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Metal-free intramolecular oxidative decarboxylative amination of primary α-amino acids with product selectivity†

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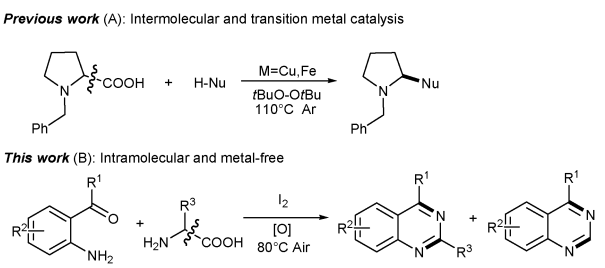
A novel metal-free intramolecular oxidative decarboxylative coupling of primary α-amino acids with 2-aminobenzoketones under mild and neutral conditions was developed. Different quinazolines can be selectively obtained by various oxidants.

Transition metal-catalyzed decarboxylative couplings have emerged as important synthetic methods for C–C or C–N bond formation because of their high efficiency, selectivity and convenience.[1] For instance, many chemists have developed transition metal-catalyzed intermolecular and intramolecular decarboxylative couplings, in which carboxylic acids or esters are directly employed as starting materials.[2–6] A large number of coupling products – the intermediates for the synthesis of natural products – have been obtained. However, these decarboxylative couplings are restricted to the transition metal-assisted approach, requiring expensive transition metals, complex ligands and harsh reaction conditions. To approach the potential application of these methods, strategies with lower cost, less waste and milder conditions are highly desirable. Metal-free catalysis may be an attractive advance as a valuable alternative to transition metal catalysis in decarboxylative couplings.

The synthesis of compounds containing nitrogen atoms has attracted much attention because of their biological and pharmaceutical properties. α-Amino acids are more readily available and more stable than other starting materials from nature. Therefore, the decarboxylative reaction of α-amino acids provides a very efficient synthetic method for heterocycles. For example, Cohen reported a decarboxylative reaction of proline with sterically congested 2-hydroxyacetophenones in 1979.[7] In 2008, Seidel and co-workers reported the reaction of proline with 2-aminobenzaldehyde to form aminals.[8a] Recently, they reported a three-component decarboxylative α-functionalization of proline and aldehydes with nucleophiles.[8b] After that, a related reaction was also reported.[8c] Concurrently, Li and co-workers reported a copper or iron-catalyzed intermolecular oxidative decarboxylative coupling of *N*-benzylproline with various nucleophiles (Scheme 1A).[9] Recently, Fu reported a copper-catalyzed synthesis of quinazolinones *via* a decarboxylative coupling of α-amino acids.[10] To our knowledge, metal-free intramolecular oxidative decarboxylative coupling of primary α-amino acids remains a significant challenge.

Recently, we have reported a metal-free decarboxylative cyclization from natural α-amino acids to construct pyridine derivatives.[11] On the basis of this work, we complete a novel I_2/oxidant-mediated intramolecular oxidative decarboxylative coupling of primary α-amino acids with 2-aminobenzaldehydes or 2-aminobenzoketones, affording a variety of quinazolines (Scheme 1B). This reaction can be carried out smoothly under mild and metal-free conditions. Moreover, the reaction could tolerate water and air.

Initially, we began our study with the reaction of 1 equiv. of 2-aminobenzophenone (**1a**) and 1.5 equiv. of phenylglycine (**2a**), 2 equiv. of *tert*-butyl hydroperoxide (TBHP, 70% in aqueous) as the oxidant and 50 mol% of molecular iodine as the catalyst. The reaction mixture was heated in DMF under air at 80 °C for 18 h. The coupling product **3a** was obtained in 68% yield by GC-MS analysis (Table 1, entry 1). To improve the reaction yield, various solvents were employed in this reaction. Among these solvents, DMA proved to be the best choice, with a yield of 85% (entries 2–5). When a transition metal, such as copper or iron, replaced iodine as the catalyst, no oxidative coupling product was obtained (entries 6–8). After examination of various oxidants, such as TBHP, DDQ, TEMPO and oxygen, TBHP gave the highest yield (entries 9–11). In addition, we explored the influence of temperature on the reaction efficacy. Either raising or reducing the reaction temperature decreased the reaction



Scheme 1 The strategies for oxidative decarboxylative couplings of α-amino acids.

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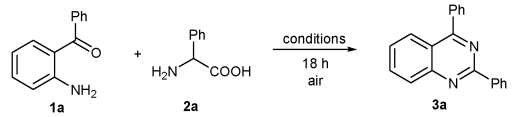
Table 1 Optimization of the oxidative decarboxylative coupling of phenylglycine with 2-aminobenzophenone[a]



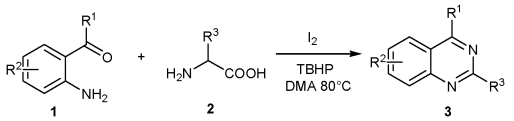
Entry	Oxidant	Catalyst	Temp (°C)	Solvent	Yield (%)[b]
1	TBHP	I_2	80	DMF	68
2	TBHP	I_2	80	CH_3CN	0
3	TBHP	I_2	80	toluene	10
4	TBHP	I_2	80	DMSO	55
5	**TBHP**	**I_2**	**80**	**DMA**	**85**
6	TBHP	$Cu(OAc)_2$	80	DMA	0
7	TBHP	CuI	80	DMA	0
8	TBHP	$FeCl_3$	80	DMA	0
9	DDQ	I_2	80	DMA	0
10	TEMPO	I_2	80	DMA	32
11	oxygen	I_2	80	DMA	5
12	TBHP	I_2	60	DMA	75
13	TBHP	I_2	70	DMA	77
14	TBHP	I_2	90	DMA	58
15	TBHP	I_2	100	DMA	56
16[c]	TBHP	I_2	80	DMA	63
17[d]	TBHP	I_2	80	DMA	66
18[e]	TBHP	I_2	80	DMA	64
19[f]	TBHP	I_2	80	DMA	84

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (0.1 mmol), oxidant (0.4 mmol), solvent (0.5 mL), 80 °C, 18 h. [b] Determined by GC-MS analysis using an internal standard. [c] 1 equiv. of iodine was used. [d] 10 mol% of iodine was used. [e] 4 equiv. of TBHP was used. [f] 10 equiv. of H_2O was added.

yields (entries 12–15). Moreover, the amount of TBHP and iodine were also optimized (entries 16–18). Notably, the addition of 10 equiv. of water had little influence on this reaction (entry 19). After optimization, the optimal reaction conditions were selected: iodine as the catalyst, TBHP as the oxidant, DMA as the reaction solvent and a reaction temperature of 80 °C.

With the optimal reaction conditions in hand, we investigated the substrate scope of the oxidative decarboxylative coupling (Table 2). Various 2-aminobenzoketones and 2-aminobenzaldehydes (**1a–1q**) were reacted with phenylglycine (**2a**) to give the corresponding 2-phenylquinazolines (**3a–3q**). When R^1 was a phenyl substituent, different substituents on the *para*-position of the phenyl ring did not affect the reaction much (Table 2, entries 1–4). However, the steric hindrance had a great influence on this reaction. For example, substrate **1e**, bearing 2,5-dimethyl substituents on the phenyl ring, only gave an 11% isolated yield of **3e** (entry 5), while substrate **1f**, bearing 2,4,6-trimethyl substituents on the phenyl ring, didn't give the desired product **3f** (entry 6). When R^1 was an aliphatic alkyl group, the corresponding products were obtained with good to excellent yields (entries 7–13). Among these alkyl substituents, the chain alkyl afforded the desired products with higher yields than cycloalkyl, perhaps due to the steric hindrance. In spite of the complete conversion, only 60% of **3n** and 70% of **3o** were obtained when a Cl and Br atom, respectively, were introduced into the 5-position of 2-aminobenzophenone (entries 14 and 15). To our surprise, **3v** and **3w** were generated as minor products. This cleavage of phenyl may occur *via* a different

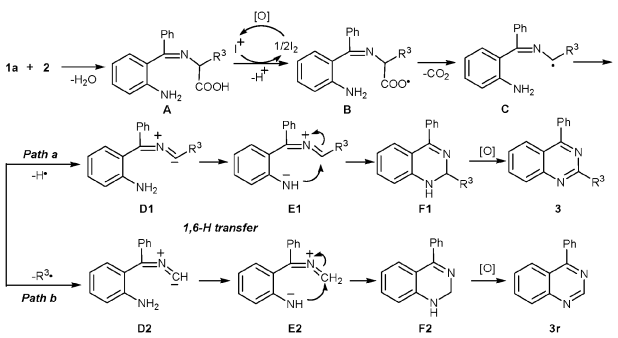
Table 2 The substrate scope of I_2/TBHP-mediated oxidative decarboxylative coupling[a]



Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[b]
1	Ph	H(**1a**)	Ph(**2a**)	**3a**	18	78
2	4-F–Ph	H(**1b**)	Ph	**3b**	18	78
3	4-Br–Ph	H(**1c**)	Ph	**3c**	18	78
4	4-Me–Ph	H(**1d**)	Ph	**3d**	18	79
5	2,5-di-Me–Ph	H(**1e**)	Ph	**3e**	18	11
6	2,4,6-tri-Me–Ph	H(**1f**)	Ph	**3f**	36	trace
7	Et	H(**1g**)	Ph	**3g**	18	86
8	*n*-Bu	H(**1h**)	Ph	**3h**	18	85
9	hexadecyl	H(**1i**)	Ph	**3i**	18	80
10	*i*-Pr	H(**1j**)	Ph	**3j**	18	86
11	*t*-Bu	H(**1k**)	Ph	**3k**	18	85
12	cyclopropyl	H(**1l**)	Ph	**3l**	18	78
13	cyclopentyl	H(**1m**)	Ph	**3m**	18	76
14	Ph	5-Cl(**1n**)	Ph	**3n**(**3v**)	18	60(30)
15	Ph	5-Br(**1o**)	Ph	**3o**(**3w**)	18	70(20)
16	H	H(**1p**)	Ph	**3p**	18	60
17	H	5-Cl(**1q**)	Ph	**3q**	18	56
18	Ph	H	H(**2b**)	**3r**	4	80
19	4-F–Ph	H	H	**3s**	4	86
20	4-Br–Ph	H	H	**3t**	4	84
21	4-Me–Ph	H	H	**3u**	4	69
22	Ph	5-Cl	H	**3v**	4	>99
23	Ph	5-Br	H	**3w**	4	>99
24	Ph	H	Me(**2c**)	**3x**(**3r**)	24	16(14)[c]
25	Ph	H	*i*-Pr(**2d**)	**3y**(**3r**)	24	0(30)[d]

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), I_2 (0.1 mmol), TBHP (0.4 mmol), DMA (0.5 mL), 80 °C. [b] Isolated yield. [c] 120 °C. [d] 45% of 2-(4-phenylquinazolin-2-yl)propan-2-ol (**4y**) was obtained at 120 °C.

reaction pathway (Scheme 2, path b). Moreover, when 2-aminobenzaldehyde and 2-amino-5-chloro-benzaldehyde were employed as the substrates, only 60% of **3p** and 56% of **3q** were obtained, respectively, due to the self-condensation of the substrates and the generation of *tert*-butyl-2-aminobenzoate (entries 16–17). Subsequently, phenylglycine was replaced with glycine (**2b**) in this reaction. The reactions between 2-aminobenzoketones and glycine gave the corresponding products **3r–3u** in 69–86% yield (entries 18–21). It is noteworthy that coupling products **3v** and **3w** were obtained in a quantitative



Scheme 2 A plausible mechanism for the I_2/oxidant-mediated intramolecular oxidative decarboxylative coupling.

yield when **1n** and **1o** were employed as the substrates (entries 22–23). However, when alanine (**2c**) was used in the reaction, only 16% of **3x** was obtained. Meanwhile, **3r** was also generated in 14% yield because of the cleavage of methyl (entry 24). Similarly, the reaction of **1a** with valine (**2d**) gave **3r** in 30% yield and 2-(4-phenylquinazolin-2-yl)propan-2-ol (**4y**) in 45% yield, which came from the further oxidation of **3y**.

To obtain **3r** exclusively, a product from the cleavage of an alkyl, other oxidants were examined. When ammonium persulfate was employed as an oxidant, the reaction of **1a** with **2d** gave **3r** exclusively in 60% yield (Table ESI-2, entry 3). The couplings of various 2-aminobenzoketones with α-amino acids also afforded the corresponding products in moderate yields (entries 1–8). When 1 equiv. of iodine was added, 6-iodo-4-phenylquinazoline (**4r**) was obtained with 50% yield (entry 9). These results indicated that the oxidation capacity of the oxidants affected the selectivity of the product.

To gain an insight into the reaction mechanism, several preliminary studies were carried out (see ESI for details†). Firstly, the effect of iodine in the decarboxylation was examined. In the absence of iodine, the coupling product **3a** was not detected in the reaction of **1a** with **2a**. When *N*-iodosuccinimide (NIS) was used as the catalyst, 42% of **3a** was obtained but no desired product was observed when $PhI(OAc)_2$ was employed as the catalyst. Therefore, a I_2–I^+ catalytic cycle may play an important role in the oxidative decarboxylation. In addition, when radical inhibitors, such as hydroquinone and benzoquinone, were added to the reaction system, the yield of **3a** was reduced from 85% to less than 5%. This indicated that the reaction may undergo a radical pathway.

On the basis of the results above and previous reports,[9,12,13] a plausible mechanism for this oxidative decarboxylative coupling is proposed (Scheme 2). Initially, imine **A** is formed by the condensation of **1a** with **2**. Then I^+, generated by the oxidation of iodine, can oxidize **A** to form radical intermediate **B**. Intermediate **B** eliminates one molecular CO_2 to generate radical **C**, which can be transformed following two pathways: (a) a key azomethine ylides intermediate **D1** is generated through removing a hydrogen radical.[9] This intermediate can be further subjected to 1,6-H transfer and intramolecular nucleophilic attack to give the coupling product **F1**. Finally, the further oxidation of **F1** by TBHP gives the quinazoline **3**; (b) **D2** is generated through removing a R^3 radical. Then **3r** is obtained *via* a similar process to **path a**.

In summary, we have developed a metal-free intramolecular oxidative decarboxylative coupling of α-amino acids under mild conditions. The reaction products can be modulated by using different oxidants. This reaction is applicable to the synthesis of quinazolines that tolerate aryl and alkyl substituents. Compared to traditional decarboxylative couplings, this coupling displays many advantages, such as being metal-free, water and air-tolerant, low toxicity and environmentally benign. Further studies on the mechanism and application of this reaction are under way in our laboratory.

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