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Authors: Yue Zhang, Jing Lu, Tianlei Lan, Shaoling Cheng, Wei Liu, and Chao Chen

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FULL PAPER

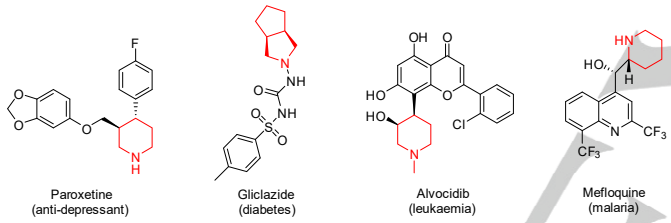
Preparation, characterization and reactivity of aliphatic amino iodane(III) reagents

Yue Zhang,[a][b] Jing Lu,[a][b] Tianlei Lan,[a][b] Shaoling Cheng,[a] Wei Liu*[a] and Chao Chen*[b][c]

Abstract: The preparation of a new class of aliphatic amino iodane(III) reagents has been realized with the *N*-TMS-amine and acetoxybenziodazole participated in the formation of N-I bond. The amino-containing iodane(III) reagent **2d** was characterized by single-crystal X-ray diffraction, which revealed the expected hypervalent iodane distorted T-shaped geometry. A practical copper-catalyzed, directed electrophilic amination of aryl amines employing amino-iodane(III) as amination agents was disclosed that proceeded smoothly without external additives.

Introduction

Many saturated nitrogen-containing heterocycles feature prominently in pharmaceuticals, such as treatments for depression (paroxetine), diabetes (gliclazide), leukaemia (alvocidib), malaria (mefloquine) (Scheme 1).[1] The development of rapid and efficient methods for the introduction of amino motifs into an organic molecule has the potential to promise candidates for the synthesis of various biologically active and medicinally important compounds[2]. Therefore, the development of amino group-transfer reagents is a desirable synthesis goal.



Scheme 1. Alicyclic amines containing drug molecules.

Cyclic hypervalent iodane reagents, especially benziodoxoles, have been an extraordinary increase in the use of group-transfer reagents in organic synthesis.[3] Essentially, nitrogen-containing iodane(III) reagents, possessing specific steric and electronic properties, are of particular importance in medicinal chemistry[3a,4]. In recent years, extensive studies of the benziodoxole-based hypervalent iodane reagents containing I-N bonds achieved great success to construct C-N bonds with step and atom economy[5].

[a] Y. Zhang, J. Lu, T-L. Lan, Prof. Dr. S –L. Cheng, Prof. Dr. W. Liu
College of Science & Material Science & Chemical Engineering
Institute, Tianjin University of Science and Technology, Tianjin 300457, P. R. China.
E-mail: liuwei2006@tust.edu.cn
[b] Y. Zhang, J. Lu, T-L. Lan, Prof. Dr. C. Chen
Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education, MOE), Department of Chemistry.
Tsinghua University, Beijing 100084, China
E-mail: chenchao01@mails.tsinghua.edu.cn
[c] Prof. Dr. C. Chen
State Key Laboratory of Elemento-Organic Chemistry
Nankai University, Tianjin 300071, China
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In 2002, Zhdankin's group reported the preparation of the complexes of benziodoxole with aromatic amines, which are useful as mild electrophiles and selective oxidizing reagents[6]. In 2015, Kiyokawa and co-workers disclosed a protocol for preparing the hypervalent iodane reagents including a phthalimidate group, which could be applicable for use in the oxidative amination[7]. In 2017, Bolm's group demonstrated a range of sulfoximidoyl-containing hypervalent iodane reagents and developed a photocatalytic addition of this hypervalent iodane reagents to styrenes[8]. Recently, our group investigated a series of bench-stable carbazole-containing hypervalent iodane reagents to introduce a carbazole group to aromatic heterocycle compounds[9]. (Scheme 2A)

Cyclic hypervalent iodanes, as electrophilic amination reagents, have attracted significant interest for organic synthesis recently[10]. It is known that C-N bonds are usually formed by the nucleophilic attack of a nitrogen to an electrophilic carbon previously bonded to a leaving group in a typical S_N2 type of reaction[11]. The reverse process in which the reagent for this "electrophilic amination" can provide an electron deficient nitrogen group, " N^+ " is interesting because of the synthetic possibilities it opens. Furthermore, electrophilic nitrogen sources are an increasingly popular class of reagents for the formation of C–N bonds[12]. Although the aforementioned nitrogen-containing hypervalent iodane reagents have been well-explored, the N-atom is commonly required to be protected, such as phenyl, acyl, p-toluenesulfonyl and Phthaloyl. To the best of our knowledge, the preparation, structure and reactivity of the aliphatic aminobenziodoxole has never been documented to date. Herein, we reported on the preparation and X-ray structural characterization of aliphatic amino iodane (III) reagents. These new reagents are stable compound soluble in dichloromethane and dimethyl sulfoxide and can be used for the Cu-catalyzed directed electrophilic amination of aryl amines (Scheme 2B).

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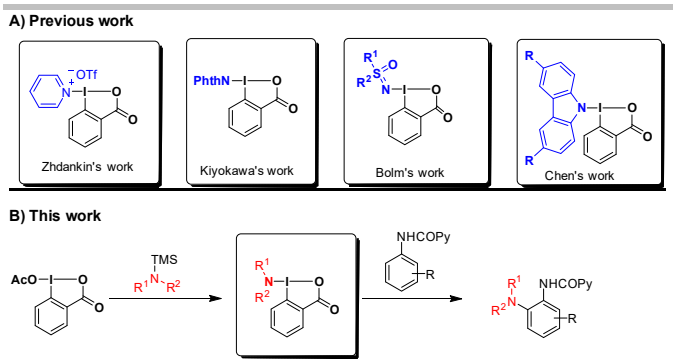
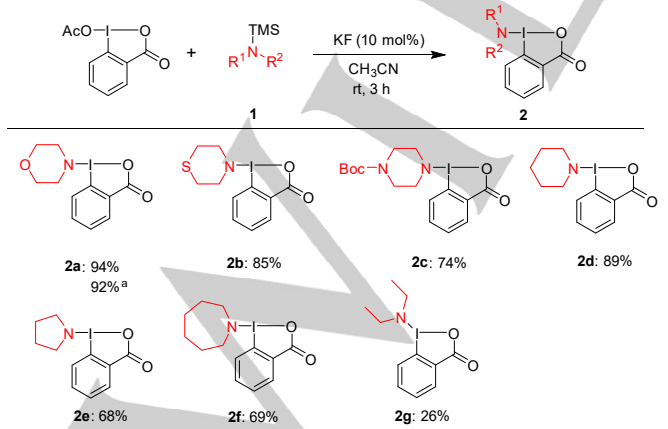


Scheme 2. Recently developed amino-containing hypervalent iodane reagents.

Results and Discussion

In the attempt to prepare a new type of amino-containing hypervalent iodane reagents, we managed initially with morpholine bearing NH group as substrates to react with acetoxybenziodoxolone for the preparation of 1-morpholino-1, 2-benzo[*d*]iodaoxol-3-(1H)-one **2a**. Unfortunately, our attempt along this line was unsuccessful. Encouraged by our group work on carbazole-substituted hypervalent iodane reagents,[9] N-TMS-Morpholine was applied as the amine source next. However, with 10 mol% KF as an additive, acetoxybenziodoxolone and **1a** were carried out in dry CH_3CN and stirred for 24 h at room temperature, and compound **2a** remained inaccessible, as well as the color of the reaction solution turned grey. We speculated that excessive reaction time caused decomposition of the product. Following this, it was found that the change of color of the reaction from yellowish to orange was observed and the color was held on for a while. It might be mentioned that this color did not change any more indicating the end of the reaction. The total time needed for the complete reaction was about 3 hours. Product **2a** was isolated in the form of a yellowish solid by filtration from the reaction mixture and washing with acetonitrile and ether. Meanwhile, it was characterized by ^{1}H and ^{13}C spectroscopy. To our delight, the desired hypervalent iodane product **2a** was obtained in 94% yield. Moreover, hypervalent iodane reagents containing five-, six-, seven-membered cyclic amines all proceed smoothly to afford the desired products in good yields (Scheme 3).



Scheme 3. Scope of amino-containing hypervalent iodane reagents. Reaction conditions: **1** (3.0 mmol), acetoxybenziodoxolone (3.0 mmol), KF (10 mol%), in CH_3CN (5 mL) at room temperature. [a]10 mmol scale.

Of note, the reaction was amenable to scale-up without loss of its yield when the reaction was performed in 92% yield in 10 mmol scale. This method was also identified for the preparation of aliphatic amino iodane(III) reagent **2g** by using *N*-TMS-Et_2N as the amine source, although the yield was not satisfactory. Gratifyingly, all iodane(III) reagents could be stored for one year or more if held at a temperature of 0-5 ℃.

Complexes **2a-2g** were characterized by ^{1}H and ^{13}C NMR spectroscopy. The structure of **2d** was unambiguously established by a single-crystal X-ray analysis (Figure 1). In particular, structural data revealed a distorted T-shaped geometry expected for hypervalent iodane with an endocyclic C-I-O bond angle of 74.6 (5) ° and N-I-O bond angle of 164.7(5) °. The length of bonds to the iodine atom, I-N 2.093(11) Å, I-O 2.369(13) Å, I-C 2.132(14) Å, are all within the range of typical single covalent bonds in organic derivatives of polyvalent iodane[13].

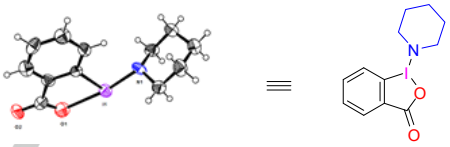
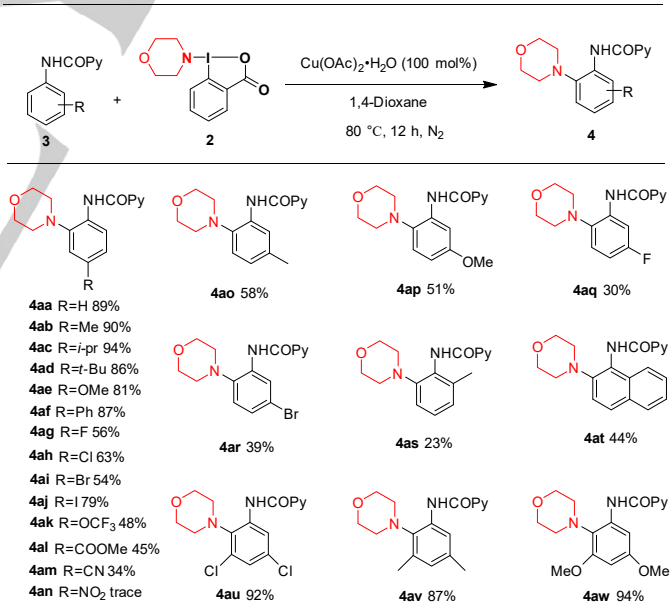


Figure 1. Single-crystal X-ray diffraction structure of **2d**. The thermal ellipsoids are shown at the 35% probability level. (CCDC 1970681)

Table 1. The scope of substrate **3**. [a, b]



[a] Reaction condition: **3** (0.2 mmol), **2** (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$(100 mol%), in 1,4-Dioxane (4 mL) at 80 °C for 12 h. [b] isolated yield.

After successful synthesis of these nitrogen-containing iodane(III) reagents **2**, the direct amination reactions on C-H bonds were explored. We chose the easily available aniline **3a** and amino-containing iodine(III) **2a** as model substrates to explore the optimized reaction conditions.[17] Having established the optimal reaction conditions (see SI), the scope of substrate was investigated to test the generality and limitations of this electrophilic amination. As shown in Table 1, aniline moieties

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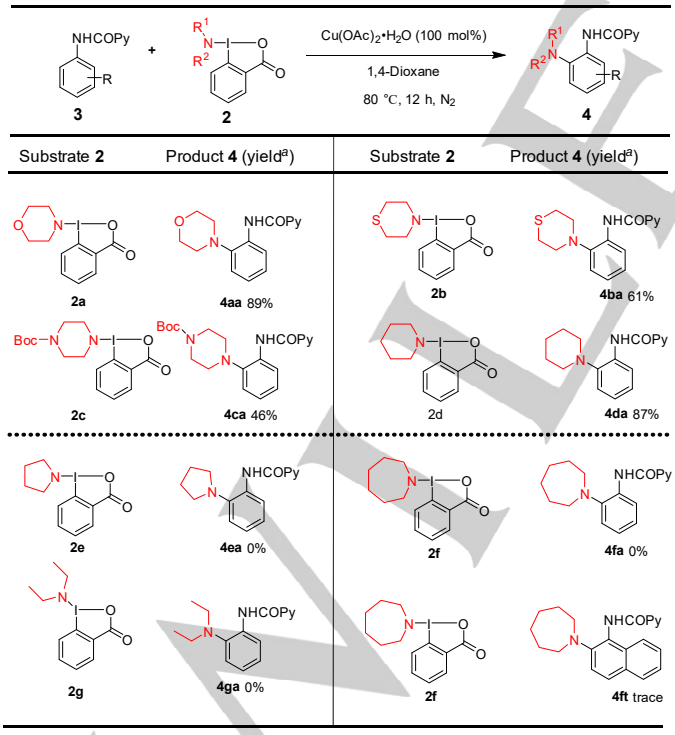
containing electron-rich and electron-deficient substrates were first employed to react with substrate **2a**. Notably, diverse functional groups in different positions were well-tolerated under the standard reaction conditions. As expected, electron-rich substrates furnished better yields than electron-deficient anilines. Electron-donating methyl, isopropyl, *t*-butyl, methoxy, phenyl groups at the *para* position (**3b-3f**) provided good yields and moderately electron-deficient halogen (F, Cl, Br, I) substituents at the same position gave moderate yields (**3g-3j**). Strongly electron-withdrawing group, such as trifluoromethoxy, ester, cyano, nitro, afforded generally lower yields (**3k-3n**) as a result of lower conversion. Methyl, methoxy, fluoro, bromo substitution at the *meta* position afforded lower yields (**3o-3r**) than their corresponding *para* substituted counterparts. The amination is proved to be sensitive toward steric encumbrance near the targeted C-H bond: the less hindered *ortho* position was preferentially aminated in the case of substrates bearing a *meta* substituent, while the 1-naphthyl derivative was aminated at C2 (**3t**). The presence of a substituent at the *ortho* position reduced reactivity (**3s**), presumably because of increased steric encumbrance. *Meta*-dimethoxy, *meta*-dichloro and *meta*-dimethyl-substituted anilines gave excellent yields (**3u-3w**).

Following amination of six-membered cyclic amine morpholine-benziodoxoles, we turned our attention to explore the reactivity of other hypervalent iodane reagents and 2-picolinamide protected aniline **3a** was chosen as model substrate (Table 2).

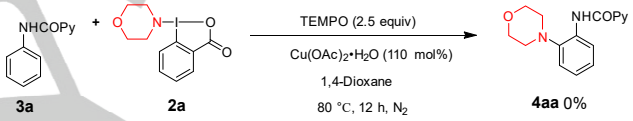
Table 2. Scope of the hypervalent iodane reagents **2**.[a, b]



[a] Reaction condition: **3** (0.2 mmol), **2** (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$(100 mol%), in 1,4-Dioxane (4 mL) at 80 °C for 12 h. [b] isolated yield.

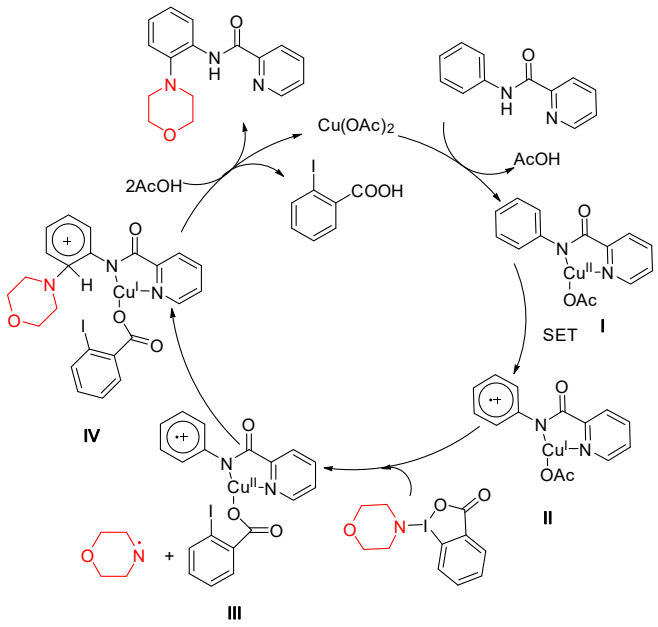
Gratifyingly, other six-membered cyclic aminobenziodoxoles, such as thiomorpholine, piperidine and *N*-Boc-protected piperazine also provided the *o*-position amination products in moderate to high yields (**2a-2d**). Unfortunately, besides six-membered cyclic aminobenziodoxoles, this method is not applicable for five-, seven-membered cyclic aminobenziodoxoles and diethylaminobenziodoxoles (**2e-2g**). Switching from 2-picolinamide protected aniline **3a** to 2-picolinamide protected naphthylamine **3t**, reacted with seven-membered cyclic aminobenziodoxoles to afford trace amount of desired product. Only hypervalent iodine reagents containing a six-membered amino group could be used in the amination and this might be attributed to their better stability than other hypervalent iodine reagents.

In order to gain insight into the mechanism of Cu-catalyzed directed electrophilic amination of aryl amines with amino-containing iodane(III) reagent, a control experiment, radical inhibition was conducted (Scheme 4). The reaction was completely suppressed when 2.5 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added, implying that a radical reaction pathway might be involved in the transformation. This observation is also consistent with a SET mechanism.



Scheme 4. Control experiments

From this control experiment and previous literature reports [14], a plausible mechanistic cycle was proposed. Initial coordination of copper with bidentate 2-picolinamide may generate complex I. Subsequently, one-electron reduction of complex I lead to the formation of copper(I) complex II. Followed by ligand exchange, deprotonation, may provide the desired product and copper(II) for the subsequent runs (Scheme 5) .



Scheme 5. Proposed mechanism.

Conclusions

In conclusion, the 1-amino-1, 2-benziodoxoles have been prepared with acetoxybenziodazole and various *N*-TMS-amino via a rapid and efficient N-I coupling reaction. These new hypervalent iodane reagents show relative stability in both solid state and solution, and the structure of which was established by single-crystal X-ray diffraction. Of importance, employing readily accessible 2-picolinamide in the presence of copper salt, amino-containing iodane(III) reagents, so-called aminobenziodazole, served as electrophilic amination reagents, providing *o*-position amination products in moderate to high yields. Thus, we anticipate that the electrophilic amination reagents will be highly applicable in scientific research.

Experimental Section

General Comments: All commercial reagents were used as received unless otherwise noted. Solvents were dried using standard methods and distilled before use. Column chromatography was performed on silica gel (particle size 10-40μm). Unless otherwise stated, all reactions were carried out in oven-dried glassware under an atmosphere of N_2 and were monitored by TLC. ^{1}H and ^{13}C spectra were recorded on a JEOL AL-400 MHz spectrometer frequency in $CDCl_3$ and CD_3SOCD_3 solvent using TMS as the internal standard. Chemical shift (δ) were given in ppm, referenced to the residual proton resonance of $CDCl_3$ (7.26) or DMSO-d_6 (2.54), to the carbon resonance of $CDCl_3$ (77.16) or DMSO-d_6 (40.45). Multiplicities are recorded as: s=singlet, d=doublet, t=triplet, dd=doublet of doublets, m=multiplet. Coupling constants, J were reported in Hertz unit (Hz). HRMS (m/z) were measured using ESI mode.

General procedure for the preparation of N-TMS-amino 1a-1f. A 100 mL sealed tube containing a stir bar was added anhydrous DCM (20 mL), then alicyclic amines (10 mmol 1.0 equiv) was added under nitrogen atmospere. Solution was cooled down to 0℃ in an ice bath and Et_3N (20 mmol, 2.8 mL, 2.0 equiv) was added and stirred at 0 ℃ for 0.5 h, then trimethylchlorosilane (12 mmol, 1.51 mL, 1.2 equiv) was added dropwise into the cooled solution. The reaction micture was stirred at room temperature for overnight. After completion, the solvent and excess trimethylchlorosilaneand was remove under reduced pressure. Then, hexane (20 mL) was added to the residue and the mixture was stirred for 0.5 h. Then the mixture was filtered and washed with hexane (10 mL×2). The filtrate was concentrated by rotary evaporation to give the desired product (**1a-1f**).

General procedure for the preparation of amino-hypervalent iodane reagents. To a sealed tube was charge with 1-acetoxy-1,2-benziodoxol-3-(1H)-one (3.0 mmol, 0.92 g) and KF (0.3 mmol, 17.4 mg). Then the tube was evacuated and recharged with N_2 for three times and dry CH_3CN (5 mL) and *N*-TMS-amino **1** (3.0 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. It should be mentioned that the excessive reaction time causes decomposition of the product. After completion, the desired products was isolated in the form of a yellowish or white solid by filtration from the reaction mixture and washing with acetonitrile (5 mL×2) and ether (5 mL×2). The solid compounds were stored at 4 °C.

General procedure for the *ortho* amination of picolinamide. In a 25mL sealed tube containing a star bar was added corresponding picolinamide (0.1 mmol, 1.0 equiv), amino-hypervalent iodine reagent (0.25 mmol, 2.5 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol, 1.0 equiv). Then 1, 4-dioxane (1.0 mL) was added and the mixture was stirred at 80 ℃ for 12 h. After cooling to room temperature, the mixture was extracted with EtOAc (5 mL×3) and washed with saturated aq. $NaHCO_3$ solution (5 mL×3), followed by brine solution (5 mL×3) and dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The resulting residue was purified by silica gel flash chromatography (petroleum ether/EtOAc) to afford the desired ortho aminated product.

1-morpholino-1, 2-benzo[*d*]iodaoxol-3-(1H)-one (2a). Yellowish solid, yield: (0.94 g, 94%); mp: 132-134 ℃; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.21 (d, *J* = 8.2 Hz, 1H), 8.03 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.94 – 7.85 (m, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 3.71 (t, *J* = 4.5 Hz, 4H), 3.51 (d, *J* = 4.5 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.58, 134.18, 133.50, 132.07, 130.74, 126.28, 117.72, 69.28, 56.35; ESI-HRMS: m/z calcd for $C_{11}H_{12}INO_3$ $[M+Na]^+$: 355.9753; found: 355.9754.

1-thiomorpholino-1, 2-benzo[*d*]iodaoxol-3-(1H)-one (2b). Yellowish solid yield: (0.89 g, 85%); mp: 131-133 ℃; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.07 – 6.97 (m, 1H), 3.21 – 3.13 (m, 4H), 2.80 – 2.74 (m, 4H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.56, 134.24, 133.37, 132.06, 130.72, 126.23, 118.00, 58.09, 30.00; ESI-HRMS: m/z calcd for $C_{11}H_{12}INO_2S$ $[M+Na]^+$: 371.9631; found: 371.9635.

Tert-butyl-4-(1, 2-benzo[*d*]iodaoxol-3-(1H)-yl) piperazine-1-carboxylate (2c). White solid, yield: (0.96 g, 74%); mp: 135-137 ℃; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.98 (td, *J* = 9.3, 8.3, 2.8 Hz, 1H), 7.85 (td, *J* = 7.8, 1.7 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 3.19 (s, 8H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.54, 154.51, 134.22, 133.41, 132.06, 130.76, 126.33, 117.74, 79.63, 55.72, 28.57; ESI-HRMS: m/z calcd for $C_{16}H_{21}IN_2O_4$ $[M+Na]^+$: 455.0433; found: 455.0438.

1-(piperidin-1-yl)-1, 2-benzo[*d*]iodaoxol-3-(1H)-one (2d). White solid, yield: (0.88 g, 89%); mp: 107-111 ℃; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.28 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 3.56 (s, 4H), 1.88 – 1.39 (m, 6H); ^{13}C NMR (101 MHz, Chloroform-d) δ 167.91, 133.64, 132.82, 132.64, 130.57, 125.03, 117.00, 58.05, 29.30, 23.31; ESI-HRMS: m/z calcd for $C_{12}H_{14}INO_2$ $[M+Na]^+$: 354.0067; found: 354.0065.

X-Ray crystal structure analysis of 2d (CCDC number: 1970681). Single Crystal suitable for XRD was obtained from a solution in DCM/PE. Formula: $C_{12}H_{14}INO_2$, M = 331.14, Colorless crystal, 0.40 x 0.02 x 0.02 mm, a = 25.721(4), b = 25.721(4), c = 9.6397(16), α = 90.00°, β = 90.00°, γ = 120.00° , V = 5523(2) Å^3 , ρ_{calc} = 1.792 gcm^{-3} , μ = 20.392 mm^{-1} , Z = 18, triclinic, space group P-1, λ = 1.54184 Å, T = 173 K. Data completeness=0.953, Theta(max)=75.178, R(reflections)=0.0918(1329), wR2(reflections)= 0.2923(2423).

1-(pyrrolidin-1-yl)-1, 2-benzo[*d*]iodaoxol-3-(1H)-one (2e). Yellowish solid, yield: (0.66 g, 68%); mp: 92-96 ℃; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.98 (d, *J* = 7.3 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.75 (m, 1H), 7.60 (t, *J* = 7.3 Hz, 1H), 3.47 (s, 4H), 1.84 – 1.68 (m, 4H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.46, 134.00, 133.76, 131.91, 130.68, 126.00, 117.88, 56.54, 26.41; ESI-HRMS: m/z calcd for $C_{11}H_{12}INO_2$ $[M+Na]^+$: 339.9913; found: 339.9919.

1-(azepan-1-yl)-1, 2-benzo[*d*]iodaoxol-3-(1H)-one (2f). Yellowish solid, yield: (0.71 g, 69%); mp: 87-90 ℃; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.03 – 7.91 (m, 2H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 3.65 (d, *J* = 38.4 Hz, 4H), 1.61 (s, 8H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.44, 134.05, 133.74, 132.09, 130.72, 125.90, 118.77, 60.14, 32.09, 27.01; ESI-HRMS: m/z calcd for $C_{13}H_{16}INO_2$ $[M+Na]^+$: 368.0225; found: 368.0228.

1-(diethylamino)-1, 2-benzo[*d*]iodaoxol-3-(1H)-one (2g). Orange soild, yield: (0.25 g, 26%); mp: 82-84 ℃; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 2.85 (q, *J* = 7.3 Hz, 4H), 1.19 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 172.12, 148.21, 139.29, 128.94, 128.54, 127.95, 93.84, 41.74, 11.94; ESI-HRMS: m/z calcd for $C_{11}H_{14}INO_2$ [M+Na]$^+$: 342.0096; found: 342.0097.

***N*-(2-morpholinophenyl)picolinamide (4aa)[14c],[15],[16],[17].** White solid, yield: 89%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.14 (s, 1H), 8.65 (d, *J* = 4.6 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.27 – 7.13 (m, 2H), 7.11 (d, *J* = 7.1 Hz, 1H), 4.02 – 3.94 (m, 4H), 2.99 – 2.92 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.97, 150.59, 148.31, 141.95, 137.68, 133.10, 126.41, 125.40, 124.17, 122.47, 120.17, 119.68, 67.71, 52.53.

***N*-(4-methyl-2-morpholinophenyl)picolinamide (4ab)[17].** White solid, yield: 90%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.03 (s, 1H), 8.64 (d, *J* = 4.6 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.89 (t, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 7.4, 4.8 Hz, 1H), 7.05 – 6.90 (m, 2H), 3.97 (t, *J* = 4.5 Hz, 4H), 2.94 (t, *J* = 4.4 Hz, 4H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.74, 150.69, 148.28, 141.88, 137.64, 133.86, 130.43, 126.30, 125.76, 122.40, 120.80, 119.55, 67.72, 52.55, 21.30.

***N*-(4-isopropyl-2-Morpholinophenyl)picolinamide (4ac)[17].** White solid, yield: 94%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.03 (s, 1H), 8.64 (d, *J* = 4.8 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.94 – 7.81 (m, 1H), 7.53 – 7.40 (m, 1H), 7.06 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 4.06 – 3.61 (m, 4H), 2.96 (t, *J* = 4.5 Hz, 4H), 2.91 – 2.81 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.73, 150.70, 148.28, 145.05, 141.93, 137.62, 130.70, 126.29, 122.99, 122.40, 119.63, 118.13, 67.73, 52.57, 34.06, 24.19.

***N*-(4-(*tert*-butyl)-2-Morpholinophenyl)picolinamide (4ad)[17].** White solid, yield: 86%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.04 (s, 1H), 8.64 (d, *J* = 4.3 Hz, 1H), 8.50 – 8.43 (m, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.50 – 7.38 (m, 1H), 7.23 – 7.15 (m, 2H), 3.97 (t, *J* = 4.4 Hz, 5H), 3.06 – 2.77 (m, 4H), 1.31 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.76, 150.70, 148.29, 147.31, 141.60, 137.62, 130.45, 126.29, 122.40, 122.14, 119.25, 117.00, 67.76, 52.58, 34.79, 31.53.

***N*-(4-methoxy-2-morpholinophenyl)picolinamide (4ae)[14c],[15],[17].** White crystalline solid, yield: 81%; ^{1}H NMR (400 MHz, Chloroform-d) δ 10.86 (s, 1H), 8.73 – 8.59 (m, 1H), 8.56 – 8.41 (m, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.45 (t, *J* = 3.8 Hz, 1H), 6.72 (q, *J* = 3.3 Hz, 2H), 3.96 (dd, *J* = 5.5, 3.4 Hz, 4H), 3.80 (d, *J* = 3.3 Hz, 3H), 2.93 (dt, *J* = 4.5, 3.1 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 156.41, 150.68, 148.26, 143.45, 137.64, 126.41, 126.25, 122.32, 120.65, 108.72, 107.34, 67.61, 55.61, 52.42.

***N*-(3-morpholino-[1, 1′-buphenyl]-4-yl)picolinamide (4af)[14c],[17].** White solid, yield: 87%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.16 (s, 1H), 8.65 (d, *J* = 8.2 Hz, 2H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.91 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.51 – 7.46 (m, 1H), 7.43 (t, *J* = 7.4 Hz, 3H), 7.38 (s, 1H), 7.32 (s, 1H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.95, 150.54, 148.34, 142.32, 140.87, 137.71, 137.20, 132.31, 128.90, 127.24, 126.97, 126.46, 124.02, 122.49, 119.93, 118.95, 67.72, 52.60.

***N*-(4-fluoro-2-morpholinophenyl)picolinamide (4ag)[14c],[16].** White solid, yield: 56%; ^{1}H NMR (400 MHz, Chloroform-d) δ 10.90 (s, 1H), 8.64 (d, *J* = 4.6 Hz, 1H), 8.53 (dd, *J* = 8.5, 6.2 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.90 (t, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 7.6, 5.0 Hz, 1H), 6.87 (d, *J* = 9.6 Hz, 2H), 3.97 (t, *J* = 4.5 Hz, 4H), 2.93 (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.77, 160.57, 158.14, 150.37, 148.31, 143.52, 143.45, 137.74, 129.08, 126.49, 122.46, 120.84, 120.76, 111.51, 111.29, 107.82, 107.58, 67.48, 52.31.

***N*-(4-chloro-2-morpholinophenyl)picolinamide (4ah)[16].** Yellow solid, yield: 63%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.00 (s, 1H), 8.64 (d, *J* = 4.6 Hz, 1H), 8.52 (d, *J* = 8.7 Hz, 1H), 8.27 (d, *J* = 7.8 H z, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.48 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 4.16 – 3.83 (m, 4H), 3.04 – 2.84 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.92, 150.24, 148.34, 143.03, 137.77, 131.62, 128.97, 126.59, 125.23, 122.51, 120.74, 120.62, 67.51, 52.36.

***N*-(4-bromo-2-morpholinophenyl)picolinamide (4ai) [14c], [17].** White solid, yield: 54%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.01 (s, 1H), 8.64 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.48 (d, *J* = 8.7 Hz, 1H), 8.28 (d, *J* = 7.7 Hz, 1H), 7.90 (td, *J* = 7.7, 1.8 Hz, 1H), 7.48 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.26 – 7.24 (m, 1H), 4.12 – 3.83 (m, 4H), 3.05 – 2.83 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.95, 150.25, 148.34, 143.23, 137.77, 132.14, 128.24, 126.60, 123.67, 122.52, 120.99, 116.55, 67.52, 52.40.

***N*-(4-iodo-2-morpholinophenyl)picolinamide (4aj)[14c],[16].** White crystalline, yield: 79%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.03 (s, 1H), 8.65 (d, *J* = 4.7 Hz, 1H), 8.35 (d, *J* = 8.7 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.91 (t, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 1.7 Hz, 1H), 3.97 (t, *J* = 4.5 Hz, 4H), 2.93 (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.97, 150.25, 148.33, 143.30, 137.77, 134.35, 132.92, 129.55, 126.60, 122.52, 121.33, 87.14, 67.52, 52.41.

***N*-(2-morpholino-4-(trifluoromethoxy)phenyl)picolinamide (4ak)[14c].** White solid, yield: 48%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.00 (s, 1H), 8.65 (d, *J* = 4.8 Hz, 1H), 8.59 (d, *J* = 9.0 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.91 (td, *J* = 7.8, 1.6 Hz, 1H), 7.49 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 4.12 – 3.86 (m, 4H), 3.07 – 2.77 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.99, 150.18, 148.35, 145.23, 143.10, 137.78, 131.71, 126.64, 122.55, 120.36, 117.64, 113.57, 67.47, 52.30.

methy 3-morpholino-4-(picolinamido)benzoate(4al)[14c],[16],[17]. White solid, yield: 45%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.30 (s, 1H), 8.86 – 8.50 (m, 2H), 8.29 (d, *J* = 8.1 Hz, 1H), 7.90 (t, *J* = 6.7 Hz, 2H), 7.84 (s, 1H), 7.50 (s, 1H), 3.99 (dt, *J* = 6.2, 3.0 Hz, 4H), 3.89 (d, *J* = 2.3 Hz, 3H), 2.97 (dd, *J* = 6.0, 2.9 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 166.81, 162.31, 150.12, 148.39, 141.62, 137.80, 137.32, 127.42, 126.75, 125.47, 122.64, 121.72, 118.81, 67.60, 52.47, 52.16.

***N*-(4-cyano-2-morpholinophenyl)picolinamide (4am)[14c][17].** White solid, yield: 34%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.26 (s, 1H), 8.71 (d, *J* = 8.6 Hz, 1H), 8.66 (d, *J* = 4.9 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.93 (td, *J* = 7.7, 1.7 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.40 (d, *J* = 1.8 Hz, 1H), 4.00 (dd, *J* = 5.2, 3.4 Hz, 4H), 2.96 (dd, *J* = 5.1, 3.4 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 162.41, 149.72, 148.44, 142.11, 137.94, 137.33, 129.90, 127.01, 124.02, 122.74, 119.69, 119.10, 106.92, 67.42, 52.27.

***N*-(2-morpholino-4-nitrophenyl)picolinamide (4an).** Yellow solid, yield: trace; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.34 (s, 1H), 8.77 (dd, *J* = 9.1, 2.9 Hz, 1H), 8.67 (d, *J* = 4.0 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 8.11 (dd, *J* = 9.0, 2.6 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.97 – 7.92 (m, 1H), 7.58 – 7.49 (m, 1H), 4.01 (dd, *J* = 5.6, 3.2 Hz, 4H), 3.03 – 2.98 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.56, 150.25, 148.36, 143.09, 137.76, 131.52, 128.96, 126.56, 125.21, 122.55, 120.73, 120.62, 67.53, 52.34. ESI-HRMS: m/z calcd for $C_{16}H_{16}N_4O_4$ [M+H]$^+$: 329.1174; found: 329.1146.

***N*-(5-methyl-2-morpholinophenyl)picolinamide (4ao)[16].** Yellow solid, yield: 58%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.14 (s, 1H), 8.64 (d, *J* = 5.0 Hz, 1H), 8.43 (d, *J* = 1.9 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 3.96 (m, 4H), 2.91 (m, 4H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.93, 150.68, 148.31, 139.53, 137.66, 133.34, 132.90, 126.36, 124.67, 122.43, 120.21, 120.01, 67.75, 52.69, 21.47.

***N*-(5-methoxy-2-morpholinophenyl)picolinamide (4ap)[16].** Brown solid, yield: 51%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.85 (s, 1H), 8.67 (td, *J* = 7.4, 6.1, 3.0 Hz, 1H), 8.27 (dd, *J* = 11.6, 8.0 Hz, 2H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.88 (td, *J* = 7.8, 2.0 Hz, 1H), 7.48 (dd, *J* = 7.5, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 4.00 – 3.93 (m, 4H), 3.84 (s, 4H), 3.74 – 3.57 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ162.35, 158.45, 150.74, 148.39, 137.59, 133.63, 133.15, 128.13, 126.32, 122.49, 111.58, 107.17, 68.39, 55.34, 50.41.

***N*-(5-fluoro-2-morpholinophenyl)picolinamide (4aq)[16].** White solid, yield: 30%; ^{1}H NMR (600 MHz, Chloroform-d) δ 11.27 (s, 1H), 8.70 – 8.64 (m, 1H), 8.39 (dd, *J* = 10.9, 3.0 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.96 – 7.88 (m, 1H), 7.24 – 7.16 (m, 1H), 7.12 (dd, *J* = 8.8, 5.2 Hz, 1H), 4.06 – 3.99 (m, 1H), 4.01 – 3.96 (m, 4H), 2.95 – 2.90 (m, 4H); ^{13}C NMR (151 MHz, Chloroform-d) δ162.23, 150.19, 148.41, 141.97, 137.80, 133.48, 128.11, 126.66, 122.61, 121.43, 121.37, 110.27, 67.72, 52.78.

***N*-(5-bromo-2-morpholinophenyl)picolinamide (4ar)[14c],[15].** White solid, yield: 39%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.09 (s, 1H), 8.78 (d, *J* = 2.3 Hz, 1H), 8.64 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.8, 1.7 Hz, 1H), 7.48 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.29 – 7.11 (m, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 4.14 – 3.78 (m, 4H), 2.91 (dd, *J* = 5.7, 3.4 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 162.02, 150.15, 148.36, 140.86, 137.78, 134.29, 126.94, 126.65, 122.57, 122.49, 121.64, 118.58, 67.57, 52.41.

***N*-(2-methyl-6-morpholinophenyl)picolinamide (4as)[14c],[16],[17].** White solid, yield: 23%; ^{1}H NMR (400 MHz, Chloroform-d) δ 10.02 (s, 1H), 8.66 (d, *J* = 4.4 Hz, 1H), 8.27 (dd, *J* = 7.7, 3.3 Hz, 1H), 7.94 – 7.86 (m, 1H), 7.48 (dd, *J* = 7.7, 4.2 Hz, 1H), 7.21 – 7.12 (m, 1H), 7.03 (dd, *J* = 7.8, 2.9 Hz, 1H), 6.93 (dd, *J* = 7.9, 3.1 Hz, 1H), 3.74 (t, *J* = 4.5 Hz, 4H), 2.95 – 2.78 (m, 4H), 2.33 (d, *J* = 3.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 162.45, 148.32, 147.29, 137.61, 135.98, 126.83, 126.54, 126.49, 122.68, 116.65, 67.50, 52.29, 19.62.

***N*-(2-morpholinonaphthalen-1-yl)picolinamide (4at)[14c],[15],[16],[17].** Light brown crystalline solid, yield: 44%; ^{1}H NMR (400 MHz, Chloroform-d) δ 10.28 (s, 1H), 8.71 (d, *J* = 4.8 Hz, 1H), 8.34 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.55 – 7.49 (m, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 3.83 – 3.76 (m, 4H), 2.99 (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 163.49, 150.09, 148.38, 144.18, 137.72, 131.26, 129.72, 128.11, 128.05, 126.65, 126.31, 126.27, 125.02, 124.61, 122.87, 118.67, 67.57, 52.15.

***N*-(3, 5-dichloro-2-morpholinophenyl)picolinamide (4au)[15].** White solid, yield: 92%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.81 (s, 1H), 8.67 (dd, *J* = 8.1, 3.7 Hz, 2H), 8.27 (d, *J* = 7.8 Hz, 1H), 8.05 – 7.81 (m, 1H), 7.64 – 7.40 (m, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 4.08 – 3.91 (m, 4H), 3.81 (dd, *J* = 11.5, 3.4 Hz, 2H), 2.65 (d, *J* = 11.6 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-d) δ 162.40, 150.01, 148.41, 138.80, 137.80, 134.81, 133.26, 126.79, 124.82, 122.67, 117.69, 68.10, 49.39.

***N*-(3, 5-dimethyl-2-morpholinophenyl)picolinamide (4av)[16].** White solid, yield: 87%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.74 (s, 1H), 8.65 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.35 (d, *J* = 2.0 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 7.93 – 7.81 (m, 1H), 7.44 (dd, *J* = 7.5, 4.7 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 4.04 (dd, *J* = 11.1, 2.4 Hz, 2H), 3.92 (dd, *J* = 10.9, 2.9 Hz, 2H), 3.59 – 3.43 (m, 2H), 2.71 (d, *J* = 11.8 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 162.02, 150.84, 148.24, 137.62, 136.77, 136.20, 136.04, 135.39, 127.40, 126.28, 122.41, 117.43, 68.27, 50.27, 21.46, 19.57.

***N*-(3, 5-dimethoxy-2-morpholinophenyl)picolinamide (4aw)[14c],[15],[16].** White solid, yield: 94%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.85 (s, 1H), 8.66 (d, *J* = 4.7 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 2.6 Hz, 1H), 7.91 – 7.82 (m, 1H), 7.45 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.21 (d, *J* = 2.7 Hz, 1H), 3.91 (d, *J* = 1.9 Hz, 4H), 3.83 (s, 3H), 3.79 (s, 3H), 3.60 (ddd, *J* = 11.7, 9.7, 5.0 Hz, 2H), 2.59 (d, *J* = 11.8 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-d) δ 162.36, 159.03, 158.95, 150.74, 148.39, 137.57, 137.35, 126.32, 122.34, 121.61, 95.28, 95.20, 68.46, 55.64, 55.25, 50.72.

***N*-(2-thiomorpholinophenyl)picolinamide (4ba)[15].** Yellow solid, yield: 61%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.07 (s, 1H), 8.68 (dt, *J* = 4.8, 1.3 Hz, 1H), 8.58 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.22 – 7.12 (m, 2H), 7.12 – 7.05 (m, 1H), 3.24 – 3.10 (m, 4H), 2.95 (d, *J* = 6.3 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-d) δ 162.01, 150.58, 148.36, 143.18, 137.66, 133.09, 126.41, 125.51, 124.10, 122.49, 120.91, 119.63, 54.65, 28.86.

***tert*-butyl 4-(2-(picolinamido)phenyl)piperazine-1-carboxylate (4ca)[14c],[15],[16].** White solid, yield: 46%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.09 (s, 1H), 8.65 (d, *J* = 4.6 Hz, 1H), 8.58 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.95 – 7.85 (m, 1H), 7.47 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 7.16 – 7.05 (m, 2H), 3.70 (s, 4H), 2.89 (t, *J* = 4.9 Hz, 4H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-d) δ 161.98, 154.88, 150.56, 148.37, 141.99, 137.67, 133.02, 126.39, 125.43, 124.13, 122.48, 120.18, 119.72, 52.12, 28.55.

***N*-(2-(piperdin-1-yl)phenyl)picolinamide (4da)[14c],[15],[16],[17].** White solid, yield: 87%; ^{1}H NMR (400 MHz, Chloroform-d) δ 11.13 (s, 1H), 8.65 (d, *J* = 4.6 Hz, 1H), 8.57 (d, *J* = 7.9 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.14 (dt, *J* = 9.6, 3.6 Hz, 2H), 7.08 (d, *J* = 7.3 Hz, 1H), 3.12 – 2.57 (m, 4H), 1.84 (p, *J* = 5.6 Hz, 4H), 1.62 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-d) δ 148.26, 143.75, 137.51, 133.10, 126.19, 124.62, 123.96, 122.39, 120.15, 119.43, 53.81, 26.83, 24.43.

The Supporting Information file contains the experimental steps and ^{1}H, ^{13}C, spectrum of compounds **2a-2g** and **4aa-4aw**, X-ray crystal spectra of compounds **2d** and optimized reaction conditions.

CCDC 1970681 (for **2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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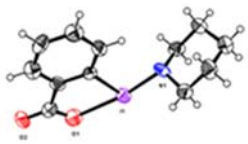

The preparation and X-ray structural characterization of aliphatic amino iodane (III) reagents has been realized. These new reagents could be used for the Cu-catalyzed directed electrophilic amination of aryl amines.

Yue Zhang, Jing Lu, TianLei Lan, Shaoling Cheng, Wei Liu, Chao Chen*.*

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Preparation, characterization, and reactivity of aliphatic amino iodane(Ⅲ) reagents