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Hydrogen-bond-assisted transition-metal-free catalytic transformation of amides to esters

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The amide C-N cleavage has drawn a broad interest in synthetic chemistry, biological process and pharmaceutical industry. Transition-metal, luxury ligand or excess base were always vital to the transformation. Here, we developed a transition-metal-free hydrogen-bond-assisted esterification of amides with only catalytic amount of base. The proposed crucial role of hydrogen bonding for assisting esterification was supported by control experiments, density functional theory (DFT) calculations and kinetic studies. Besides broad substrate scopes and excellent functional groups tolerance, this base-catalyzed protocol complements the conventional transition-metal-catalyzed esterification of amides and provides a new pathway to catalytic cleavage of amide C–N bonds for organic synthesis and pharmaceutical industry.

amides, C–N bond cleavage, esterification, hydrogen bonding, transition-metal-free catalysis

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1 Introduction

Amide bonds are widely existed in natural products, pharmaceuticals and functional materials [1–6]. Unlike the construction, their cleavage remains largely underdeveloped [7], due to their weak electrophilic property and high C–N bond energy (15−20 kcal/mol) stabilized by two resonance contributors (Figure 1(a)) [8–10]. A number of strategies have been developed for C–N bond activation to realize transamidation and esterification of amides [11–33]. It has to be noted, esterification of amides is more difficult, due to inferior nucleophilicity of alcohols than amines. In general, harsh conditions and a large excess of alcohols are required [1,19–23,34,35].

Transition-metal-catalyzed reactions may represent one of the most successful catalytic approaches for this purpose [36,37]. For example, using a Ni^0/NHC catalyst, Garg and co-workers esterified amides [14,15], and Danoun *et al.* [16] further extended it to a cobalt system. In all these cases the C–N bond undergoes resonance destabilization and is cleaved by oxidative addition to generate an acyl metal intermediate (Figure 1(a)) [38]. Recently, the Szostak group [29] reported the first transition-metal-free esterification of amides using excess K_3PO_4 (ca. 3 equiv.), in which tetrahedral intermediate may be involved. During the preparation of this manuscript, Lei and co-workers [30] realized the transformation of activated amides to esters with Cs_2CO_3. Besides these advances, the substrate scope

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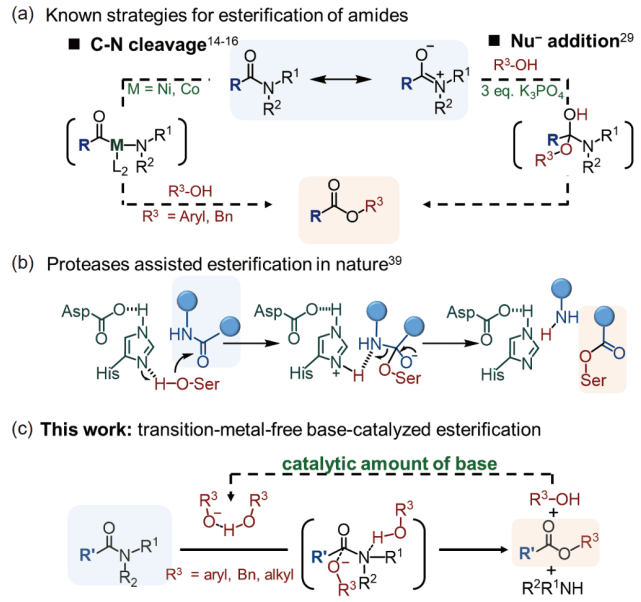


Figure 1 Different strategies for esterification of amides (color online).

still restricted to imide-type amides. How to develop a new transition-metal-free protocol also suitable for normal amides with H/alkyl/aryl substitutes is still very challenging and attractive.

Unlike the challenging situation in laboratory, nature has many efficient methods for the esterification of amides. Many peptidases such as proteases or amidases can readily increase the esterification rate up to 10^{15} fold [39]. Upon formation of hydrogen-bonding between the aspartate carboxyl group and histidine (Figure 1(b)), the nitrogen atom of imidazole is more electronegative for bonding to the serine OH and thereby increasing the nucleophilicity of serine [40]. Attacking the carbonyl group of an amide forms an oxyanion tetrahedral intermediate with the concomitant hydrogen transfer to histidine nitrogen. The basicity of the substrate nitrogen increases significantly in the tetrahedral intermediate (due to the loss of amide resonance), and the formation of a hydrogen bond to the histidine NH allows rapid collapse of the intermediate to form an ester (an acyl-enzyme intermediate) and release amine [41].

Inspired by the plausible mechanism of serine proteases for amide-to-ester transformation [40], we have designed a model reaction (Figure 1(c)), in which several considerations are pre-set down. Firstly, phenol with a small amount of base may generate a mixture of phenol and phenolate, which can form a hydrogen bond pair. Next, *N*-Boc-substituted amide **1a** is initially selected because the resulting amine is a poor nucleophile, thereby avoiding the possible reverse transformation to reform the amide. Finally, strong polar solvents, protic solvents or other solvents containing hydrogen accepter are avoided for the possibility to disrupt the hydrogen bonding formation.

2 Experimental

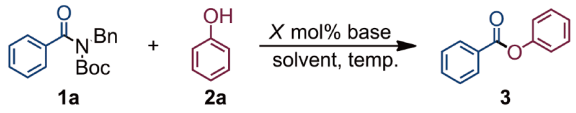
General procedure for NaO^{t}Bu-catalyzed esterification of amides. To a dry 35 mL sealed tube with a stir bar, amide (0.5 mmol), NaO^{t}Bu (0.1 mmol), phenol/alcohol (1.0 mmol) and toluene (5.0 mL) were added. After sealed with a Teflon-lined cap, the reaction mixture was stirred at 150 °C for 24 h. Then the mixture was cooled to room temperature and quenched with H_2O (5.0 mL). The mixture was separated and extracted with ethyl acetate (EA) (15 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography with ethyl acetate/petroleum ether to give the desired product. More experimental details and characterizations are available in the Supporting Information online.

3 Results and discussion

To test our hypothesis, we performed the model reaction by using amide **1a** and phenol **2a** as substrates in toluene in a sealed tube at 150 °C (bath temp.) for 24 h. As expected, no reaction was observed without base (Table 1, entry 1). In order to mimic the catalytic system of serine proteases, 20 mol% catalytic amounts of organic bases like imidazole, triethylamine and pyridine were examined. These conditions only gave trace amounts of ester **3** (0–9%, Table S1, Supporting Information online). In contrast, the use of 20 mol% inorganic bases including K_2CO_3, K_3PO_4 and NaOH all resulted in excellent yields (91%–93%, entries 2–4, Table 1). A quantitative yield of ester **3** was achieved when NaO^{t}Bu was applied (entry 5, Table 1), inferior yields were observed with LiO^{t}Bu and KO^{t}Bu (48% and 95%, respectively, entries 8 and 10, Table S1). When the amount of NaO^{t}Bu was decreased to 10 mol%, slightly lower yield was obtained (86%, entry 6, Table 1). Poor outcomes were found with *o*-xylene, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), anisole and other selected organic solvents (10%–26%, Table S1). Although the reaction proceeded smoothly in toluene with trace water (entry 22, Table S1), additional water dramatically prevented the esterification (entries 8, 9, Table 1).

With optimal reaction conditions in hand, the scope of phenols was investigated (Scheme 1). A broad range of phenols with electron-donating (**4**, **5**, **8**), electron-withdrawing (**6**), and sterically hindered groups (**8a**, **10**–**12**) were all well tolerated. The conversion of halo-phenols, which were often problematic in the transition-metal-catalyzed reactions [42], also gave good yields (**6a**–**6d**, 73%–86%). Sensitive functional groups including allyl (**12**, 80%) and ketone (**16**, 81%) were well preserved. Disappointedly, no esterification was detected with 4-nitrophenol and 4-cyano-

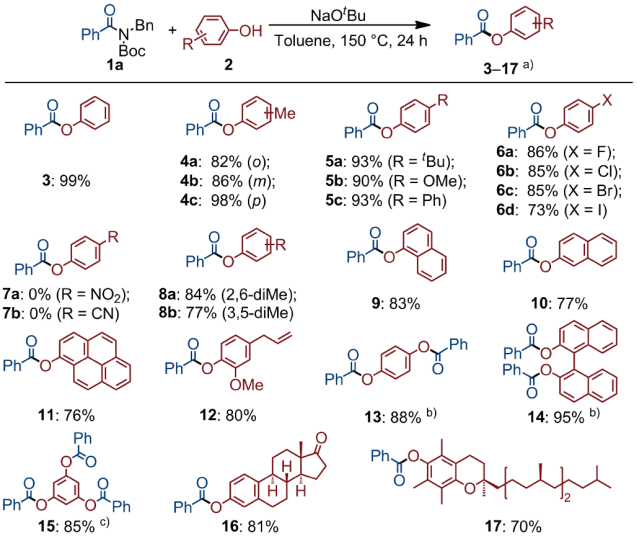
Table 1 Optimization of reaction conditions [a)]



1a **2a** **3**

Entry	Base	*X* (mol%)	Solvent	Temperature (°C)	Yield (%) [b)]
1	–	–	Toluene	150	0
2	K_2CO_3	20	Toluene	150	92
3	K_3PO_4	20	Toluene	150	91
4	NaOH	20	Toluene	150	93
5	NaO^{t}Bu	20	Toluene	150	99 [c)]
6	NaO^{t}Bu	10	Toluene	150	86 [c)]
7	NaO^{t}Bu	20	Toluene	100	44 [c)]
8	NaO^{t}Bu	20	Toluene/H_2O (19:1)	150	58
9	NaO^{t}Bu	20	Toluene/H_2O (3:1)	150	/

a) Reaction was carried out with amide **1a** (0.5 mmol), phenol **2a** (1.0 mmol), base in 5.0 mL solvent and heated for 24 h; b) yields were determined by ^{1}H nuclear magnetic resonance (^{1}H NMR) using 1,3,5-trimethoxybenzene as an internal standard; c) isolated yield.

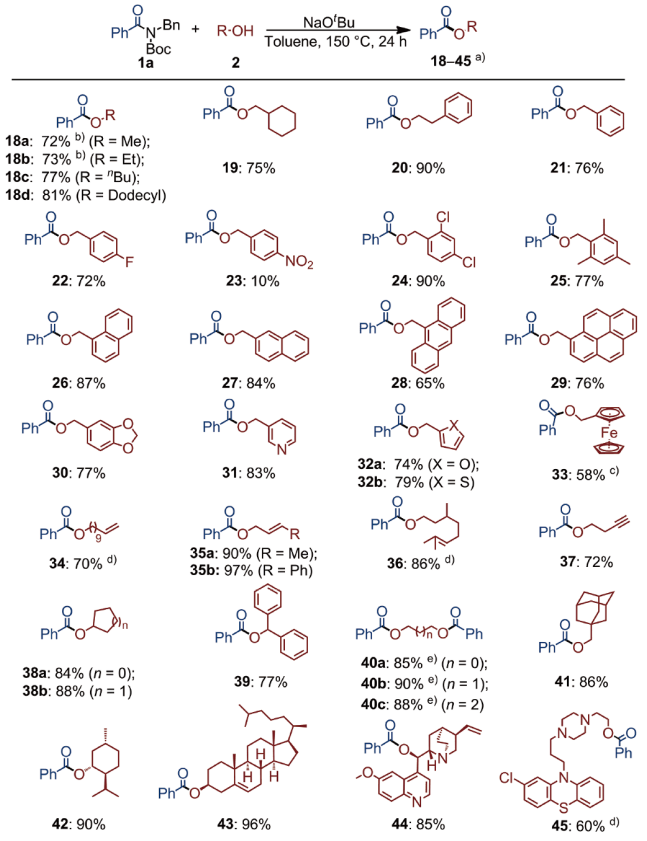


Scheme 1 Esterification of amide **1a** with diverse phenols in 0.5 mmol scale with 20 mol% NaO^{t}Bu in 5.0 mL toluene in a sealed tube at 150 °C for 24 h. Superscript a) isolated yields; b) with 2.5 equiv. amide and 50 mol% NaO^{t}Bu at 150 °C for 36 h; c) with 4.0 equiv. amide and 80 mol% NaO^{t}Bu at 150 °C for 48 h (color online).

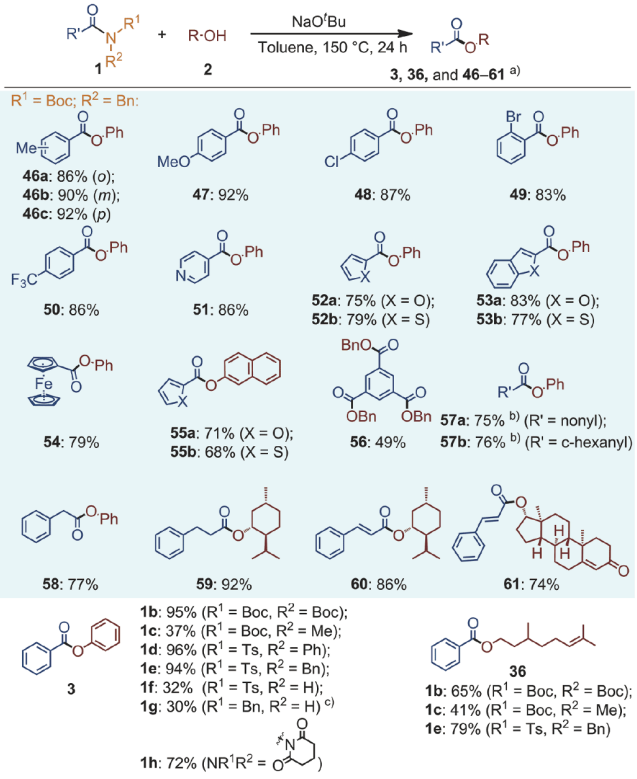
phenol (**7**), but the corresponding amide was fully converted. The diphenols and triphenol reacted well and released the corresponding diesters **13**, **14** and triester **15** in excellent yields (85%–95%). The protocol readily accommodates chiral estrone and Vitamin E, generating the desired esters **16**, **17** in good yields (70%–81%) with unchanged chiral centers.

In light of lower reactivity of alkyl alcohols than phenols [43], we subsequently examined the applicability of the protocol towards a variety of alkyl alcohols (Scheme 2). All tested linear primary alcohols with different chain lengths reacted smoothly with amide **1a**, affording esters **18**–**37** in moderate to excellent yields (58%–97%). Due to their low boiling points, excess (5 equiv.) methanol or ethanol were required to achieve good results for esters **18a**–**18b**. All tested benzylic alcohols with electron-deficient, electron-rich, sterically hindered substituents as well as heterocyclic substrates were readily converted to esters **21**–**33** in good to excellent yields (58%–90%). Although the conversion of highly active ferrocene-methanol (Fc-MeOH) was nearly quantitative, the product **33** was not very stable during the purification, thus leading to relatively low isolated yield (58%). Pleasingly, the linear alcohols bearing alkenyl or alkynyl groups, were successfully converted to esters **34**–**37** in good to excellent yields (70%–97%). This methodology was readily extended to the secondary alcohols and esters **38** and **39** were obtained in good yields (77%–88%). Furthermore, diols were well tolerated and the corresponding diesters **40a**–**40c** were attained in excellent yields (85%–90%). Selected natural products featuring chiral or achiral primary or secondary alcohols were well compatible and readily delivered the desired esters **41**–**44**. The important utility of the protocol was demonstrated by the late-stage diversification of pharmaceuticals. Under the optimized reaction conditions, quinine (cinchona alkaloid, an antimalarial medication) and perphenazine (for mental disorder therapy) were successfully transferred into the esters **44** and **45** in 85% and 60% yields, respectively.

With the broad scope of phenols and alkyl alcohols, the applicability of the protocol towards diverse amides was then explored (Scheme 3). The *N*-Boc substituted aryl amides bearing electron-rich, electron-deficient substituents or heterocyclic amides were all well compatible and gave corresponding esters **46**–**55** in good to excellent yields (68%–92%). The protocol was readily extended to synthesis of triester **56** from the corresponding tri-amide. Aliphatic amides, one type of challenging substrates in the transition-metal-



Scheme 2 Esterification of amide **1a** with primary and secondary alcohols in 0.5 mmol scale with 20 mol% NaO^{t}Bu in 5.0 mL toluene in a sealed tube at 150 °C for 24 h. Superscript a) isolated yields; b) 5 equiv. **2** was used; c) stirred at 35 °C for 15 h; d) after 36 h; e) with 2.5 equiv. amide and 50 mol% NaO^{t}Bu at 150 °C for 36 h (color online).



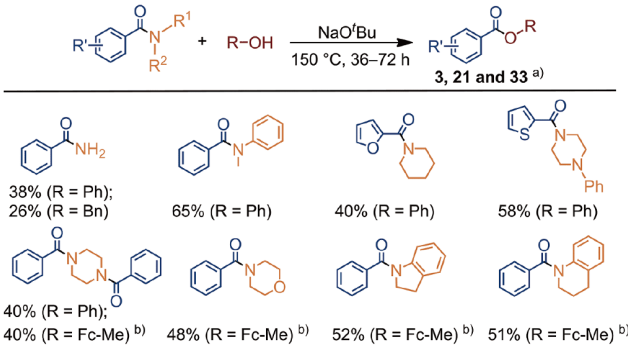
Scheme 3 The scope of *N*-Boc-substituted amides. 0.5 mmol scale with 20 mol% NaO^{t}Bu in 5.0 mL toluene at 150 °C for 24 h. Superscript a) isolated yields; b) with 4.0 equiv. phenol at 150 °C for 36 h; c) with 6.0 equiv. phenol at 150 °C for 72 h (color online).

catalyzed esterification [15], were easily converted into desired esters **57**–**61** in good to excellent yields (74%–92%). Remarkably, benzenepropanamide and cinnamamide were readily esterified by (+)-menthol to give excellent yields of esters **59** and **60**. This protocol is also suitable for natural derivative, cinnamamide was converted to its ester derivative of testosterone **61** in a good yield (74%).

To our delight, amides with diverse (de)activating groups were also compatible with the protocol (Scheme 3). Selected *N*-Boc-benzamides and *N*-Ts-benzamides (Ts: *p*-toluenesulfonyl) bearing Boc, Bn, or Ph groups all resulted in good to excellent yields (65%–96%, **3** and **36**, Scheme 3), whenever phenol or vinyl alcohol was applied. When 1-benzoylpiperidine-2,6-dione was esterified, ester **3** was produced in 72% yield. However, *N*-Boc-benzamide containing methyl group only generated ester **3** and **36** in 37% and 41% isolated yields, respectively. In addition, secondary *N*-Boc/Bn-benzamides **1f** and **1g** were also suitable for the esterification, 32% and 30% yields of ester **3** were obtained, respectively (Scheme 3). The applicability of the protocol was further demonstrated by gram-scale synthesis of butoxycaine **62** (Supporting Information online), a local anesthetic drug [44], in 80% yield.

Pleasingly, beside imide-type amides, the unprotected benzamide (R^1=R^2=H), an extremely inactive substrate in the previously reported transition-metal-free catalyzed esterification [29,30], was also compatible by our protocol, delivered the ester product **3** in 38% yield (Scheme 4). When less-active benzyl alcohol was applied, the esterified product could also be obtained in a slightly lower yield (26%). With these results in hand, other inactive benzamides with diverse alkyl, aryl or cyclic substituents as well as heterocyclic amides were therefore examined. Pleasingly, all these selected inactive amides reacted smoothly with phenol to release the corresponding esters in moderate to good yields, even for di-esterification (40%–65%). When organometallic alcohol Fc-MeOH was applied, amides were readily converted into corresponding esters **33** in moderate yields (40%–55%).

To explore the plausible mechanism, a series of control experiments were carried out. Firstly, a stoichiometric amount of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was used as radical inhibitor (Scheme S1, Supporting Information online). Only a small decrease of yield was observed (99% *vs*. 89%), suggesting no radical intermediate is involved [45]. Secondly, the amount of NaO^{t}Bu strongly affects the esterification process, with excess base usually leading to poorer yields (Scheme S2 and Table S2). Inspired

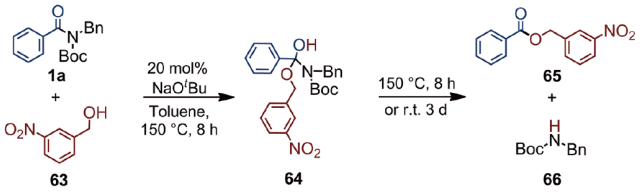


Scheme 4 The scope of N–H/alkyl/aryl substituted amides. Reaction conditions: 0.5 mmol scale with 6.0 equiv. phenol/alcohol and 20 mol% NaO^{t}Bu in 5.0 mL toluene at 150 °C for 72 h. Superscript a) isolated yields; b) with2.0 equiv. alcohol and 20 mol% NaO^{t}Bu in 5.0 mL toluene at 150 °C for 36 h (color online).

by the serine protease-catalyzed esterification [40], the adduct of phenol and phenoxide anion may be responsible for the esterification. When the ratio of phenol and sodium phenoxide was 1:1, a 75% yield was achieved, which further increased to 91% when the ratio was 9:1 (entries 2 and 3, Table S2). Thirdly, the competition experiments were carried out. The electron-deficient amide was found to be more reactive (Scheme S3), which in accord with the relative electrophilicity of the amide bond. At last, an intramolecular and intermolecular competition reaction with 4-hydroxyphenethyl alcohol or the mixture containing equal amount of phenol and benzyl alcohol were selected to react with amide **1a** under the otherwise identical reaction conditions (Scheme S4). The hydroxyl groups of phenols are inherently more reactive than that of alkyl hydroxyl analogues, and 3:1 ratio for phenol esters to alcohol esters were found in both cases, which further supported the nucleophilic substitution pathway.

To gain further insight of the reaction mechanism, attempts of capturing and isolating the possible reaction intermediates were made. As shown in Scheme 1, no esterification products **7a** and **7b** were detected when phenols with strong electron-withdrawing groups (–NO_2 or –CN) were applied as substrates. Similar situation was observed with 3-nitrobenzyl alcohol **63** as the substrate. It is worth noting that, only in this case, a tetrahedral compound **64** was isolated (Scheme 5), which was the possible intermediate for the esterification. No tetrahedral intermediate was isolated when 4-nitrobenzyl alcohol was applied, instead, ester product **23** was isolated in 10% yield (Scheme 2). Pleasingly, compound **64** was readily converted into ester **65** after heating at 150 °C for several hours or at ambient condition for several days. The isolation and conversion of **64** demonstrates that a catalytic amount of base can lead to the formation of a tetrahedral intermediate, which is crucial for the esterification.

Computational density functional theory (DFT) calculations revealed the conjugated acid-base pair formation



Scheme 5 Capture and transformation of **64** (color online).

(Figures S3 and S4, Supporting Information online) is crucial for the esterification. Although this hydrogen-bonding formation may increase the solubility, computational study on the esterification of amide **1a** indicated the anion pair (species **I**, Figure 2) formed by 3-nitrobenzyl alcohol had a higher stability than pure 3-nitrobenzyloxide anion under the basic conditions (–16.9 kcal/mol), with a hydrogen bond to disperse the negative charge on oxygen atom, especially in non-polar solvent like toluene. This is further confirmed by the similar computational outcome found for phenol (–12.3 kcal/mol).

Excess base will deprotonate all the phenols so that there is no H-bond acceptor left. Consequently, species **I** will not be generated and thus the catalytic process was hampered. After generation, the species **I** can undergo nucleophilic attack at the amide to form a very unstable intermediate **II** (14.6 kcal/mol), leading to the formation of a relatively stable tetrahedral intermediate anion **III** (6.1 kcal/mol), stabilized by additional alcohol molecule *via* hydrogen-bonding. The anion **III** could be converted to intermediate **IV** (12.6 kcal/mol) through the electron transfer from oxygen atom to nitrogen atom. The C–N bond between the carbonyl group and nitrogen atom in intermediate **IV** could be cleaved into an ester, along with the release of amine alkyloxide pair **V** (–2.4 kcal/mol). Finally, protonolysis of the pair **V** with another molecular alcohol could produce amine product **VI** (–9.1 kcal/mol) and regenerate species **I** to complete the catalytic cycle. When benzamide was applied instead of **1a** in the DFT calculations, the ΔG for all intermediates are relatively high, especially for amine formation **VI** (9.0 kcal/mol, Figure S3). This is also consistent with our experiment results—benzamide is more challenging to be transformed to esters, with only 38% yield obtained even with extended reaction times (72 h, **3** in Scheme 4).

The calculation of apparent activation energy was carried out (Figures S1 and S2). In light of the nucleophilic substitution reaction pathway, we assumed a quasi-second order reaction mechanism. To simplify the calculation process, all possible sub-reaction and concentration effects were omitted and the reaction of amide and phenol to give the ester was assumed to be quantitative. According to Arrhenius formula, the apparent activation energy of benzamide to phenyl benzoate **3** is to be 9.27 kcal/mol, which is in good agreement with the DFT calculation (9.1 kcal/mol).

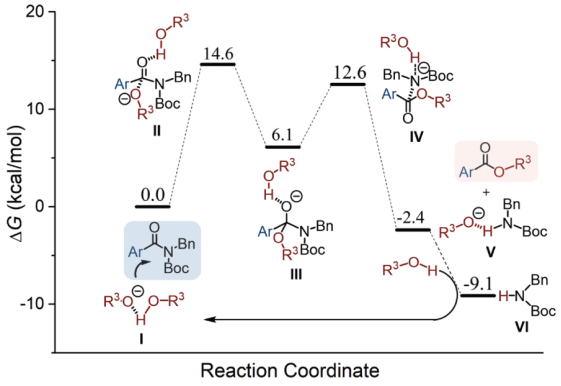


Figure 2 Free-energy profile of the catalytic cycle. All calculations were performed with the Gaussian 09 program. The DFT method M06-2X was employed to calculate the full catalytic cycle for the amide-to-ester conversion (R^3=3-nitrobenzyl group, assuming a temperature of 298 K) (color online).

4 Conclusions

In summary, inspired by serine proteases-catalyzed esterification in nature, a general transition-metal-free hydrogen-bond assisted base-catalyzed esterification of diverse amides has been realized. Good to excellent yields were obtained for electron-rich, electron-poor and sterically hindered substrates. Diverse alkyl amides, aryl amides, phenols and alcohols were all compatible. Control experiments and DFT calculations revealed that hydrogen-bonding assisted nucleophilic substitution was crucial for the esterification. The base-catalyzed protocol developed complements the conventional transition-metal-catalyzed esterification of amides and provides a plausible new pathway to catalytic cleavage of amide C–N bonds for organic synthesis and the pharmaceutical industry.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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