C–H Amination

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Selective Iodine-Catalyzed Intermolecular Oxidative Amination of C(sp^3)–H Bonds with *ortho*-Carbonyl-Substituted Anilines to Give Quinazolines**

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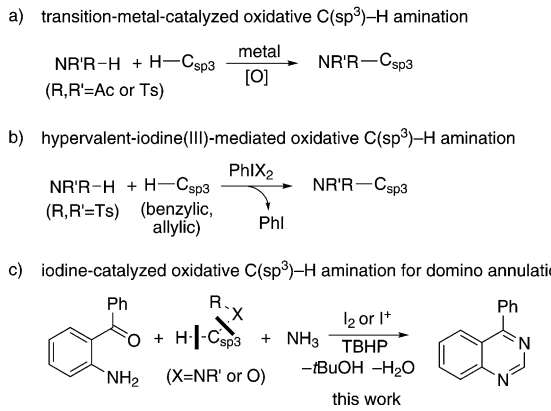
Transition-metal-catalyzed intermolecular or intramolecular direct oxidative aminations of C(sp^3)–H bonds, including activated and unactivated C(sp^3)–H bonds, have emerged as important methods for C–N bond formations, because they are straightforward and have economic advantages over present procedures by employing prefunctionalized substrates (Scheme 1a).[1–3] However, these aminations are restricted because of the toxicity of catalysts and their use of expensive transition metals as catalysts. Furthermore, only amides (acetamides or sulfonamides) were employed as coupling partners in most cases. Recently, Chang[4] and Muniz[5] have developed interesting metal-free aminations of benzylic and allylic C–H bonds, respectively, with sulfonamides in the presence of stoichiometric amounts of hypervalent iodine(III) reagents. Although a transition metal was not required, large amounts of iodobenzene were generated as by-product, and the substrate scope was limited to sulfonamides (Scheme 1b). Therefore, a new, more efficient, and environmentally friendly catalyst for oxidative C(sp^3)–H amination with anilines is highly desirable.

Recently, Ishihara[6] and Wan[7] have developed Bu_4NI-catalyzed oxidative functionalization of C(α)–H bonds for C–O bond formations. Meanwhile, our group has focused on the development of metal-free C(sp^3)–H functionalization for C–C or C–N bond formation.[8] We hoped to realize iodine-catalyzed intermolecular oxidative aminations of C(sp^3)–H bonds with anilines. To the best of our knowledge, such a protocol has not been reported to date.

Herein, we report an iodine-catalyzed intermolecular oxidative amination of a C(sp^3)–H bond adjacent to the nitrogen or oxygen atom of N-alkylamides, ethers, or alcohols with *ortho*-carbonyl-substituted anilines. A domino process that includes C–N or C–O bond cleavage, attack of ammonia, condensation, and oxidation subsequently leads to quinazolines in good to excellent yields (Scheme 1c). The additional nitrogen and carbon atom of the quinazolines originate from ammonia and the methyl group adjacent to the nitrogen or oxygen atom of the solvents, respectively. To the best of our knowledge, this is the first example of using a combination of inorganic nitrogen sources and organic solvents for the formation of hetercycles.



Scheme 1. Strategies for oxidative C(sp^3)–H amination.

We began our study with the reaction of one equivalent of 2-aminobenzophenone (**1a**), two equivalents of NH_4HCO_3, four equivalents of *tert*-butyl hydroperoxide (TBHP, 70% in water) as the oxidant, and 20 mol% of *N*-iodosuccinimide (NIS) as the catalyst. When the reaction mixture was heated in *N*,*N*-dimethylacetamide (DMA, **2a**) in air at 120°C for four hours, 4-phenylquinazoline (**3a**) was obtained in more than 99% yield, determined by GC–MS analysis (Table 1, entry 1). In the absence of NH_4HCO_3, desired product **3a** was not detected, thus indicating that NH_4HCO_3 is the source of the additional nitrogen atom of the product (Table 1, entry 2). Various ammonia-based reagents could be used as N sources without influencing the reaction yields (Table 1, entries 3–6). To examine the source of the additional carbon atom, various solvents (**2b**–**2f**) were tested in the reaction. Use of solvents **2b**, **2d**, and **2f** gave desired product **3a**, whereas solvents **2c** and **2e** gave 2-methyl-4-phenylquinazoline (**3a′**) with low yields, rather than product **3a** (Table 1, entries 7–11). These results implied that the additional carbon atom of **3a** presumedly originated from the N,N-dimethyl moiety of DMA. In addition, various iodine reagents were used as the catalyst; while PhI gave **3a** in a similar yield, other iodine-containing catalysts gave **3a** in lower yields (Table 1, entries 12–15). Among the various oxidants that were examined, such as di-*tert*-butylperoxide (DTBP), 2,3-dichloro-5,6-

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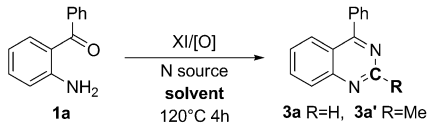
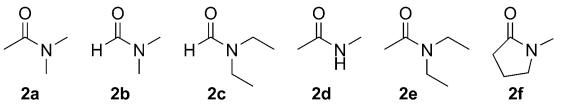
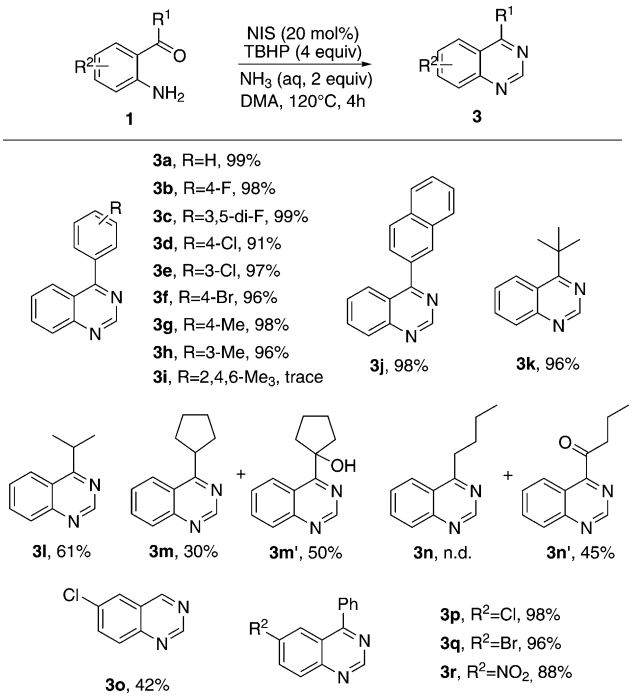
Table 1: Optimization of reaction conditions.[a]





Entry	XI	Oxidant	N source	Solvent	Yield [%][b]
1	NIS	TBHP	NH_4HCO_3	**2a**	>99
2	NIS	TBHP	none	**2a**	n.d.
3	NIS	TBHP	NH_4OAc	**2a**	>99
4	NIS	TBHP	NH_4Cl	**2a**	99
5	NIS	TBHP	NH_4F	**2a**	99
6	**NIS**	**TBHP**	**NH_3(aq)**	**2a**	**>99 (99)**
7	NIS	TBHP	NH_3(aq)	**2b**	50
8	NIS	TBHP	NH_3(aq)	**2c**	n.d.[c]
9	NIS	TBHP	NH_3(aq)	**2d**	99
10	NIS	TBHP	NH_3(aq)	**2e**	n.d.[d]
11[e]	NIS	TBHP	NH_3(aq)	**2f**	40
12	I_2	TBHP	NH_3(aq)	**2a**	95
13	Bu_4NI	TBHP	NH_3(aq)	**2a**	89
14	KI	TBHP	NH_3(aq)	**2a**	76
15	PhI	TBHP	NH_3(aq)	**2a**	99
16	NIS	DTBP	NH_3(aq)	**2a**	83
17	NIS	Oxone	NH_3(aq)	**2a**	n.d.
18	NIS	DDQ	NH_3(aq)	**2a**	n.d.
19	NIS	O_2	NH_3(aq)	**2a**	10

[a] Reaction conditions: **1a** (0.2 mmol), N source (0.4 mmol), XI (0.04 mmol), oxidant (0.8 mmol), solvent (1 mL), 120°C, 4 h. [b] Determined by GC–MS analysis using an internal standard, yields of isolated products given in parentheses; n.d. = not detected. [c] 5% of **3a′** was obtained. [d] 38% of **3a′** was obtained. [e] 24 h. Entry in bold marks optimized reaction conditions.



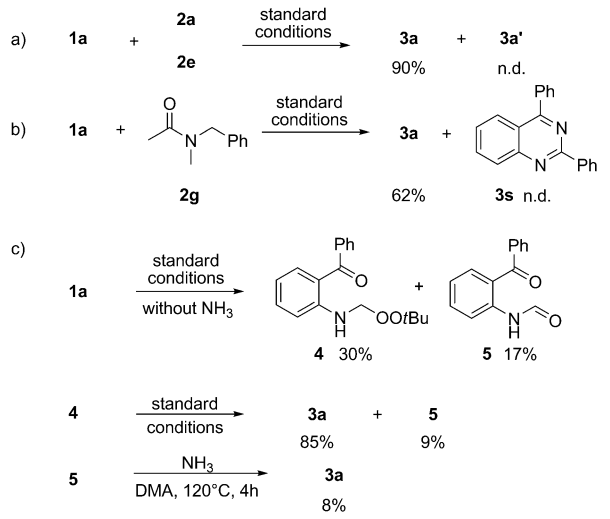
Scheme 2. Substrate scope of *ortho*-carbonyl-substituted anilines. Reaction conditions: **1** (0.2 mmol), ammonia (25% in H_2O, 0.4 mmol), NIS (0.04 mmol), TBHP (70% aq, 0.8 mmol), DMA (1 mL), 120°C, 4 h; yields of isolated products are given; n.d. = not detected.

dicyano-1,4-benzoquinone (DDQ), oxone, and oxygen, TBHP gave **3a** in the highest yield (Table 1, entries 16–19).

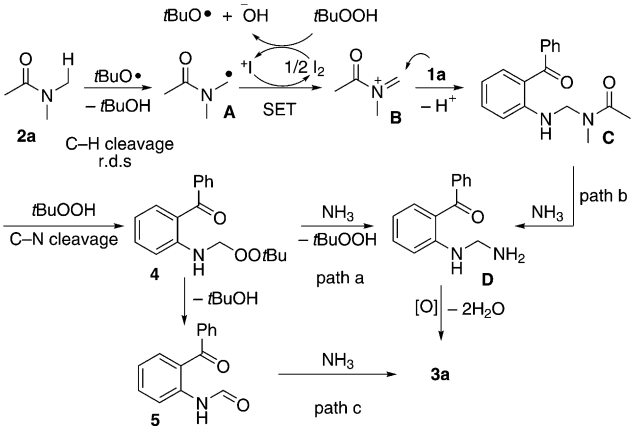
We next investigated the substrate scope of the oxidative C–N coupling reaction under the optimized reaction conditions (Scheme 2). Firstly, when R^1 is an aromatic substituent, the reaction of substrates **1a**–**1h** can be carried out smoothly to give the corresponding products **3a**–**3h** with excellent yields, regardless of electron-withdrawing or electron-donating groups on the phenyl ring of R^1. However, substrate **1i** (R^1 = mesityl) didn't give the desired product **3i**, perhaps as a result of steric hindrance. Product **3j** (R^1 = 2-naphthyl) could be obtained in 98% yield of isolated produt. In contrast, substrates with aliphatic substituents usually afforded the desired products in lower yields, except that with a *tert*-butyl substituent (**3k**). For example, **3m** was obtained in only 30% yield, while its oxidative product **3m′** was generated with a yield of 50%. Moreover, desired product **3n** could not be obtained, whereas its oxidative product **3n′** was generated with a yield of 45%. This result indicated that benzylic C–H bond oxidation of the R^1 group in these quinazolines could occur under standard conditions. In addition, when Cl, Br, and NO_2 substituents were introduced at the 5 position of 2-aminobenzophenone, the desired products **3p**–**3r** were obtained in excellent yields. Notably, the C–F, C–Cl, and C–Br bonds of the substrates remained intact during all reactions, thus providing an additional handle for further functionalization of the products (Scheme 2, **3b**–**3f** and **3o**–**3q**).

The amination selectivity of primary versus secondary C–H bonds was also investigated. When a 1:1 mixture of **2a** and **2e** was employed in the reaction, only **3a** was obtained in 90% yield, and 2-methyl-4-phenylquinazoline (**3a′**) was not detected (Scheme 3a). When *N*-benzyl-*N*-methylacetamide (**2g**) was employed in the reaction, only **3a** was obtained in 62% yield, and 2,4-diphenylquinazoline (**3s**) was not detected (Scheme 3b). To the best of our knowledge, this is the first report of excellent selectivity of the amination of primary and secondary C–H bonds in oxidative C(sp^3)–H aminations. Currently, the cause of the high selectivity of primary C–H bond amination is not clear to us.

To gain an insight into the reaction mechanism, we carried out several control experiments. Expectedly, in the absence of ammonia, direct C–N coupling products **4** and **5** were formed because domino annulation was inhibited (Scheme 3c). When product **4** was subjected to the standard reaction conditions, **3a** (85%) and **5** (9%) were obtained. Treatment of **5** with ammonia also generated **3a** through direct condensation, albeit in a low yield (8%). These results indicate that **4** and **5** may be reaction intermediates, and that different yields may be a result of different reaction pathways. When the reactions of **1a** with formic acid or formamide were subsequently carried out under standard conditions, trace amounts of **3a** were obtained (see the Supporting Information). Therefore,



Scheme 3. Selectivity between primary and secondary C(sp^3)–H bonds and control experiments for mechanism.

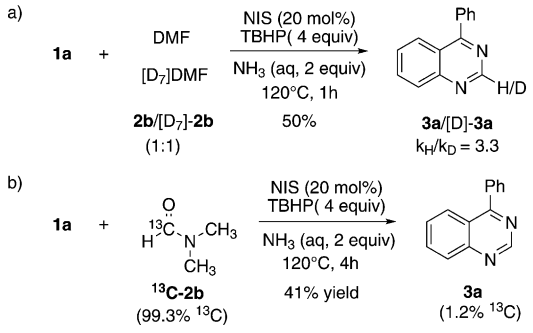


Scheme 5. Mechanism for domino synthesis of quinazolines by oxidative C(sp^3)–H amination. r.d.s. = rate-determining step, SET = single-electron transfer.

formamide and formic acid can be excluded as intermediates. Moreover, when stoichiometric amounts of hypervalent iodine reagents (such as $PhI(OAc)_2$ or *ortho*-iodoxybenzoic acid) were employed instead of our catalytic system, no desired product was obtained. This result indicates that the reaction pathway is not followed in catalysis involving in situ generated hypervalent iodine. Finally, radical trapping experiments were also carried out (see the Supporting Information). We observed that the reaction was inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT). This observation implied that the reaction presumably underwent a radical pathway.

On the other hand, a large intermolecular kinetic isotope effect (KIE, $k_H/k_D = 3.3$) was observed with *N*,*N*-dimethylformamide (DMF) and [D_7]DMF, thus indicating that the C–H bond cleavage was the rate-determining step (Scheme 4a). Moreover, a ^{13}C-labeling experiment unambiguously established that the additional carbon atom of quinazolines was derived from the N-methyl group of N-methylamide, rather than the acyl group (Scheme 4b).[9]

On the basis of results described above and in previous reports,[10] a plausible mechanism is proposed (Scheme 5). Initially, DMA is presumably involved a hydrogen abstraction from the C–H bond adjacent to the nitrogen atom to give a carbon radical **A**, and generation of an imine ion **B** by

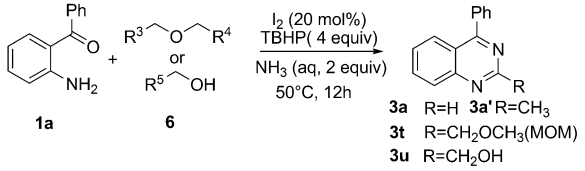


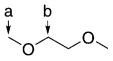
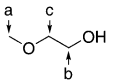
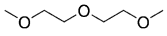
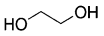
Scheme 4. KIE and ^{13}C-labeling experiments.

oxidation with I^+.[11] The nucleophilic addition of **1a** to **B** provides amide intermediate **C**.[12] In the presence of *t*BuOOH, a sequential C–N bond cleavage in **C** gives unstable intermediate **4**, which is converted to **D** through an attack by ammonia (path a). Finally, **3a** is formed by oxidative cyclization. However, in the presence of NH_3, **D** could also be formed directly from **C** (path b). Furthermore, a minor pathway may occur according to control experiments. Intermediate **4** could generate **5** through elimination of *t*BuOH. Then, **3a** could be formed through direct condensation of **5** and ammonia (path c). Overall, the I_2–I^+ redox process[13] plays a key role in the C–N bond formation by promoting the reductive cleavage of the O–O bond in the peroxide and oxidation of the N-bound carbon radical to an imine ion.

Recently, functionalizations of C(sp^3)–H bonds adjacent to oxygen atoms have been developed for oxidative C–C and C–X bond formations.[14] In these reactions, an oxonium ion intermediate was generated. According to our proposed mechanism, C(sp^3)–H amination of ethers should also be possible through nucleophilic addition of **1a** to oxonium ions, which are generated in situ by our catalyst system. After optimization,[15] reaction of **1a** with methyl *tert*-butyl ether (**6a**) instead of DMA afforded the desired product **3a** in 95% yield in the presence of 20 mol% iodine under very mild conditions (Table 2, entry 1). However, when anisole (**6b**) was employed, a trace amount of **3a** was obtained, probably because the following C–O cleavage proceeded with difficulty (Table 2, entry 2). When diethyl ether (**6c**) was employed, the corresponding product **3a′** was also obtained in 80% yield (Table 2, entry 3). In addition, ethers that bear various C(sp^3)–H bonds adjacent to the oxygen atom were examined (Table 2, entries 4–6). For example, 1,2-dimethoxyethane (**6d**), which have two types of C(sp^3)–H bonds (a and b) adjacent to the oxygen atom, afforded **3a** and **3t** in 70% and 18% yields, respectively. Similarly, 2-methoxyethanol (**6e**), which bears three types of C(sp^3)–H bonds adjacent to its oxygen atoms, afforded **3a, 3t**, and **3u** in 62%, 17%, and 9% yields, respectively. It is noted that reactions with primary C–H bonds gave products in higher yields than with secondary C–H bond (see also Scheme 3). Alcohols, such as

Table 2: The scope of various ethers or alcohols.[a]



Entry	Ether (Alcohol)		Products	Yields [%][b]
1		**6a**	**3a**	95
2		**6b**	**3a**	trace
3		**6c**	**3a′**	80
4		**6d**	**3a/3t**	70/18
5		**6e**	**3a/3t/3u**	62/17/9
6		**6f**	–	–
7	MeOH	**6g**	**3a**	92 (85[c])
8	EtOH	**6h**	**3a′**	75
9		**6i**	**3a/3u**	49/32

[a] Reaction conditions: **1a** (0.2 mmol), ammonia (25% aq, 0.4 mmol), iodine (0.04 mmol), oxidant (0.8 mmol), ethers or alcohols (1 mL), 50°C, 12 h. [b] Yields of isolated products. [c] 10 mmol scale.

methanol, ethanol, and glycol, were also investigated as substrates (Table 2, entries 7–9). Methanol and ethanol gave the corresponding products **3a** and **3a′** in good yields, while glycol gave the corresponding product **3u** in a low yield of 32%, because **3a** was unexpectedly obtained in 49% yield. Finally, the reaction conditions summarized in entry 7 (Table 2) turned out to be scalable, and product **3a** was obtained in a good yield under mild conditions. Compared to typical methods for the synthesis of quinazolines,[16] requiring a high temperature (150°C) and an excess of Brønsted acid, our protocol represents a facile, efficient, and mild method with a broad substrate scope (giving products, such as **3a′**, **3t**, and **3u**) using ethers or alcohols and ammonia as "clean" reagents. These factors indicated that this method could be widely applied in organic synthesis.

In summary, we have developed an iodine-catalyzed oxidative amination of C(sp^3)–H bonds adjacent to nitrogen or oxygen atoms for the synthesis of quinazolines from *ortho*-carbonyl-substituted anilines, ammonia, and solvents, such as N-alkylamides, ethers, and alcohols. Compared with previous reports, this novel protocol is distinguished by 1) the lack of expensive transition metals, 2) operational simplicity, 3) the fact that an inert atmosphere or dry solvents are not required, 4) a wide tolerance of various functional groups, and 5) the production of alcohol and water as the only waste. More importantly, the selectivity of the reactions of primary and secondary C–H bonds was the first observed in oxidative C(sp^3)–H aminations. The development of iodine-catalyzed oxidative C–H aminations for the synthesis of other heterocycles is ongoing in our laboratory.

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[12] The nucleophilic addition of ammonia to **B** may also occur and generate formamide through further oxidation. The final product **3a** was formed through the direct condensation of formamide with **1a**. However, when the reaction of formamide and **1a** was carried out under our standard conditions, a trace amount of **3a** was obtained. Therefore, an attack of ammonia to **B** and generation of formamide can be excluded.
[13] For I_2-I^+ redox process, see: Y. Z. Yan, Z. Y. Wang, *Chem. Commun.* **2011**, *47*, 9513. In this paper, amino acids were used as carbon and nitrogen sources of quinazolines rather than solvents; for $I^- - I_2$ redox process, see reference [7].
[14] For selected examples of functionalization of $C(sp^3)$–H bond adjacent to an oxygen atom, see: a) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242; b) Y. Zhang, C.-J. Li, *Angew. Chem.* **2006**, *118*, 1983; *Angew. Chem. Int. Ed.* **2006**, *45*, 1949; c) S. G. Pan, J. H. Liu, H. R. Li, Z. Y. Wang, X. W. Guo, Z. P. Li, *Org. Lett.* **2010**, *12*, 1932, and reference [7].
[15] See the Supporting Information for details of the optimization.
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