl)urea exclusively by replacing the ethyl group with the phenyl or tolyl group (Table 6, entries 3 and 4, **5a** and **5c**). The reaction of 1-phenylurea and aniline resulted in diphenylurea in 96% yield. In contrast, the reaction of 1-phenylurea and 4-toluidine gave 1-phenyl-3-(*p*-tolyl)urea as the only product (Table 6, entries 5 and 6, **5a**, and **5d**).

Finally, our study was focused on the reaction of thioamide with various amines. To the best of our knowledge, there are no reports about the transamidation of aromatic thioamide with amines in previous documents. Due to the high stability of the thioamide, the reaction time was extended to 36 h (Table 7). It was observed that moderate yields (50–61%) of the corresponding products were obtained when the substituents on the phenyl ring are fluoro, chloro or methoxy groups.

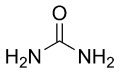
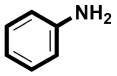
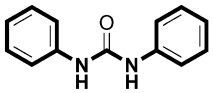
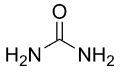
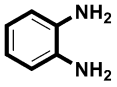
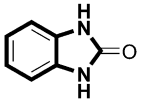
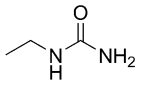
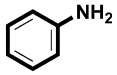
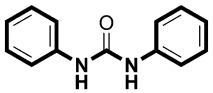
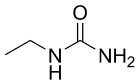
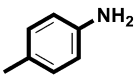
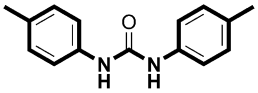
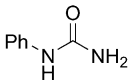
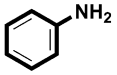
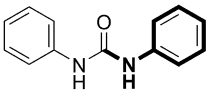
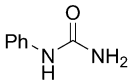
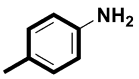
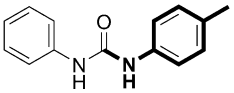
We were excited to find that the current method had a very good selectivity (Scheme 2). The transamidation of benzamide with 3-aminobenzylamine and tryptamine gave, respectively, **7a** and **7b** as the only products. So the developed method has the potential to be applied for the selective protection of the amino group.

In order to elucidate the mechanism, some control experiments were carried out and the results are presented in Scheme 3. First, we collected the gas of Eq. (1). Then, we observed a dark blue precipitate when the gas was passed into a saturated aqueous solution of $CuSO_4$ which identified that NH_3 was formed in Eq. (1). Then the secondary and tertiary amides were employed to react with benzylamine and only **1a** was obtained which indicated that the C–N bond of the amides was broken [Eqs. (2) and (3)]. The yield of the target product decreased obviously with methyl benzoate instead of benzoic acid as the catalyst [Eq. (4)]. According the results of Eq. (4) and Allen's

Table 6. The transamidation of ureas with amines.[a]

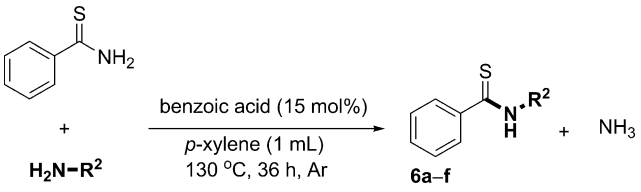


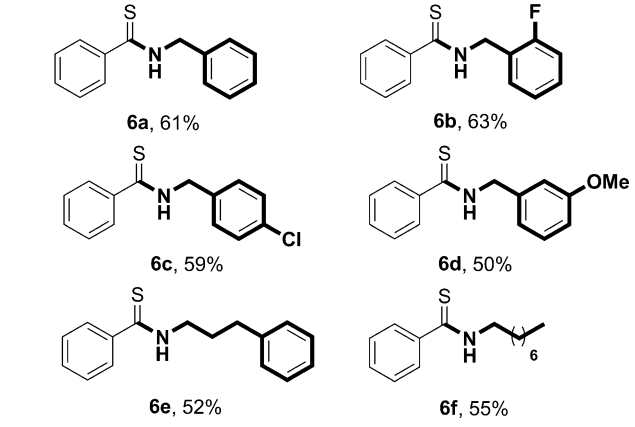
5a–f

Entry	Urea	Amine	Product		Yield [%]
1				5a	95
2				5b	90
3[b]				5a	90
4[b]				5c	87
5				5a	96
6				5d	85

[a] Isolated yields of **5** based on amide are shown.
[b] Urea (1 mmol), amine (2 mmol).

Table 7. The transamidation of thioamide with amines.[a]

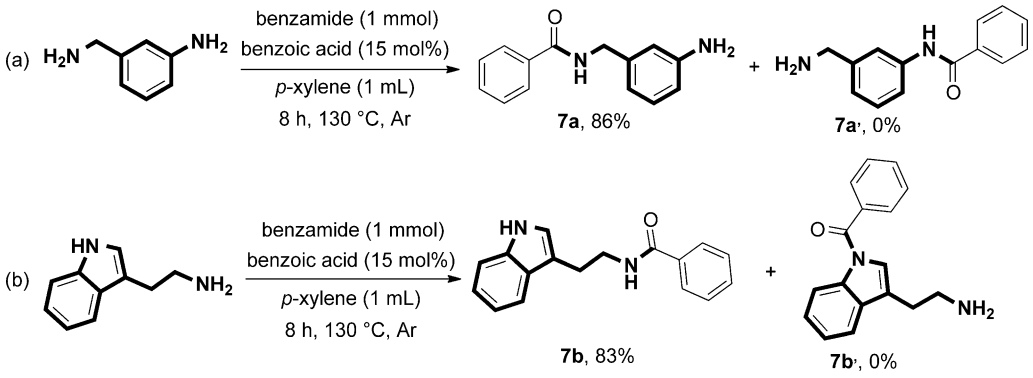




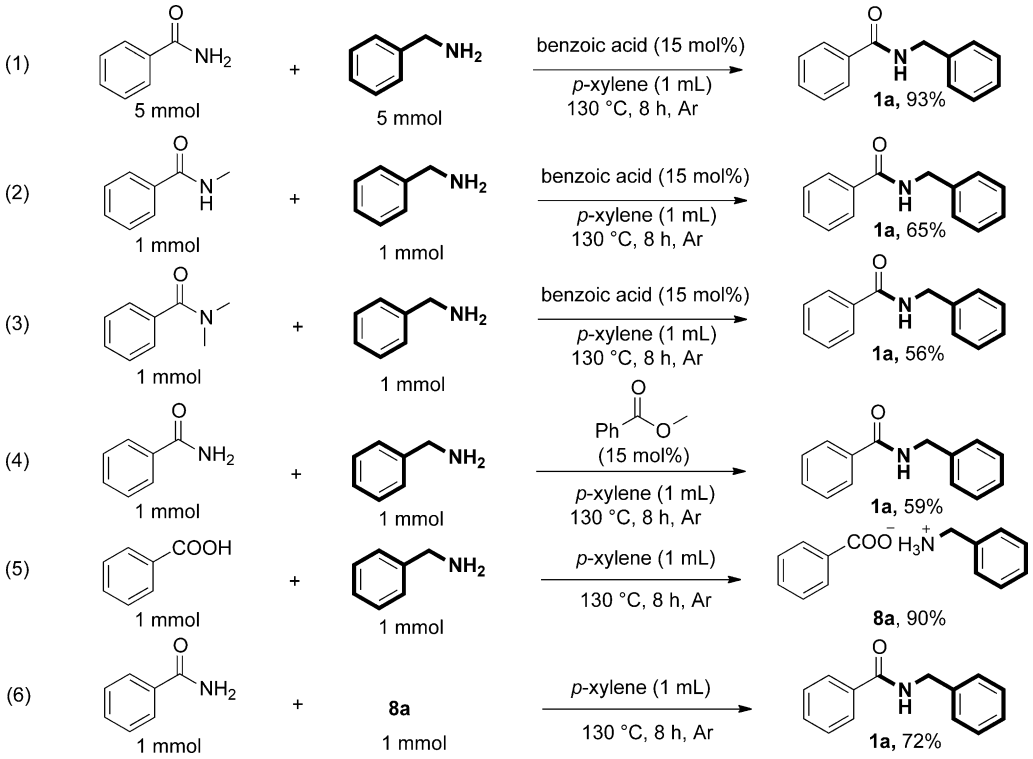
[a] Isolated yields of **6** based on amide are shown.

report,[23] we speculated that the hydrogen atom of the −COOH group is important for efficient transamidations. Additionally, the conglomerate of benzylamine and benzoic acid was found in this reaction system. Furthermore, **8a** could react with the benzamide to form the target product in moderate yield [Eqs. (5) and (6)]. So we speculated that **8a** is the intermediate of the reaction.

Based on the above results and previous literature reports,[23,24,26] a tentative mechanism was proposed as shown in Scheme 4. Firstly, the reaction is started by a proton transfer from benzoic acid to the amine to generate ammonium salt **A**. Then amide attacks ammonium salt **A** to form the target product, NH_3 is released and simultaneously the benzoic acid is regenerated. Compared with the pathway I, another pathway is possible, because under the aforementioned conditions the reaction of **8a** with benzamide gave only **1a** in 72% isolated yield which is much lower than the real yield (92%). Simultaneously, Allen[23] and Nguyen[24] have verified that the transamidation of amides with amines could proceed smoothly under the influence of hydrogen bonding. So, we think the hydrogen bond of the benzoic acid to the amide through a two-point contact could happen in this re-



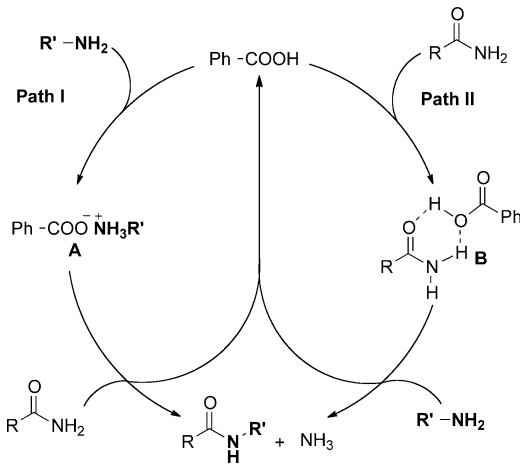
Scheme 2. The experiments on selectivity.



Scheme 3. The control experiments.

action system. In pathway II, the reaction is started by intermolecular hydrogen bonds between benzoic acid and amide to generate the intermediate **B**. Then amine attacks the intermediate **B**, generating the target product and NH_3.

In conclusion, we have developed an efficient and simple method for the transamidation of carboxamides, phthalimide, ureas and thioamide with amines catalyzed by commercially available benzoic acid under metal-free conditions. Compared to known catalysts, benzoic acid is inexpensive, effective, and readily available. Due to the mild reaction conditions, wide range of substrates, good to excellent yields and an easy work-up procedure, the present protocol has the potential to be widely applied.



Scheme 4. The possible reaction mechanism.

Experimental Section

General Procedure

Amide (1 mmol) and benzoic acid (18.3 mg, 0.15 mmol) were added to a 25-mL Schlenk tube equipped with a magneton. The Schlenk tube was purged with argon three times and was charged with amine (1.0 mmol) and *p*-xylene (1.0 mL) by syringe. The reaction mixture was stirred at 130 °C for 8 h. After cooling to room temperature, the resulting solution mixture was diluted by ethyl acetate (10 mL). The reaction mixture was purified by column chromatography on silica gel to give the desired product.

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[28] For the process of catalyst optimization, please see Table I of the Supporting Information.

