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RESEARCH ARTICLE

n-$Bu_4NI/K_2S_2O_8$-MEDIATED C–N COUPLING BETWEEN ALDEHYDES AND AMIDES

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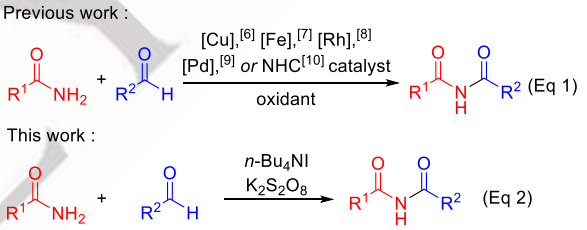
Abstract: *n*-$Bu_4NI/K_2S_2O_8$ mediated C-N coupling between aldehydes and amides is reported. A strong electronic effect is observed on the aromatic aldehyde substrates. The transformylation from aldehyde to amide takes place exclusively when an aromatic aldehyde bears electron-donating groups at either the *ortho* or *para* position of the formyl group, while the cross-dehydrogenative coupling dominates in the absence of these groups. Both the density functional theory (DFT) thermochemistry calculations and experimental data support the proposed single electron transfer mechanism with the formation of an acyl radical intermediate in the cross-dehydrogenative coupling. The *n*-$Bu_4NI/K_2S_2O_8$ mediated oxidative cyclization between 2-aminobenzamide and aldehydes is also reported, with four quinazolin-4(3*H*)-ones prepared in 65-99% yields.

Introduction

Imide motifs widely exist in natural products, pharmaceuticals, and materials,[1] which has prompted chemists to develop a number of synthetic methods for their preparation.[2] The traditional synthetic routes focus on the acylation of amides with carboxylic acids,[3] acid chlorides,[4] and acid anhydrides.[5] However, these methods have limitations, such as the lability of the activated acid derivatives, low atom economy, environmental pollution, and tedious procedures. Recently, the *N*-acylation of amides by aldehydes or alcohols via cross dehydrogenative coupling has attracted great interest. The known methods include transition-metal such as copper,[6] iron,[7] rhodium,[8] or palladium,[9] and *N*-heterocyclic carbene (NHC)[10] catalyzed oxidative *N*-acylation of amides by aldehydes (Scheme 1, Eq 1) and copper[11] catalyzed oxidative *N*-acylation of amides by alcohols.

Iodine[12] or persulfate[13] mediated cross dehydrogenative coupling[14] reactions have aroused the great interest of chemists. These transformations are superior to the classical transition metal-catalyzed couplings in terms of their green chemistry features including environmental compatibility and economic impact. In addition, the iodine or persulfate-mediated cross-dehydrogenative coupling reactions in general undergo single electron transfer pathways, which are different from the classical transition metal catalysis and often display different chemical reactivity from the latter. Inspired by the rapid progress in the iodine and persulfate-mediated oxidative cross-couplings in recent years and the lack of research on the iodine or persulfate mediated imide coupling, we have explored the imide synthesis by an *n*-$Bu_4NI/K_2S_2O_8$ mediated cross dehydrogenative C–N coupling between amides and aldehydes (Scheme 1, Eq 2). Herein, we report the details of our study.



Scheme 1. Synthesis of imides by cross-dehydrogenative coupling between aldehydes and amides.

Results and Discussion

Initially, the coupling of acetamide and benzaldehyde was explored in the presence of either 10 mol% of *n*-Bu_4NI or 2.0 equivalents of $K_2S_2O_8$ (Table 1, entries 1–2). No imide product was observed in either case. On the other hand, *N*-acetylbenzamide (**1a**) was obtained in a 27% yield in the presence of 2.0 equivalents of ammonium peroxydisulfate ($(NH_4)_2S_2O_8$) (Table 1, entry 3). The combination of one equivalent of 18-crown-6 and 2.0 equivalents of $K_2S_2O_8$ led to a 43% yield of **1a** (Table 1, entry 4). The combination of 10 mol% of *n*-Bu_4NI and 2.0 equivalents of $K_2S_2O_8$ further enhanced the yield of **1a** to 66% (Table 1, entry 5). Under the same conditions, other tetrabutylammonium halides (*n*-Bu_4NCl and *n*-Bu_4NBr) only led to extremely low yields (Table 1, entries 6–7). No products were observed if other peroxides such as *tert*-butyl hydroperoxide (TBHP), cumene hydroperoxide (CHP), hydrogen peroxide (H_2O_2), and benzoyl peroxide (DBPO) were used (Table 1, entries 8–11). Lower yields of **1a** were obtained in other solvents such as toluene, THF and DMF (Table 1, entries 12–14). No product **1a**

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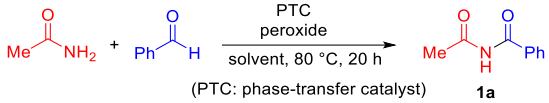
was observed in DMSO (Table 1, entry 15). When the amount of *n*-Bu_4NI was raised to 20 mol%, the yield of **1a** dropped to 50% (Table 1, entry 16). The reaction time was not optimized, but we later found that the yield of **1a** reached a maximum after approximately 12 hours.

Table 1: Optimization of the cross dehydrogenative coupling between acetamide and benzaldehyde.[a]

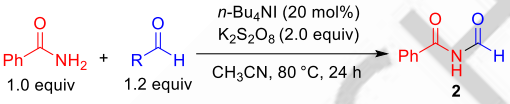


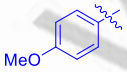
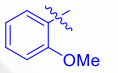
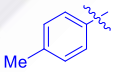
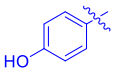
Entry	PTC (10 mol%)	Peroxide (2.0 equiv)	Solvent	Yield [%][b]
1	*n*-Bu_4NI	-	CH_3CN	NR
2	-	$K_2S_2O_8$	CH_3CN	NR
3	-	$(NH_4)_2S_2O_8$	CH_3CN	27
4	18-crown-6[c]	$K_2S_2O_8$	CH_3CN	43
5	*n*-Bu_4NI	$K_2S_2O_8$	CH_3CN	66
6	*n*-Bu_4NCl	$K_2S_2O_8$	CH_3CN	8
7	*n*-Bu_4NBr	$K_2S_2O_8$	CH_3CN	2
8	*n*-Bu_4NI	TBHP	CH_3CN	ND[d]
9	*n*-Bu_4NI	CHP	CH_3CN	NR
10	*n*-Bu_4NI	H_2O_2	CH_3CN	NR
11	*n*-Bu_4NI	DBPO	CH_3CN	NR
12	*n*-Bu_4NI	$K_2S_2O_8$	toluene	47
13[e]	*n*-Bu_4NI	$K_2S_2O_8$	THF	51
14	*n*-Bu_4NI	$K_2S_2O_8$	DMF	23
15	*n*-Bu_4NI	$K_2S_2O_8$	DMSO	NR
16[f]	*n*-Bu_4NI	$K_2S_2O_8$	CH_3CN	50

[a] General procedure: The catalyst (0.1 mmol, 10 mol%), peroxide (2.0 mmol, 2.0 equiv), acetamide (59.0 mg, 1.0 mmol, 1.0 equiv), benzaldehyde (127.2 mg, 1.2 mmol, 1.2 equiv), and solvent (7 mL) were added in a 20 mL glass vial. The reaction mixture was sealed with a pressure relief cap, and stirred at 80 °C for 20 h. [b] Isolated yields after column chromatography. [c] One equiv. of 18-crown-6 (264.3 mg, 1.0 mmol, 1.0 equiv) was added. [d] No **1a** was detected in the reaction mixture, and benzoic acid was obtained. [e] The reaction was carried out at 60 °C. [f] 20 mol% of *n*-Bu_4NI was added instead of 10 mol%.

After optimizing the reaction conditions, we investigated the scope of the aldehydes in the cross-dehydrogenative coupling with benzamide and observed a strong electronic effect on the aromatic aldehyde substrates. When an aryl aldehyde bears an electron-donating group at either the *para* or *ortho* position of the formyl group, such as *p*-anisaldehyde, *o*-anisaldehyde, *p*-tolualdehyde, 4-hydroxybenzaldehyde, 2-hydroxybenzaldehyde and thiophene-2-carbaldehyde, the reaction all exclusively led to the transformylation product **2** (Table 2). Among all the aryl aldehydes examined, *p*-anisaldehyde afforded the highest yield of **2**.[15] In the cases where the transformylation products were obtained in low yields, the unreacted amides were recovered. At the same time, the rest of the aldehydes were oxidized to the corresponding carboxylic acids.

Table 2: *n*-$Bu_4NI/K_2S_2O_8$-Mediated transformylation from electron-rich aromatic aldehydes to benzamide.[a]



Entry	R	Yield [%][b]
1		80
2		78
3		57
4		22
5		13
6		26

[a] General procedure: *n*-Bu_4NI (73.8 mg, 0.2 mmol, 20 mol%), $K_2S_2O_8$ (540.6 mg, 2.0 mmol, 2.0 equiv), benzamide (121.1 mg, 1.0 mmol, 1.0 equiv), aldehyde (1.2 mmol, 1.2 equiv), and CH_3CN (7 mL) were added in a 20 mL glass vial. The reaction mixture was sealed with a pressure relief cap and stirred at 80 °C for 24 h. [b] Isolated yields after column chromatography.

When benzaldehyde (Table 3, **1a**, **1e**-**1i**, **1l**-**1r**), *ortho*-bromobenzaldehyde (Table 3, **1j**), or an aliphatic aldehyde (Table 3, **1f** obtained in 73% yield) was employed, only a small amount of transformylation product (less than 10%) was observed, and the cross-dehydrogenative coupling product, imide, predominated. On the other hand, when the aromatic aldehydes bearing strong electron-withdrawing substituents were employed, such as methyl 4-formylbenzoate (Table 3, **1b**), 4-nitrobenzaldehyde (Table 3, **1c**), and picolinaldehyde (Table 3, **1d**), the reactions all exclusively led to the cross-dehydrogenative coupling products – imides. *m*-Anisaldehyde led to a mixture of the transformylation and cross-dehydrogenative coupling products almost in equal amounts (Table 3, **1k**). A broad scope of amides was well accommodated in the coupling, including alkyl (Table 3, **1a**-**i**),

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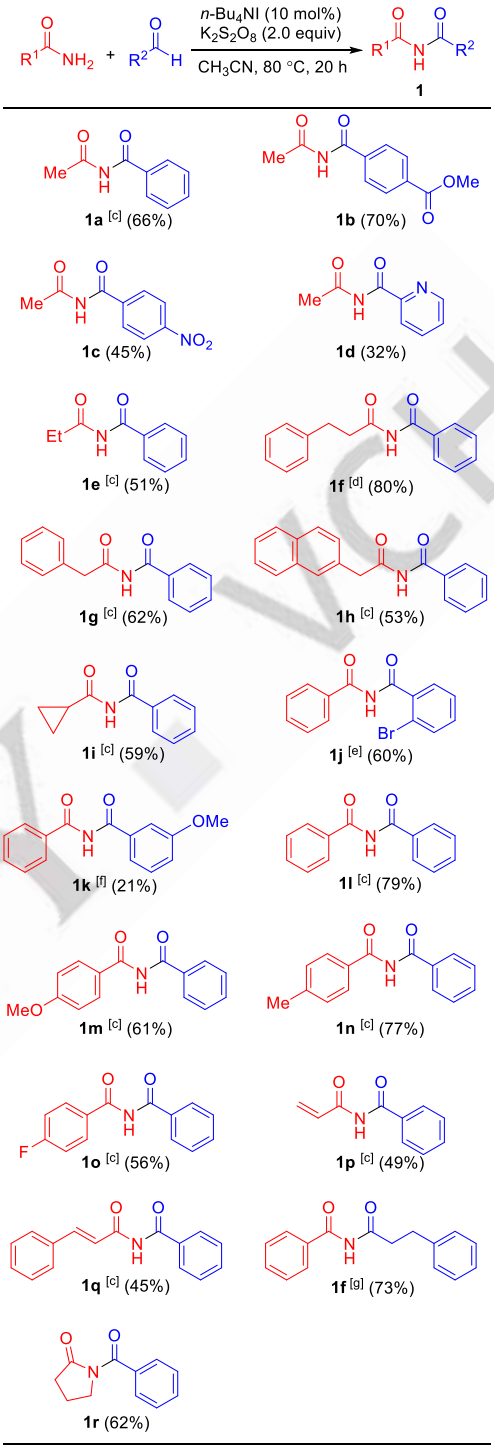
alkenyl (Table 3, **1p**-**q**), and aromatic amides (Table 3, **1j**-**o**). Both the electron-donating group such as methoxy (Table 3, **1m**), and the electron-withdrawing group such as fluorine (Table 3, **1o**) were compatible on the aromatic amides. Secondary amide (pyrrolidin-2-one) was also well accommodated in the coupling with benzaldehyde affording the imide product in a 62% yield (Table 3, **1r**). It is worth noting that imide **1f** was successfully prepared in comparable yields by the coupling of two sets of different amide and aldehyde substrates, which offers chemists more flexibility in the choice of the starting materials when employing the current protocol to synthesize imides.

Table 3: *n*-$Bu_4NI/K_2S_2O_8$-Mediated cross dehydrogenative coupling between amides and aldehydes.[a,b]



[a] General procedure: *n*-Bu_4NI (36.9 mg, 0.1 mmol, 10 mol%), $K_2S_2O_8$ (540.0 mg, 2.0 mmol, 2.0 equiv), amide (1.0 mmol, 1.0 equiv), aldehyde (1.2 mmol, 1.2 equiv), and CH_3CN (7 mL) were added to a 20 mL glass vial. The reaction mixture was sealed with a pressure relief cap, and stirred at 80 °C for 20 h. [b] Isolated yields after column chromatography. [c] A trace amount of transformylation product (less than 10%) was observed by analysis of the crude ^1H NMR spectra but was not isolated and characterized. [d] 3-Phenylpropanamide (149.2 mg, 1.0 mmol) and benzaldehyde (106.1 mg, 1.2 mmol) were added. [e] Product **2** was isolated in an 8% yield together with **1j**. [f] Product **2** was isolated in a 16% yield together with **1k.** [g] Benzamide (121.1 mg, 1.0 mmol) and 3-phenylpropanal (134.2 mg, 1.2 mmol) were added.

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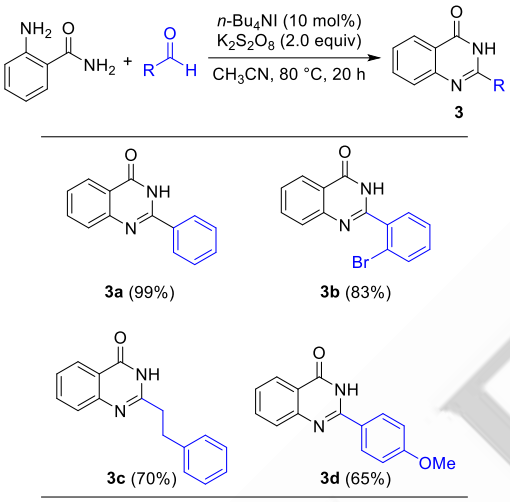
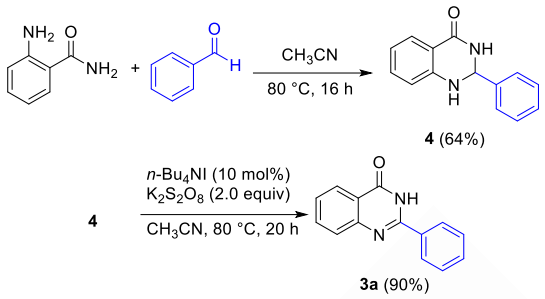
The reaction between 2-aminobenzamide and aldehydes, however, resulted in cyclization products – quinazolin-4(3*H*)-ones (Table 4, **3**) instead of imides. Both aromatic and aliphatic aldehydes were well accommodated in the reaction with 2-aminobenzaimde (Table 4, **3a**-**d**). It is worth noting that *p*-anisaldehyde also led to the quinazolin-4(3*H*)-one product in a 65% yield (Table 4, **3d**), which suggests the cyclization undergoes a different mechanistic pathway than the *n*-$Bu_4NI/K_2S_2O_8$ mediated C-N coupling between aldehydes and amides discussed in Tables 2 and 3. The former is believed to undergo an imine formation between aldehyde and the amino group of 2-aminobenzamide, followed by an intramolecular cyclization and oxidation.[16]

Table 4: *n*-$Bu_4NI/K_2S_2O_8$-Mediated synthesis of quinazolin-4(3*H*)-ones from aldehydes and 2-aminobenzamide.[a,b]



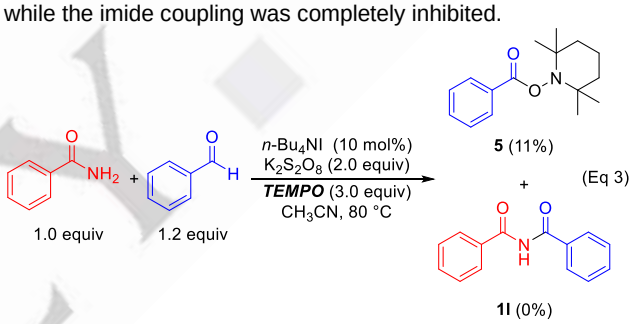
[a] General procedure: *n*-Bu_4NI (36.9 mg, 0.1 mmol, 10 mol%), $K_2S_2O_8$ (540.0 mg, 2.0 mmol, 2.0 equiv), 2-aminobenzamide (136.2 mg, 1.0 mmol, 1.0 equiv), aldehyde (1.0 mmol, 1.0 equiv), and CH_3CN (7 mL) were added in a 20 mL glass vial. The reaction mixture was sealed with a pressure relief cap, and stirred at 80 ℃ for 20 h. [b] Isolated yields after column chromatography.

In order to gain more insights into the cyclization reaction, we examined the reaction between 2-aminobenzamide and benzaldehyde in the absence of *n*-Bu_4NI and $K_2S_2O_8$ and obtained 2,3-dihydroquinazolin-4(1*H*)-one (**4**) in a 64% yield (Scheme 2). When **4** was subjected to our optimized cross-dehydrogenative coupling conditions, quinazolin-4(3*H*)-one (**3a**) was obtained in a 90% yield. Therefore, we believe the cyclization between 2-aminobenzamide and aldehydes undergoes a reaction pathway similar to that reported in the literature,[16] including the condensation of primary amines with aldehydes to form imines, and subsequent intramolecular cyclization and oxidation.



Scheme 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one (**4**) and *n*-$Bu_4NI/K_2S_2O_8$-mediated oxidation of **4** to **3a**.

The literature reports indicated that *n*-Bu_4NI and $K_2S_2O_8$ mediated reactions usually take place via single electron transfer mechanisms.[17] When three equivalents of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) were added to the coupling reaction between benzamide and benzaldehyde, a benzoyl-TEMPO adduct (**5**) was obtained in an 11% yield (Eq 3), while the imide coupling was completely inhibited.



To gain more insights into the reaction mechanism, we also carried out DFT calculations (see the supporting information for details). The calculated DFT reaction enthalpies reflected the endo- and exothermicity for each elementary step, from which the probable rate-limiting step(s) may be singled out. The identified endothermic steps (i.e. the homolysis of peroxydisulfate anion, and the nucleophilic acyl substitution between benzoic sulfuric anhydride anion **B** and amides, see Scheme 3; and the oxidation of *p*-anisaldehyde to a phenyl cation radical **C** by a sulfate anion radical, see Scheme 4) are consistent with the fact that the reactions only start at an elevated temperature (80 ℃).

Based on our experimental data, DFT calculations,[18] and the prior literature reports,[19] a plausible mechanism for the cross dehydrogenative coupling between amides and aldehydes is described in Scheme 3. First, the more soluble bis(tetrabutylammonium) peroxydisulfate is generated from *n*-Bu_4NI and $K_2S_2O_8$, which undergoes homolytic cleavage producing sulfate anion radical at the elevated temperature. The sulfate anion radical abstracts the formyl hydrogen from the aldehyde resulting in an acyl radical **A** and a bisulfate anion. **A** reacts with a second equivalent of sulfate anion radical forming benzoic sulfuric anhydride[20] anion **B**, which undergoes a nucleophilic acyl substitution with amides leading to the imide product.

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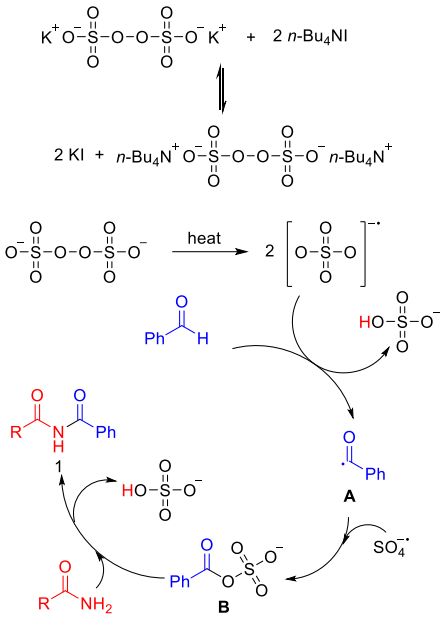
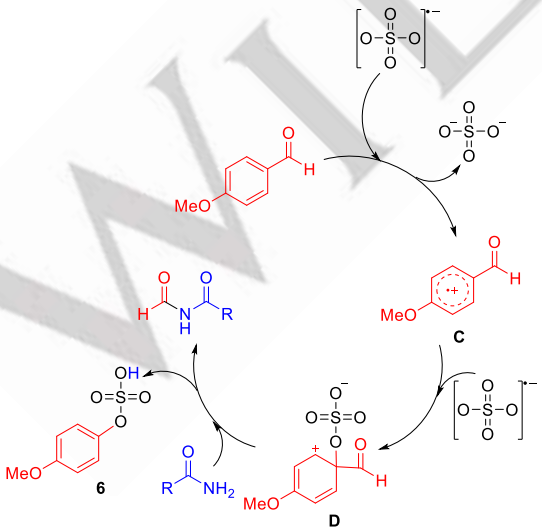


Scheme 3. Proposed mechanism for the *n*-$Bu_4NI/K_2S_2O_8$-mediated cross dehydrogenative coupling between aldehydes and amides.

On the other hand, since the sulfate anion radical is a well-known strong oxidant,[13] in the presence of electron-rich aromatic aldehydes such as *p*-anisaldehyde, the sulfate anion radical first oxidizes *p*-anisaldehyde to a phenyl cation radical (**C**). A second equivalent of sulfate anion radical then adds to the *ipso* position of the formyl group forming an arenium ion (1-formyl-4-methoxycyclohexa-3,5-dien-2-ylium-1-yl sulfate) **D**, which is stabilized by the electron-donating *para*-methoxy group. A subsequent nucleophilic acyl substitution between **D** and amide takes place at the formyl group leading to the formyl imide and 4-methoxyphenyl hydrogen sulfate (**6**).



Scheme 4. Proposed mechanism for the *n*-$Bu_4NI/K_2S_2O_8$-mediated transformylation from *p*-anisaldehyde to primary amides.

Conclusion

In summary, a *n*-$Bu_4NI/K_2S_2O_8$ mediated C–N coupling between aldehydes and amides is reported. The reaction takes place via a single electron transfer mechanism, employing inexpensive and user-friendly reagents. A broad scope of amide substrates is well accommodated in the coupling reaction, but the aldehyde substrates have displayed a strong electronic effect. Aliphatic and electron-neutral or -deficient aromatic aldehydes predominantly undergo the cross dehydrogenative coupling pathway forming imides. On the other hand, the aromatic aldehydes bearing electron-donating groups at either the *ortho* or *para* position of the formyl group exclusively go through the transformylation pathway forming formyl imides. Both the experimental data and DFT calculations support the proposed mechanism with the formation of an acyl radical intermediate in the cross-dehydrogenative coupling. Quinazolin-4(3*H*)-ones were also prepared by the cyclization between aldehydes and 2-aminobenzamide under the reported oxidative coupling conditions, but *via* a different mechanistic pathway. More *n*-$Bu_4NI/K_2S_2O_8$ mediated cross-coupling reactions are under investigation in our laboratory and will be reported in due course.

Experimental Section

General procedure for the preparation of imides (1) via *n*-$Bu_4NI/K_2S_2O_8$-mediated cross-dehydrogenative coupling between amides and aldehydes. An oven-dried 20 mL glass reaction vial was charged with amide (1.0 mmol, 1.0 equiv), aldehyde (1.2 mmol, 1.2 equiv), tetrabutylammonium iodide (36.9 mg, 0.1 mmol, 10 mol%), potassium persulfate (540.6 mg, 2.0 mmol, 2.0 equiv), and anhydrous acetonitrile (7 mL). The reaction mixture was sealed with a pressure relief cap and stirred at 80 °C for 20 h. The reaction mixture was diluted with 20 mL of ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the corresponding products **1**.

Supporting Information

The general procedure for the coupling reaction, the ^1H, ^{13}C NMR data and spectra, and the Density Functional Theory (DFT) thermochemistry calculations for the proposed mechanism that support the findings of this study are available in the supplementary material of this article.

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Keywords: C–N coupling • cross-dehydrogenative coupling • imides • potassium persulfate • quinazolin-4(3*H*)-ones

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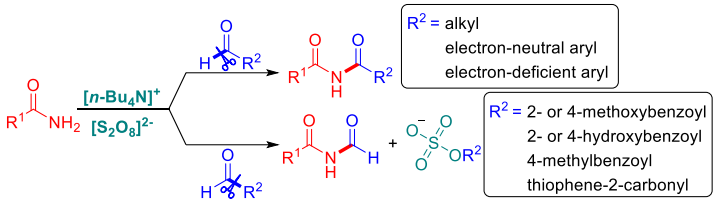

An *n*-$Bu_4NI/K_2S_2O_8$-mediated substrate-dependent C-N coupling between aldehydes and amides is reported. When an aromatic aldehyde bears electron-donating groups at either the *ortho* or *para* position of the formyl group, a transformylation takes place exclusively. Without these groups, a cross-dehydrogenative coupling dominates. Furthermore, when 2-aminobenzamide is employed, only quinazolin-4(3*H*)-ones are obtained regardless of the aldehyde used.