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Chemoselective Cu-catalyzed synthesis of diverse *N*-arylindole carboxamides, β-oxo amides and *N*-arylindole-3-carbonitriles using diaryliodonium salts†

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Chemoselective copper-catalyzed synthesis of diverse *N*-arylindole-3-carboxamides, β-oxo amides and *N*-arylindole-3-carbonitriles from readily accessible indole-3-carbonitriles, α-cyano ketones and diaryliodonium salts has been developed. Diverse *N*-arylindole-3-carboxamides and β-oxo amides were successfully achieved in high yields under copper-catalyzed neutral reaction conditions, and the addition of an organic base (DIPEA) resulted in a completely different selectivity pattern to produce *N*-arylindole-3-carbonitriles. Moreover, the importance of the developed methodology was realized by the synthesis of indoloquinolones and *N*-((1*H*-indol-3-yl)methyl)aniline and by a single-step gram-scale synthesis of the naturally occurring cephalandole A analogue.

Introduction

N-Arylamide and related compounds are ubiquitous units present in numerous medicinally potent molecules and organic materials.[1] Particularly, arylamides are recognized for their various medicinal properties such as anti-inflammatory, anti-tumour, and potassium channel activation.[2] Therefore, the synthesis of *N*-arylamide has attracted greater interest from organic and medicinal chemists. One of the most widely used synthesis methods to obtain *N*-arylamides is the Goldberg reaction, involving the coupling of aryl(alkyl)amides and aryl halides in the presence of a copper catalyst and a base at high temperature.[3] However, this method typically suffers from the need for harsh reaction conditions, a narrow substrate scope and low product yields. In recent years, the Goldberg reaction has been advanced by employing ligands with copper catalysts in non-polar solvents.[4] In this regard, the alkyl- or arylamide reactants used in the Goldberg reaction could be prepared easily from their corresponding nitriles by hydrolysis.[5] In 2013, Pan and colleagues described a copper-catalyzed synthesis of benzanilides in water by the reaction of haloarenes or alkenyl halides with arylnitriles using ionic liquid as a phase transfer catalyst.[6] Similarly, in 2016, Yang and co-workers developed a protocol for amidation involving the reaction of arylboronic acids with various arylnitriles under copper-catalyzed conditions.[7] In recent years, diaryliodonium salts have been widely employed as highly electrophilic and relatively benign arylating coupling partners under mild reaction conditions.[8] In relation to this, the reaction of diaryliodonium salts with arylnitriles has been utilized to access diversely substituted nitrogen-heterocycles such as quinazolines, quinolines, phenanthridines, isoindolines and benzoxazines.[9] These copper-catalyzed reactions of arylnitriles with diaryliodonium salts proceeded through *N*-aryl nitrilium intermediates. Furthermore, cascade annulation of this intermediate with nitriles or acetylenes provided quinazoline and quinoline derivatives at high temperatures. While developing an efficient method for the synthesis of quinazoline and quinoline derivatives, the Chen group detected *N*-arylamide as a side product[10] and rationalized its formation by preparing *N*-phenyl pentanamide and *N*-phenyl-1-naphthamide. However, Chen's research work mainly focused on the synthesis of various nitrogen-heterocycles. Therefore, we envisioned that the use of easily accessible (*NH*)-indole-carbonitriles or α-cyano ketones as substrates instead of amides and diaryliodonium salts as arylating agents could be an alternative convenient approach to obtain *N*-arylamides. Particularly, we aimed to capably synthesize bioactive *N*-arylindole-carboxamides and β-oxo amides from the reaction of readily accessible free (NH)-indole-carbonitriles or α-cyano ketones with diaryliodonium salts under milder conditions. Furthermore, multisite-selective C–N bond formation is critically important due to its applications in the structural modifications of medicinally potent and privileged scaffolds. However, chemoselective C–N bond formation for the introduction of aryl groups remains a distinct challenge because of

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the problems associated with controlling the arylation at precise positions.

On the other hand, indole amides are a class of very important heterocyclic compounds which are widely present in many natural products and pharmacological agents. In this context, the development of a new synthetic route to access a variety of indole-carboxamides is still desirable because the existing methods often suffer from low product yields and narrow substrate scope.[11] In addition, indole carboxamides have found many applications as pharmacophores. As depicted in Fig. 1, APICA (**1**) is identified as a cannabinoid receptor agonist, JNJ-7777120 (**2**) acts as a selective antagonist at the histamine H4 receptor, and phenylglycine-01 (PG-01) (**3**) is known as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator.[12] Cephalandole B (**4**) is a naturally occurring alkaloid which was isolated from the cytotoxic methanol extract of the Taiwanese orchid *Cephalanceropsis gracilis* (Orchidaceae).[12e]

Among the amides, β-oxo amides represent a valuable structural unit in medicinal and synthetic organic chemistry.[13] Recently, extensive research efforts have been directed towards the synthesis of β-oxo amides because they are potential precursors to achieve a variety of bioactive heterocyclic compounds,[14] *i.e.*, pyridones,[15] quinolones,[16] and chromones.[17] But, most of the existing methods to prepare β-oxo amides suffer from disadvantages such as the formation of undesirable side products in stoichiometric amounts, the need for high reaction temperatures, and a narrow substrate scope.[18]

In 2015, the Kassiou group prepared indole-3-carboxamides **5** by the reaction of *N*-protected indole-3-carbonyl chlorides **6** and their corresponding amine derivatives using triethylamine (TEA) in DCM (Scheme 1).[19] Veale *et al.* performed the synthesis of **5** by refluxing indole-3-carbonyl cyanides **7** and amine derivatives (3.0 equiv.) in acetonitrile.[20] Likewise, Xu and co-workers prepared *N*-arylindole-3-carboxamides **5** by the reaction of different anilines and indole-3-carboxylic acids **8** using 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent) and tributylamine in toluene at 90 °C.[21] Using the reaction of indole-3-carboxylic acids **8** with arylamines in the presence of EDCI·HCl (1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide hydrochloride) and HOBt (hydroxybenzo-triazole), Nakano *et al.* prepared indole amide derivatives **5** (Scheme 1).[22]

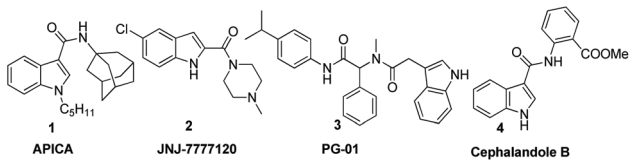
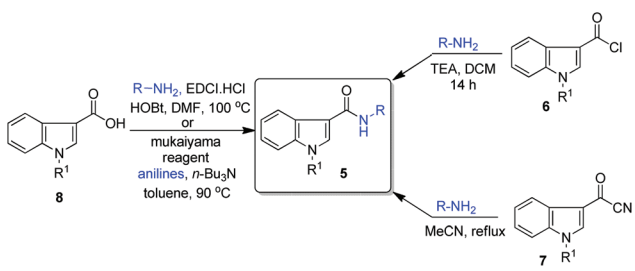


Fig. 1 Potent pharmacophores with indole carboxamide linkages **1–4**.



Scheme 1 General synthetic routes for indole carboxamides **5**.

Results and discussion

Although syntheses of *N*-arylindole-3-carboxamides have been disclosed in the literature, the substrate scope is limited.[19–24] Furthermore, there is no report available to access *N*-arylindole-3-carboxamides from indole-3-carbonitriles and diaryliodonium salts. The broad substrate scope and easy preparation of indole-3-carbonitriles prompted us to explore the reaction of indole-3-carbonitriles and the relatively benign diaryliodonium salts to achieve a library of bioactive *N*-arylindole-3-carboxamides[24] under mild reaction conditions.

Indole-3-carbonitriles **9** can be easily accessed in two synthetic steps from their corresponding substituted indoles. The Vilsmeier–Haack reaction of indole produced 3-formylindole which upon treatment with hydroxylamine and sodium formate in formic acid afforded the corresponding indole-3-carbonitriles **9** (refer to the ESI†).

Initially, we chose indole-3-carbonitrile (**9a**) and diphenyliodonium triflate (**10a**) as model substrates to investigate the reaction conditions (Table 1). The reaction of **9a** with **10a** using CuCl (10 mol%) as the catalyst and 1,2-dichloroethane (DCE) as solvent at 80 °C under a N_2 atmosphere resulted in the expected *N*-phenylindole-3-carboxamide (**11a**) in 20% yield (Table 1, entry 1). The use of CuI instead of CuCl as the catalyst decreased the yield of **11a** (Table 1, entry 2). Gratifyingly, changing the catalyst from CuI to $Cu(OTf)_2$ produced **11a** in 91% yield (Table 1, entry 3). The use of $Cu(OAc)_2H_2O$ instead of $Cu(OTf)_2$ afforded **11a** only in trace amounts (Table 1, entry 4). Noticeably, the reaction failed to provide the expected product **11a** in the absence of the catalyst or when iodobenzene was used as a coupling partner (Table 1, entry 5). This control experiment revealed the essential role of the copper catalyst and high reactivity of diphenyliodonium triflate (**10a**). Next, we focused on optimizing the catalyst loading. No significant improvement in the yield of **11a** was observed when the amount of $Cu(OTf)_2$ was increased from 10 mol% to 20 mol% (Table 1, entry 6). Notably, a lower product yield (**11a**, 80%) was observed when the catalyst loading was reduced (5 mol%) (Table 1, entry 7). Furthermore, variation in the reaction temperatures also did not improve the yield of **11a** significantly (Table 1, entries 8 and 9). The reaction yield also decreased in the absence of a N_2 atmosphere (Table 1, entry 10) and no product was detected under strictly anhydrous conditions (Table 1, entry 11). The use of solvents such as toluene, DMF, and THF resulted in lower product yields (Table 1, entries 12–14). Next, the reactivity of diphenyliodonium salts with

Table 1 Optimization of reaction conditions[a,b]

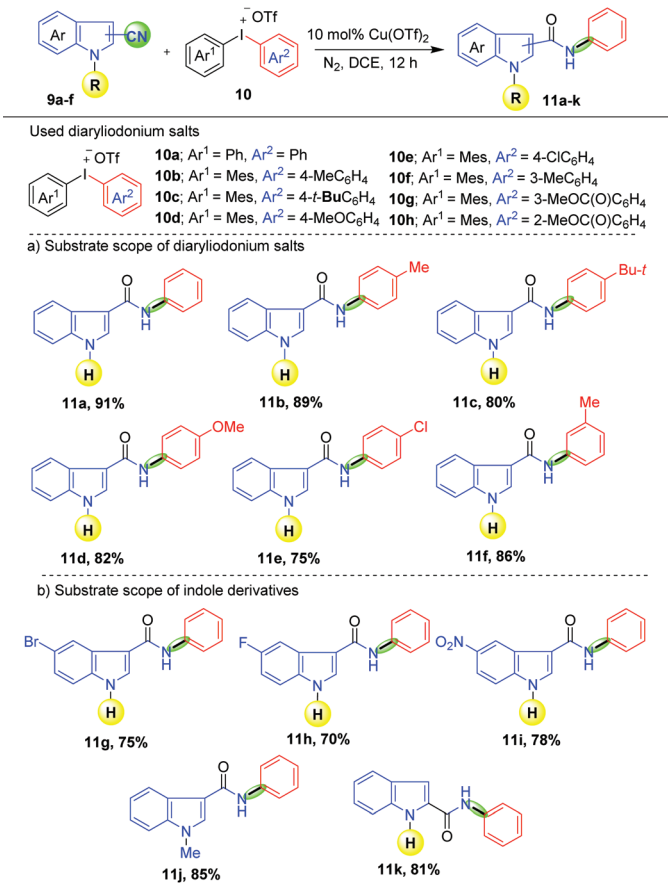
Entry	Counterion (X)	Catalyst (10 mol%)	Solvent	Temp. (°C)	Yield[b] (%)
1.	OTf	CuCl	DCE	80	20
2.	OTf	CuI	DCE	80	10
3.	OTf	$Cu(OTf)_2$	DCE	80	91
4.	OTf	$Cu(OAc)_2H_2O$	DCE	80	Trace
5.	OTf	—	DCE	80	NR[c,d]
6.	OTf	$Cu(OTf)_2$	DCE	80	92[e]
7.	OTf	$Cu(OTf)_2$	DCE	80	80[f]
8.	OTf	$Cu(OTf)_2$	DCE	100	90
9.	OTf	$Cu(OTf)_2$	DCE	60	75
10.	OTf	$Cu(OTf)_2$	DCE	100	40[g]
11.	OTf	$Cu(OTf)_2$	Dry DCE	80	NR
12.	OTf	$Cu(OTf)_2$	Toluene	80	79
13.	OTf	$Cu(OTf)_2$	DMF	80	10
14.	OTf	$Cu(OTf)_2$	THF	80	78
15.	OTs	$Cu(OTf)_2$	DCE	80	55
16.	Br	$Cu(OTf)_2$	DCE	80	45
17.	PF_6	$Cu(OTf)_2$	DCE	80	85

[a] Reaction conditions: **9a** (0.70 mmol, 1.0 equiv.), **10a** (0.84 mmol, 1.2 equiv.), catalyst (0.07 mmol, 0.1 equiv.), DCE (2.5 mL) under a N_2 atmosphere at 80 °C for 12 h. [b] Isolated yield of the product. [c] NR = no reaction. [d] Iodobenzene was used instead of **10a**. [e] 20 mol% catalyst was used. [f] 5 mol% catalyst was used. [g] Reaction was performed in the absence of a N_2 atmosphere.

OTs, Br and PF_6 counterions (Table 1, entries 15–17) was investigated. The reaction of **9a** with diphenyliodonium salt **10a** having OTs and Br counterions afforded 11a in poor yields (55% and 45%, respectively), whereas the reaction of **10a** with PF_6 counterions provided **11a** in 85% yield. The relatively better coordinating and nucleophilic nature of OTs and Br counterions in diphenyliodonium salts could be responsible for the poor product yields when compared to **10a** bearing OTf and PF_6 counterions.[25]

With the optimized conditions in hand, the generality of the protocol was then examined with indole-3-carbonitrile (**9a**) and various diaryliodonium salts (**10a–h**). The reaction of **9a** with diaryliodonium salts having electron-donating substituents such as methyl (10b), *t*-butyl (10c) and methoxy (10d) at the *para*-position proceeded smoothly to afford the corresponding products **11b** (89%), **11c** (80%) and **11d** (82%) (Table 2a). Compound **9a** with an electron-withdrawing group also reacted effectively with (4-chlorophenyl)(mesityl)iodonium triflate (**10e**) to furnish **11e** in 75% yield. Interestingly, *meta*-substituted mesityl(*m*-tolyl)iodonium triflate (**10f**) afforded the product **11f** in excellent yield (86%). Furthermore, we explored the viable substrate scope by employing diversely substituted indole-3-carbonitriles (Table 2b). Indole-3-carbonitriles with halogen substituents such as Br (**9b**) and F (**9d**) worked well, and the corresponding products **11g** and **11h** were obtained in good yields of 75% and 70%, respectively. The tolerance of the halogen group can provide great potential to prepare more

Table 2 Synthesis of *N*-arylindole-carboxamides[a,b]

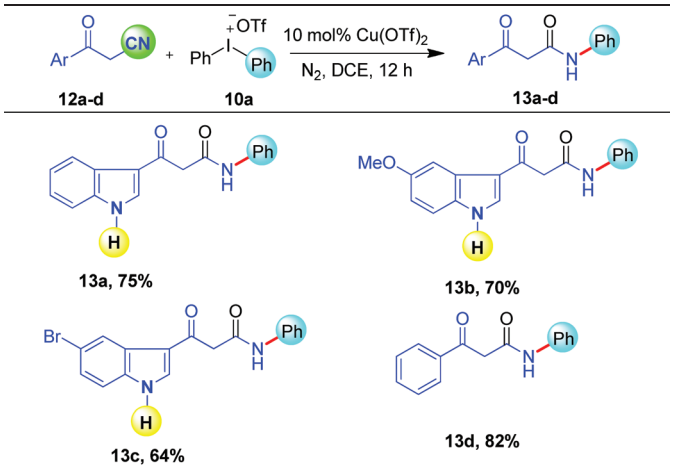


[a] Reaction conditions: **9a–f** (0.70 mmol, 1.0 equiv.), **10** (0.84 mmol, 1.2 equiv.), $Cu(OTf)_2$ (0.07 mmol, 0.1 equiv.), DCE (2.5 mL) under a N_2 atmosphere at 80 °C for 12 h. [b] Isolated yield of the product.

complex structures through various cross coupling reactions. The strong electron-withdrawing nitro group (**9e**) at the C5 position of indole-3-carbonitrile showed credible reactivity to give the product **11i** in 78% yield. Furthermore, when the *N*-methyl protected substrate (**9e**) was subjected to reaction with **10a**, delightfully, the reaction worked well to provide **11j** in 85% yield (Table 2b). It is noteworthy that indole **9f** with a cyano group at the C2 position reacted smoothly under the optimized reaction conditions to produce **11k** in 81% yield.

Next, we moved our attention to explore the amidation of structurally different α-cyano ketones (**12a–d**, Table 3) under the optimized reaction conditions. In this ambiance, the reaction of α-cyano ketone (**12a**) with diphenyliodonium triflate (**10a**) under standard conditions successfully afforded the corresponding β-oxo amide **13a** in 75% yield (as shown in Table 3). Under the developed reaction conditions, the electron donating group (methoxy, **12b**) and the halo substituted (bromo, **12c**) α-cyano ketone underwent facile amidation to afford the desired *N*-phenyl-β-oxo amides **13b** and **13c**, **respectively**, in good yields (64–70%). Furthermore, 3-oxo-3-phenylpropane-nitrile (**12d**) also reacted well to produce **13d** in 82% yield.

Table 3 Synthesis of various β-oxo amides (**13a–d**) [a,b]

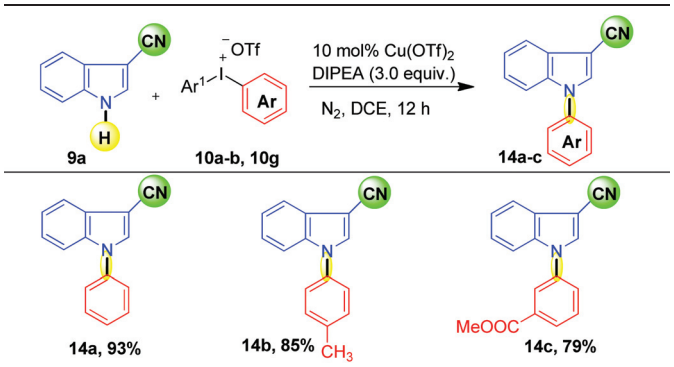


[a] Reaction conditions: **12a–d** (0.70 mmol, 1.0 equiv.), **10a** (0.84 mmol, 1.2 equiv.), $Cu(OTf)_2$ (0.07 mmol, 0.1 equiv.), DCE (2.5 mL) under a N_2 atmosphere at 80 °C for 12 h. [b] Isolated yield.

N-Arylation of various heterocycles utilizing diaryliodonium salts as the coupling partner has been reported under copper-catalyzed basic reaction conditions.[26] Interestingly, the addition of 3.0 equiv. of an organic base (DIPEA) under the developed copper-catalyzed amidation conditions led to the tuning of the selectivity pattern and resulted in *N*-arylindole-3-carbonitriles, which may be useful to access various dibenzazepine, pyrrolo[3,2,1-*jk*]carbazole and indoloquinoline derivatives.[27] The chemoselective reaction of indole-3-carbonitrile (**9a**) with **10a** using 10 mol% $Cu(OTf)_2$ and DIPEA (3.0 equiv.) in dichloroethane at 80 °C under an inert atmosphere provided 1-phenylindole-3-carbonitrile (**14a**) in 93% yield (as depicted in Table 4).

To test the feasibility of the reaction, the present strategy was suitably utilized to prepare two more 1-arylindole-3-carbonitrile derivatives **14b** (85%) and **14c** (79%) by the reaction of

Table 4 Chemoselective synthesis of *N*-arylindole-3-carbonitriles[a,b]

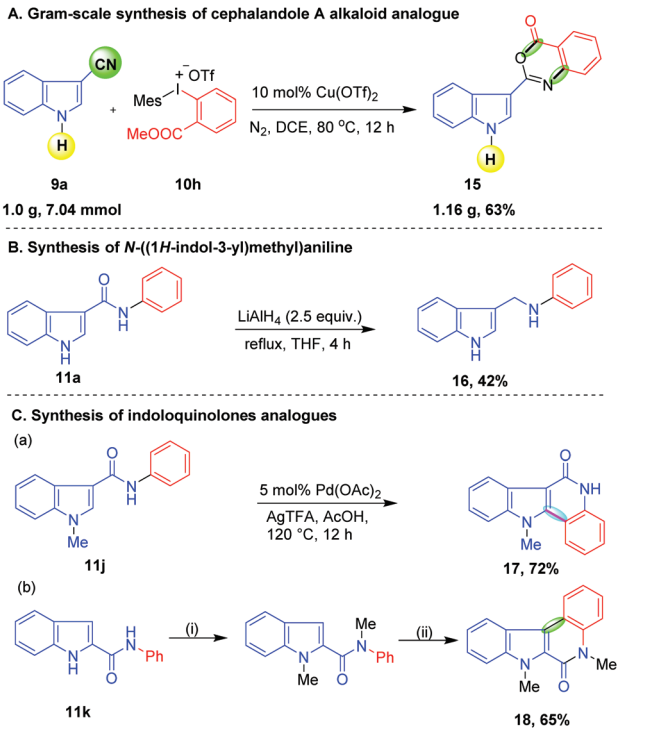


[a] Reaction conditions: **9a** (0.70 mmol, 1.0 equiv.), **10** (0.84 mmol, 1.2 equiv.), $Cu(OTf)_2$ (0.07 mmol, 0.1 equiv.), DIPEA (2.1 mmol, 3.0 equiv.), DCE (2.5 mL) under a N_2 atmosphere at 80 °C for 12 h. [b] Isolated yield.

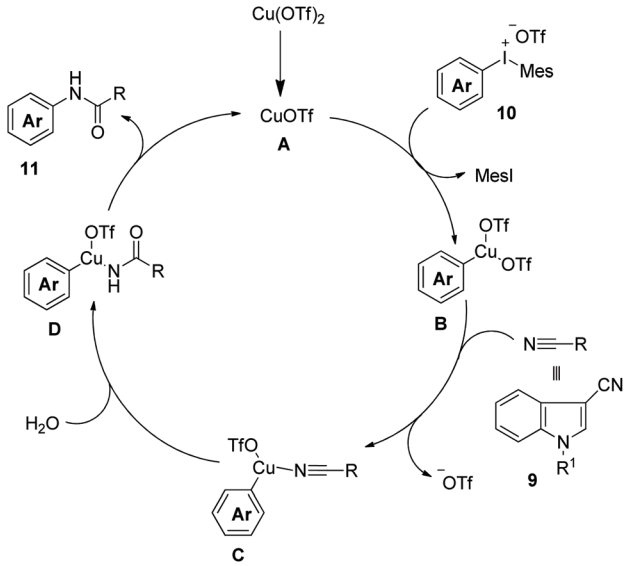
9a with diaryliodonium salts having electron rich methyl (**10b**) and electron deficient ester (**10g**) groups.

To demonstrate the synthetic usefulness of the amidation methodology, we targeted the gram-scale synthesis of the naturally occurring alkaloid, cephalandole A analogue, isolated from the Taiwanese orchid *Cephalanceopsis gracilis*.[28] Fortunately, under standard conditions, the reaction of **9a** (1.0 g, 7.04 mmol) with **10h** directly gave the cyclic product **15** (63%) in a single step as shown in Scheme 2A. Furthermore, the released iodomesitylene was also recovered in 60% yield after the reaction and it was reused to prepare mesityl(*p*-tolyl) iodonium triflate (**10b**). Next, we successfully reduced **11a** to achieve the useful precursor (for spirooxindoles) *N*-((1*H*-indol-3-yl)methyl)aniline (**16**) in 42% yield (Scheme 2B).[29] As depicted in Scheme 2C, the prepared indole carboxamides **11j** and **11k** were effectively utilized to prepare the corresponding indoloquinolones **17** (72%) and **18** (65%) in good yields. Indoloquinolones have great pharmaceutical value as they are present in several biologically active molecules[30] and are key precursors for the synthesis of various indoloquinoline alkaloids such as cryptosanguinolentine and isoneocryptolepine.[31]

Based on our results and previous literature reports,[7,9a,10-a,32] a plausible reaction mechanism for this transformation is illustrated in Scheme 3. Initially, disproportionation or reduction of $Cu(OTf)_2$ by the substrate molecule may generate the active catalyst Cu(I)OTf. Next, oxidative addition of diaryliodonium triflate **10** may convert Cu(I)OTf **A** to copper(III) inter-



Scheme 2 Synthetic applications to access various heterocycles. Reaction conditions: (i) Methyliodide (3.0 equiv.), NaH (2.0 equiv.), THF, 0 °C to reflux, 4 h. (ii) 10 mol% $Pd(OAc)_2$, 20 mol% *t*-BuOK, AgOAc (3.0 equiv.), PivOH : AcOH (3 : 1), 130 °C for 12 h.



Scheme 3 Plausible reaction mechanism for amidation.

mediates **B** which undergo the ligand-exchange reaction with nitriles **9**, possibly furnishing **C**. The tentative attack of a water molecule possibly from moist DCE on copper(III) species **C** may promote the formation of the intermediate **D** which upon reductive elimination may generate **11** *via* the release of Cu(I) OTf in the catalytic cycle.

Conclusions

In summary, we have developed a copper-catalyzed general strategy for chemoselective C–N bond formation to prepare *N*-arylindole-carboxamides, β-oxo amides and *N*-arylindole-3-carbonitriles using readily available indole-carbonitriles, α-cyano ketones and relatively benign diaryliodonium salts under mild reaction conditions. The addition of an organic base plays an important role in tuning the chemoselectivity of the two reactive sites. Diaryliodonium salts with different substituents including the electron-donating and electron-withdrawing groups could smoothly deliver the desired products in good to excellent yields (up to 93%). Furthermore, structurally different and readily available α-cyano ketones also afforded the corresponding arylated β-oxo amides in high yields (64–82%) under the developed amidation conditions. Moreover, the applicability of the developed protocol was proved by the single-step gram-scale synthesis of the naturally occurring cephalandole A analogue. The preparation of *N*-((1*H*-indol-3-yl)methyl)aniline and potent heterocyclic scaffold indoloquinolones showed the further synthetic usefulness of indole carboxamides. Also, the prepared indole carboxamides and arylated β-oxo amides could be useful precursors to access other heterocycles.

Conflicts of interest

There are no conflicts to declare.

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