

# $n$ -Bu<sub>4</sub>Ni-catalyzed selective dual amination of $sp^3$ C–H bonds: oxidative domino synthesis of imidazo[1,5-*c*]quinazolines on a gram-scale†

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**An  $n$ -Bu<sub>4</sub>Ni catalyzed domino reaction that involves selective dual amination of  $sp^3$  C–H bonds has been developed. The protocol affords a facile and efficient approach to the synthesis of imidazo[1,5-*c*]quinazolines under mild conditions.**

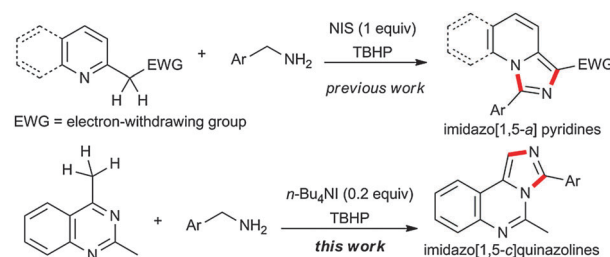
In recent years, considerable achievements have been made in transition-metal-catalyzed C–H bond activation. Direct C–N bond formation *via* C–H bond activation is more preferable than traditional synthetic strategies in the construction of nitrogen-containing molecules.<sup>1</sup> Despite the major advances achieved in transition-metal-catalyzed C–H amination, the cost effectiveness as well as the presence of heavy transition metal impurities in the final products is a major problem regarding their practical applicability, especially in preparing pharmaceutical agents. Thus, the alternative metal-free direct C–H amination is highly desirable. Recently, iodine-based catalytic systems in C–H bond activation have been established and received much attention.<sup>2</sup> Furthermore, these efficient and environmentally friendly strategies also promote the more challenging  $sp^3$  C–H amination.<sup>3</sup> For example, iodine promoted benzylic C–H amination has been developed by Chang<sup>4a</sup> and Zhu.<sup>4b</sup> However, nitrogen sources were limited to sulphonamides and benzoazoles. Therefore, the benzylic C–H bond, especially the more challenging primary C–H oxidative amination with primary amine remains highly desirable.

The domino strategy has been widely applied to the synthesis of organic compounds due to its high atom and synthetic efficiency.<sup>5</sup> A variety of iodine promoted oxidative domino reactions that involve C–N bond formation have been demonstrated to date, while the catalytic variants of iodine-initiated domino reactions are still rarely documented.<sup>2c</sup> Thus, we focused our attention on iodine catalyzed domino  $sp^3$  C–H amination.

Nitrogen-containing fused heterocycles constitute an important class of biologically active agents and play an important role in medicinal chemistry. Imidazoquinazoline is the critical skeleton in

drug molecules, such as those used clinically as anti-thrombotic and cardiotoxic agents.<sup>6</sup> Structural variants of imidazoquinazoline show a wide range of biological activities, including anticonvulsants,<sup>7a</sup> antitumor<sup>7b</sup> and antihypertensive<sup>7c,d</sup> effects. Despite the high interest, synthetic routes available for these molecules often suffer from some disadvantages, such as strict reaction conditions, complex manipulations and inaccessible starting materials.<sup>8</sup> Therefore, alternative synthetic approaches for imidazoquinazoline derivatives under mild conditions are desired. Very recently, the analogous imidazo-N-heterocycle, imidazo[1,5-*a*]pyridine, was synthesized from electron-withdrawing group substituted 2-methylpyridines and benzylamines *via* iodine-mediated benzylic secondary C–H amination (Scheme 1).<sup>9</sup> Encouraged by the above results, and in continuation of our research on quinazoline derivatives,<sup>10</sup> we herein report a direct approach for the synthesis of imidazo[1,5-*c*]quinazolines from readily available 4-methylquinazolines and benzylamines. To the best of our knowledge, imidazo[1,5-*c*]quinazolines possess a novel heterocyclic skeleton to date. Besides, benzylic primary C–H oxidative amination with primary amines has been scarce until now.

Initially, our studies began from an exploration of the reaction conditions on 4-methyl-2-phenylquinazoline (**1a**) and benzylamine (**2a**) (Table S1, see ESI†). In the presence of 20 mol%  $n$ -Bu<sub>4</sub>Ni, the desired product **3aa** was afforded in 36% yield when 4 equiv. of TBHP was used as an oxidant (entry 1). In the absence of a catalyst, no **3aa** was detected (entry 2). Next, various iodine reagents were investigated, but no further improvement in the yield was



**Scheme 1** Synthesis of imidazo-N-heterocycles *via* iodine promoted dual benzylic C–H aminations.

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observed (entries 3–6). Among the examination of various oxidants, gratifyingly, 70% aqueous TBHP gave a yield similar to a decane solution of TBHP, which indicated that a small amount of water would not inhibit this reaction (entries 7–11). Further experimental data suggested that both organic and inorganic acids could facilitate this reaction and acetic acid improved the yield significantly (entries 12–20). Performing the reaction in other organic solvents instead of DMSO did not enhance the yield (entries 21–28). In addition, the amount of TBHP as well as acetic acid was also optimized and the results are listed in Table S1, ESI† (entries 29–31 and 37). The investigations on reaction temperature and time showed that reacting at 90 °C for 10 h was optimal for the process. Finally, the optimal conditions were 20 mol% *n*-Bu<sub>4</sub>NI with 4 equiv. TBHP and 3 equiv. acetic acid in DMSO under air.

With the optimized conditions in hand, various benzylamines were reacted with 4-methyl-2-phenylquinazoline (**1a**) to give the corresponding imidazo[1,5-*c*]quinazolines (**3aa–an**) (Table 1). We found that the steric hindrance had little influence on the reaction (entries 2–4). In all cases, both electron-donating and withdrawing substituents in the phenyl ring were well tolerated, and gave good yields (entries 5–10). Notably, functional groups such as F, Cl and Br were also compatible with the reaction conditions, which provided an additional handle for further functionalization of the products. Moreover, naphthalen-1-ylmethanamine and several heterocyclic benzylamines were also proved applicable, giving the desired products in good yields (entries 11–13). However, pyridin-2-ylmethanamine (**2n**) failed to yield the desired product, but gave an unexpected byproduct *via* self-condensation and cyclization (for details, see ESI†).

To evaluate the generality of this reaction, a variety of quinazolines and benzylamine were further tested. As shown in Table 2, 2-position substituted quinazolines with the benzene ring bearing alkyl, methoxy, fluoro and chloro groups were well tolerated to give excellent yields, and those with strong electron-withdrawing groups, such as trifluoromethyl and nitro group still gave target products in good yields (**3ba–ga**). 4-Methylquinazoline with other aryl

Table 2 Substrate scope of 4-methylquinazolines<sup>a</sup>

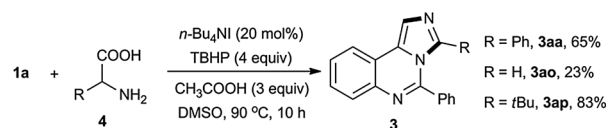
	<p>3ba, R' = 4-<i>t</i>Bu, 96%            3ca, R' = 4-OMe, 97%            3da, R' = 4-CF<sub>3</sub>, 79%            3ea, R' = 4-NO<sub>2</sub>, 80%            3fa, R' = 3-Cl, 90%            3ga, R' = 2-F, 98%            3ha, X = O, 94%            3ia, X = S, 76%            3ja, 98%            3sa, 35%            3ta, 69%            3ua, Nd</p>
	<p>3ka, R = Me, 76%            3la, R = <i>n</i>Pr, 55%            3ma, R = <i>t</i>Bu, 91%            3na, R = cyclopropyl, 91%            3oa, R = cyclohexyl, 87%            3pa, R = Cl, Nd            3qa, X = CH<sub>2</sub>, 37%            3ra, X = O, 48%</p>

Nd = Not detected. <sup>a</sup> Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), *n*-Bu<sub>4</sub>NI (0.06 mmol), 70% aq. TBHP (1.2 mmol), CH<sub>3</sub>COOH (0.9 mmol), DMSO (2 mL), 90 °C, 10 h. Isolated yield.

substituents such as furyl, thienyl and pyridyl groups also underwent the reaction efficiently (**3ha–ja**). 2,4-Dimethylquinazoline (**1k**) was successfully transformed in 76% yield with excellent regioselectivity probably due in part to the weaker C–H bond of the 4-methyl substituent.<sup>11</sup> Moreover, exclusive selectivity was also observed for amination at methyl over the methylene sp<sup>3</sup> C–H bond (**3la**). Other alkyl substituents, such as branched and cycloalkyl groups were also suitable for the present transformation (**3ma–oa**). 2-Cl substituted quinazoline failed to yield the product, but gave a byproduct (**3pa'**, for details, see ESI†). Substituted 2-aminoquinazolines (**1q** and **1r**), substituted phenylquinazoline (**1s**) and pyridopyrimidine (**1t**) were also tested and the corresponding products were afforded in moderate to good yields. However, 4-methylpyrimidine showed no reactivity under current conditions.

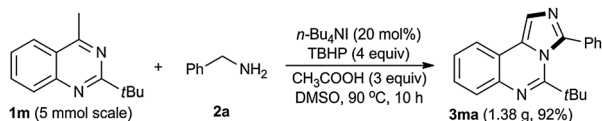
Recently,  $\alpha$ -amino acids have been applied to the preparation of nitrogen-containing heterocycles *via* decarboxylative reaction under metal-free conditions.<sup>12</sup> The success of benzylamines gives us a hint to further test the scope of this reaction with  $\alpha$ -amino acids (Scheme 2). To our delight, when an aryl or alkyl group was connected to the  $\alpha$ -carbon atom of the amino acid, the corresponding products were obtained with satisfactory yields. When glycine was employed as the substrate, the reaction also worked although gave a low yield. We believe that the wide tolerance of various functional groups in the imidazolyl ring makes this reaction highly practical and reliable.

The scalability of the method was verified by running the reaction of **1m** with **2a** on a 5 mmol scale (Scheme 3), and the product was isolated in identical high yield.

Scheme 2 Synthesis of imidazo[1,5-*c*]quinazolines from amino acids.Table 1 Substrate scope of benzylamines<sup>a</sup>

 <b>1a</b>	 <b>2a-n</b>	$n\text{-Bu}_4\text{NI}$ (20 mol%) TBHP (4 equiv) $\text{CH}_3\text{COOH}$ (3 equiv) DMSO, 90 °C, 10 h	 <b>3aa-an</b>
Entry	R	Product	Yield <sup>b</sup> (%)
1	Ph ( <b>2a</b> )	<b>3aa</b>	88
2	2-Me-Ph ( <b>2b</b> )	<b>3ab</b>	83
3	3-Me-Ph ( <b>2c</b> )	<b>3ac</b>	75
4	4-Me-Ph ( <b>2d</b> )	<b>3ad</b>	71
5	4- <i>t</i> Bu-Ph ( <b>2e</b> )	<b>3ae</b>	76
6	4-OMe-Ph ( <b>2f</b> )	<b>3af</b>	75
7	4-F-Ph ( <b>2g</b> )	<b>3ag</b>	85
8	4-Cl-Ph ( <b>2h</b> )	<b>3ah</b>	76
9	4-Br-Ph ( <b>2i</b> )	<b>3ai</b>	80
10	4-CF <sub>3</sub> -Ph ( <b>2j</b> )	<b>3aj</b>	77
11	1-Naphthyl ( <b>2k</b> )	<b>3ak</b>	90
12	2-Furyl ( <b>2l</b> )	<b>3al</b>	62
13	2-Thienyl ( <b>2m</b> )	<b>3am</b>	76
14	2-Pyridyl ( <b>2n</b> )	<b>3an</b>	Nd <sup>c</sup>

<sup>a</sup> Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), *n*-Bu<sub>4</sub>NI (0.06 mmol), 70% aq. TBHP (1.2 mmol), CH<sub>3</sub>COOH (0.9 mmol), DMSO (2 mL), 90 °C, 10 h. <sup>b</sup> Isolated yield. <sup>c</sup> Nd = Not detected.

Scheme 3 Large scale synthesis of **3ma**.

Further control experiments have been performed to obtain insights into the mechanism (Scheme S1, see ESI†). It was thought that iodo product **5** may be the key reaction intermediate derived from **1a**. However, **1a** under standard conditions in the absence of **2a** and acetic acid did not afford **5** (Scheme S1A, ESI†), suggesting that an 'in situ iodination' based oxidative coupling pathway<sup>2c</sup> could be excluded. When 20 mol%  $\text{PhI}(\text{OAc})_2$  was employed, the reaction did not work (Scheme S1B, ESI†). This result indicated hypervalent iodine reagents might not be involved in the transformation. Adding a radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) or TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) to the reaction system, a negative influence on the yield was observed (Scheme S1C, ESI†). This result suggested that the reaction probably proceeded *via* a free radical process. When **1a** was used as a substrate under standard conditions in the absence of benzylamines, an unexpected benzylic acetate **6** was obtained (Scheme S1D, ESI†). To help ascertain whether **6** is a potential intermediate, we explored the coupling of **6** with **2a** under standard conditions (Scheme S1E, ESI†). The desired product was obtained in 76% yield within 5 h, suggesting that **6** was most likely a possible intermediate for the present transformation. Additionally, no reaction occurred in the absence of *n*-Bu<sub>4</sub>NI or TBHP, indicating that the proper oxidation state of the iodine catalyst was an important requirement for reactivity. When sodium acetate was subjected to the reaction conditions, no benzylic acetate was detected (Scheme S1F, ESI†). Thus, a benzyl cation is not involved in this reaction.

On the basis of the above evidence and previously reported results,<sup>9,13</sup> a possible mechanism is proposed as shown in Scheme S2 (see ESI†). Initially, TBHP decomposes to generate the *tert*-butoxyl and *tert*-butylperoxy radicals in the presence of iodide ions ( $\text{I}^-$ ). These radicals subsequently abstract hydrogen atoms from the acetic acid and **1** to provide both the acyloxy and benzylic radical **A**, respectively. Then the coupling of these two radicals forms the intermediate **6**. **B** is generated *via* amination of **6** under current conditions,<sup>14</sup> followed by oxidation to give **C** or **C'**. Subsequently, **C** or **C'** is oxidized to **E** *via*  $\text{sp}^3$  C–H functionalization under iodine-catalyzed reaction conditions. Then **E** is converted to the product after intramolecular amination/cyclization and rearrangement in a tandem process.

In summary, a facile and efficient approach to the synthesis of imidazo[1,5-*c*]quinazolines was developed *via* a tandem reaction following  $\text{sp}^3$  C–H functionalization under metal-free conditions. Moreover, the reaction showed a broad scope of substrates including the common commercially available benzylamines and  $\alpha$ -amino acids. The new protocol serves not only as a method to construct a new class of imidazo-*N*-heterocycles but also as a rare example of benzylic primary C–H oxidative amination with primary amines. The investigation of the mechanism indicated that benzylic acetate as a possible intermediate was involved in the reaction. Ongoing research involves further application of

the methodology in other heterocycle synthesis and bioactive evaluation of imidazo[1,5-*c*]quinazolines is currently underway in our laboratory.

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