Copper-Catalyzed Electrophilic Amination of ArylZinc Pivalates mediated by N-based Hypervalent Iodine(III) Reagents

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Abstract:

We describe a new Cu-catalyzed electrophilic amination of stable polyfunctional organozinc compounds using new hypervalent iodine reagents bearing transferable alkyl and aryl amines. A wide range of aryl, heteroaryl and alkyl amines were prepared, and the method applied to the synthesis of chloroquine drug. The mechanism of the reaction was investigated by DFT calculations.

Keywords: Electrophilic amination • hypervalent iodine compounds • organozinc reagents• secondary amines • aromatic amines
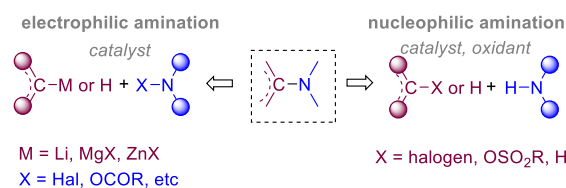
The formation of C–N bond holds a prominent position in organic and medicinal chemistry. The importance of nitrogen-containing molecules is evident from their substantial presence among FDA-approved small-molecule drugs.[1] Among nitrogen-based compounds, aromatic amines comprise a remarkable assortment of building blocks in the synthesis of biologically active natural products, pharmaceuticals, agrochemicals and in material science.[2]

Several successful strategies have been developed to form C–N bonds. In organic synthesis, substitution reactions, reductive amination,[3] and transition-metal (TM)-catalyzed C–N cross-coupling reactions [4] remain as the most commonly utilized methods for C–N bond formation. The synthesis of hetero(aryl) amines has been mostly attained via (TM)-catalyzed C–N cross-coupling reactions,[5] (Scheme 1), particularly by the Buchwald–Hartwig[6] and Ullmann-Goldberg-type[7] couplings. All of these approaches involve nucleophilic sources of nitrogen, which poses problems in the synthesis of complex molecules, e.g. overalkylation of amine nucleophiles, which is often circumvented by the use of protecting groups, requiring additional synthetic steps to introduce a new C–N bond.[8]

These limitations have been addressed by developing umpolung strategies that utilize electrophilic nitrogen sources, offering the ability to functionalize typically unreactive bonds - electrophilic amination [9] (Scheme 1).

The most used N-based electrophiles for substitutions are *N*–chloroamines, [10] oxaziridines [11] and hydroxylamines. [12] While azo compounds [13] and iminomalonates, [14] tend to undergo addition processes, azides [15] and oximes [16] undergo both reaction pathways.
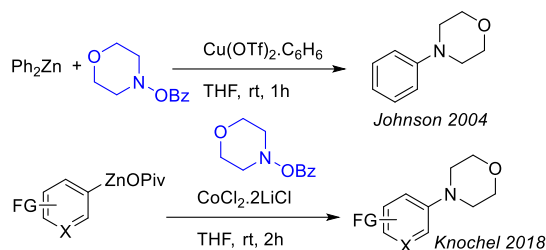
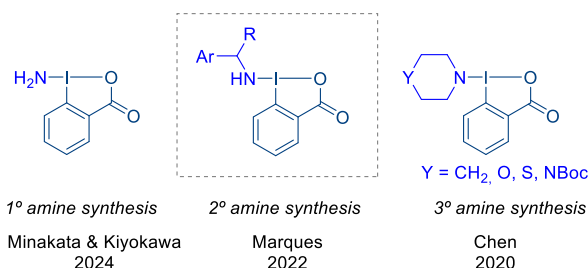**TM-catalysed approaches towards (hetero)aryl amines**

electrophilic amination
catalyst

C–M or H + X–N

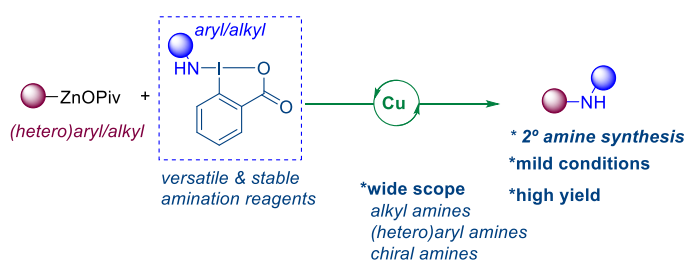M = Li, MgX, ZnX
X = Hal, OCOR, etc

nucleophilic amination
catalyst, oxidant

C–X or H + H–N

X = halogen, OSO$_2$R, H

- - - - - - - - - - - - - Electrophilic Aminating Reagents - - - - - - - - - - - - -

Previous work:

a) O-acyl hydroxylamine with organozinc reagents

Ph$_2$Zn + (morpholine-OBz) →[Cu(OTf)$_2$.C$_6$H$_6$][THF, rt, 1h] (phenylmorpholine)
Johnson 2004

FG—(ring)(X)—ZnOPiv + (morpholine-OBz) →[CoCl$_2$.2LiCl][THF, rt, 2h] FG—(ring)(X)—(morpholine)
Knochel 2018

b) Hypervalent Iodine Reagents

H$_2$N–I(=O)(benzene ring)

Ar–CH(R)–HN–I(=O)(benzene ring)

Y(piperazine)N–I(=O)(benzene ring)
Y = CH$_2$, O, S, NBoc

1° amine synthesis
Minakata & Kiyokawa
2024

2° amine synthesis
Marques
2022

3° amine synthesis
Chen
2020

This work:

aryl/alkyl
HN–I(=O)(benzene ring)

—ZnOPiv +
(hetero)aryl/alkyl

versatile & stable aminating reagents

→[Cu]→ —NH

* 2° amine synthesis
*mild conditions
*high yield

*wide scope
alkyl amines
(hetero)aryl amines
chiral amines

Scheme 1: TM-catalyzed methods for C–N Bond formations: nucleophilic amination and electrophilic amination: previous electrophilic aminations reagents and this work.

Johnson and co-workers reported an alternative electrophilic amination by using O-benzoylhydroxylamine derivatives and diarylzinc reagents to afford tertiary amines under mild conditions.[17] This amination has been extended to organometallic compounds, and despite the impressive progress made, the use of air-sensitive reagents, ligands, or toxic Ni catalysts remains a drawback. Knochel reported a new class of highly functionalized organozinc reagents with enhanced air-and moisture-stability [18] and described the describe the first cobalt-catalyzed electrophilic amination of organozinc pivalates with O−benzoylhydroxylamines (Scheme 1).[19]

In the context of electrophilic amination, cyclic hypervalent iodine reagents (HIRs) have shown great promise due to their stability and high reactivity, commonly associated with metal

reagents, combined with the lower toxicity and costs of main-group elements.[20] Remarkable progress has been made in this field, and these reagents have emerged as powerful tools in electrophilic amination reactions.[21]

Liu and Chen reported the first 1-amino-1,2-benziodoxoles, featuring a secondary amine, and the copper-catalyzed electrophilic amination reagents, providing tertiary aromatic amines.[22] In 2022, our group described the first HIRs bearing a primary amine, which proved to be efficient in the electrophilic a-amination of stabilized enolates.[23] An interesting feature of these new reagents is their ease of purification and stability, since they are prepared on a gram scale from readily available and inexpensive 2-iodobenzoic acid. In parallel with our work, Minakata and Kiyokawa have just reported the use of amino-λ^3-iodanes, including one with an NH_2 group, in the electrophilic amination of arylboronic acids and boronates to give anilines.[24]

We sought to extend this family of HIRs beyond benzylic amines and combine the reactivity of the primary amine-bearing HIR with the versatility of zinc pivalate reagents. Herein, we describe the first copper-catalysed electrophilic amination of aryl/alkyl zinc pivalates with hypervalent iodine reagents containing transferable primary amine groups to afford N-aryl/alkyl amines.

We started our work with the preparation of a series of novel benziodoxolone-derived HIRs (Scheme 2).
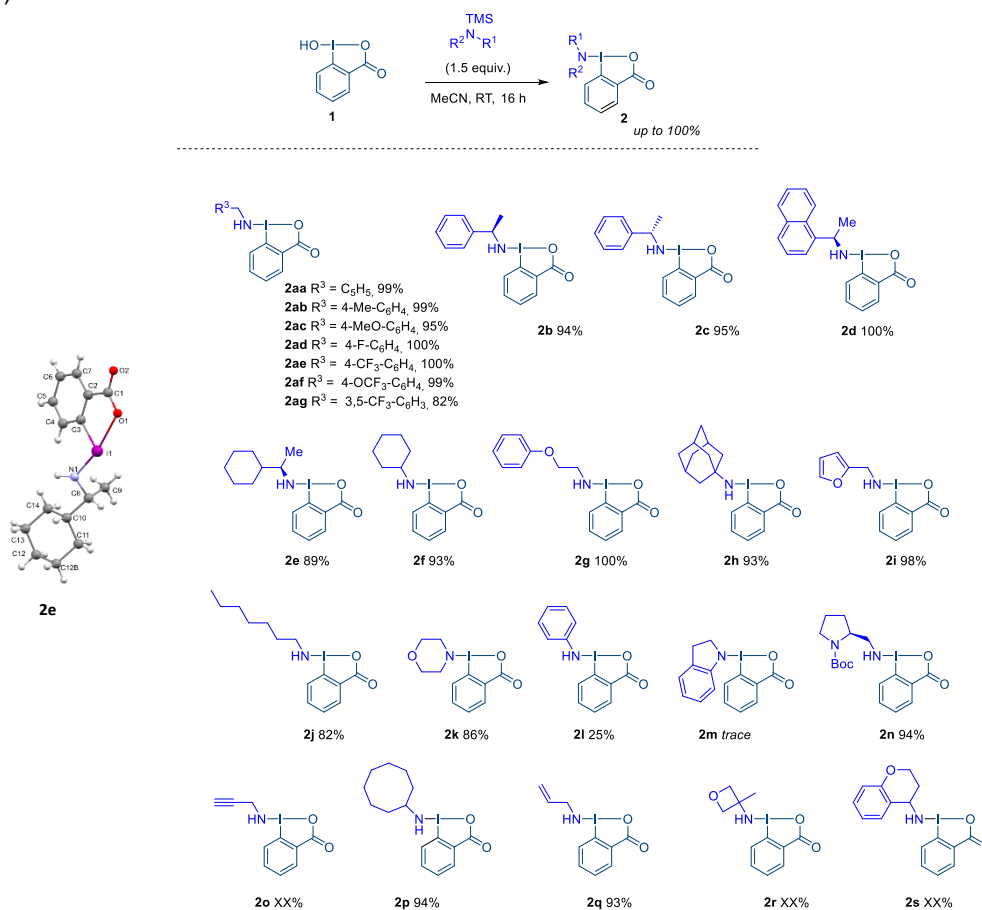

Scheme 2: Synthesis of amino-λ^3-iodanes **2** from silylated amines and hydroxybenziodoxolone **1** in acetonitrile. Yields are isolated yields. ORTEP representation of compound **2e**, using 50% level ellipsoids. One independent molecule of **2e** present in the asymmetric unit was omitted for clarity.

We began by extending the family of iodine(III) reagents to a series of benzylamines substituted with both electron donating and electron withdrawing groups, compounds **2aa-2ag**. We were pleased to find that the same procedure could be applied to non-benzylamines to provide five novel chiral examples, **2c**, **2d**, **2e** and **2o**.

Cyclic and acyclic aliphatic amines were also explored giving compounds **2f**, **2j, 2n** and **2s**. Further amines were explored and HIRs bearing phenoxy (**2g**) and furfuryl (**2i**) functionalities and even bulkier moieties such as adamantyl **2h** were also successfully obtained. Secondary amine morpholine is also an excellent substrate for the reaction (**2k**). Reagents **2f** and **2k, 2o** and **2q** were already known in the literature.[22,24] All the mentioned reagents were prepared by ligand exchange reaction between hydroxybenziodoxolone **1** and the silylated amines in acetonitrile at room temperature. The desired products precipitated from the reaction mixture affording the desired reagents in good to excellent yields. The new primary-amine-bearing hypervalent iodine reagents and corresponding amines were successfully synthesized on the gram-scale and were obtained in high yields. Compound 2e crystallized as the R enantiomer in the monoclinic system, P21 space group, as colourless prisms, with two independent molecules in the asymmetric unit. Similar to previously reported N-bound hypervalent iodine reagents, the X-ray analysis disclosed a distorted T-shaped geometry. The N–I bond length is 2.027(6) Å and 2.041(5) Å for molecules 1 and 2, respectively, being similar to the values reported previously by our group [23]. All the remaining bond lengths and angles are within the expected range for similar compounds [25].

With these novel compounds in hand, our focus then shifted to investigating the reactivity of **2aa** with phenylzinc pivalate **3a**, which was chosen as a model compound for optimization studies (Table 1).

*Table 1: Optimization of reaction conditions for the Cu-catalyzed electrophilic amination of phenylzinc pivalate **3a**.[a] [a] Determined by quantitative ¹H NMR. [b] Isolated yields. [c] Reaction was carried at 80 °C.*
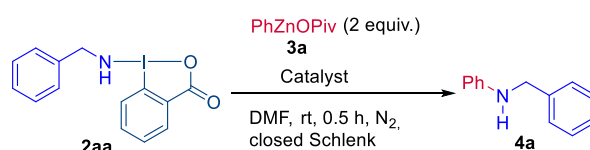
Entry	Catalyst (mol%)	**2aa** (equiv.)	Time (h)	Yield[a] **4a** (%)
1	----	1	24	30[b]
2	----	0.5	24	44
3	----	3	24	13
4	----	0.5	48	43
5[c]	----	0.5	2	32
6	Co(acac)$_2$(10)	0.5	24	20[b]
7	CoCl$_2$ (10)	0.5	24	9
8	Zn(OTf)$_2$ (10)	0.5	1	33
9	Ni(OTf)$_2$ (10)	0.5	1	34
10	CoCl$_2$.2LiCl(10)	0.5	1	59
11	Cu(OTf)$_2$ (10)	0.5	1	78
12	CuCl$_2$ (10)	0.5	1	74

|				
13	CuCl (10)	0.5	1	75
14	Cu(OAc)$_2$ (10)	0.5	1	82
15	**Cu(OAc)$_2$ (10)**	**0.5**	**0.5**	**90[b]**
16	Cu(OAc)$_2$ (5)	0.5	1	79

Preliminary studies demonstrated that phenylzinc pivalate **3a** is aminated with benzylaminobenziodoxolone (BBX) **2aa** at room temperature using DMF as solvent (entry 1). Using an excess of arylzinc pivalate (2 equivalents) of **3a** for **2aa** (1 equivalent), proved to be the best stoichiometry, although the yield was still not satisfactory (entry 2). As increasing time (entry 4) and temperature (entry 5) did not improve our results, a screening of various catalysts was carried out. Copper salts revealed to give the best results for the amination reaction and a loading of 10 mol% of copper(II) acetate led to the desired N-benzylaniline in 90% yield (entry 15). Once established the best reaction conditions and using phenylzinc pivalate **3a** as a model nucleophile for this Cu-catalyzed electrophilic amination, we proceeded to evaluate the reactivities of the λ^3-iodanes amination reagents **2** (Scheme 3).
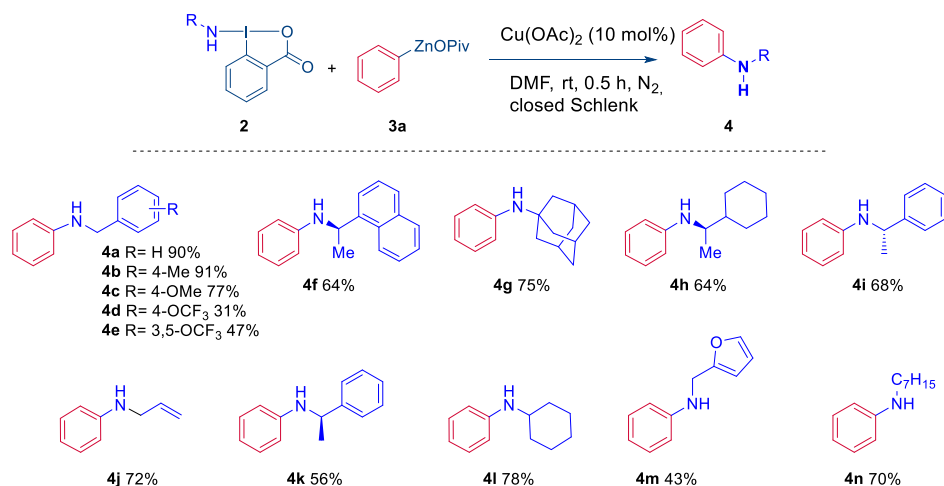
Scheme 3: Scope of the reaction of phenylzinc pivalate with **3a** with various amino-λ^3-iodanes **2**. Yields are isolated yields.

Interestingly, for the substituted benzylic amines, no significant deviation from the model reaction was observed with electron-donating groups (**4b**, **4c**) whereas the presence of electron-withdrawing substituents led to considerably lower yields (**4d**, **4e**). As for the amination reagents **2** bearing alkyl moieties, the desired aminated products were obtained in good yields (**4g**, **4h**, **4k**, **4l**, **4n**).

The extent of the amination reaction was further investigated using various aryl/heteroaryl/alkyl zinc pivalates (Scheme 4).
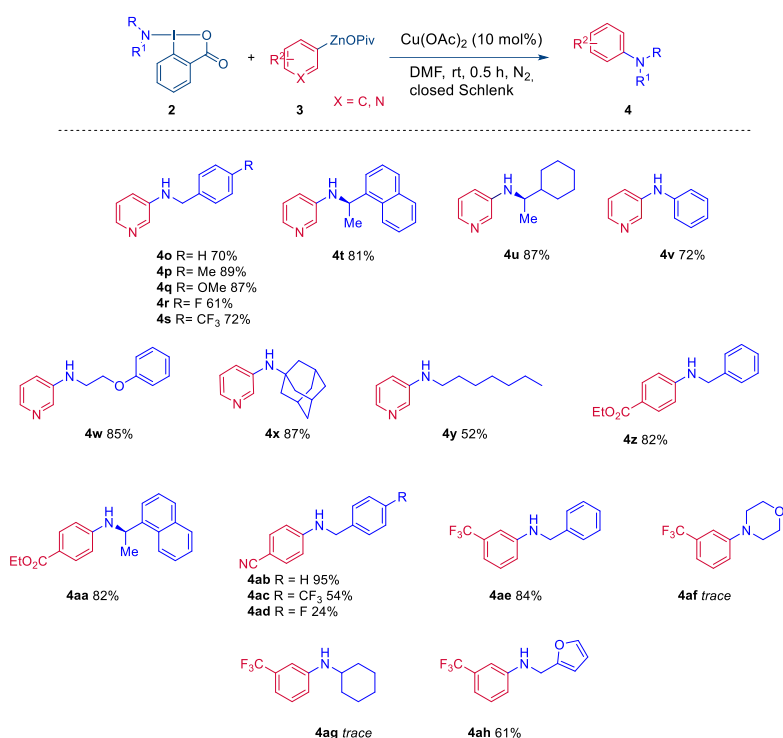
Scheme 4: Substrate scope of the electrophilic amination reaction. Yields are isolated yields.

All substrates tested gave the corresponding amines. Reagents **2** with benzylic amines efficiently transferred to pyridyl organozinc **3** (amines **4o-4y**). Reagent **2l** gave the corresponding aniline **4v** in 72% high yield. The adamantyl amine was also arylated in 87% yield (**4x**) however, a lower yield was observed for the transfer of the alkylamine (**4y**).

The protocol is also compatible with the phenyl ester organozinc and amines **4z** and **4aa** were both obtained in 82% yields. The reaction of **2** with organozinc pivalates **3** bearing electron withdrawing group, such as the nitrile and CF$_3$ groups also afforded the corresponding amines in moderate to high yields, except for the alkyl amine (**4ag**).

However, amine **4af** was isolated in lower yield. Secondary amines were also transferred, although in only trace amount (**4af**). The method proved to be suitable for the preparation of chiral amines (e.g. **4t**).

We propose that electrophilic amination reaction of 2 involves an initial formation of a tetracoordinate anionic organozincate species through deprotonation of **2** by the neutral organozinc reagent **3**, followed by reaction with a second equivalent of 3. Subsequently, this increase of electron density at the zinc center promotes a 1,2 aryl migration[26,27] with concomitant reduction of iodine(III) to produce the amine product **4**. To validate this proposed mechanism, density functional theory (DFT) calculations were performed with **2aa** and PhZnOAc. The 1,2-phenyl migration via transition state TS1 yields the final deprotonated amine product coordinated to zinc center and has an energy barrier of 42.4 kcal mol^{-1} (Scheme 5A). Further investigation of the role of Cu(II) on the transformation, shows that coordination to the carboxylate group of the amino-λ3-iodane decreases the electron density at the iodine center. This role as Lewis acid facilitates the 1,2-phenyl migration via TS2, which has a lower energy barrier of 15.6 kcal mol^{-1} (Scheme 5B).
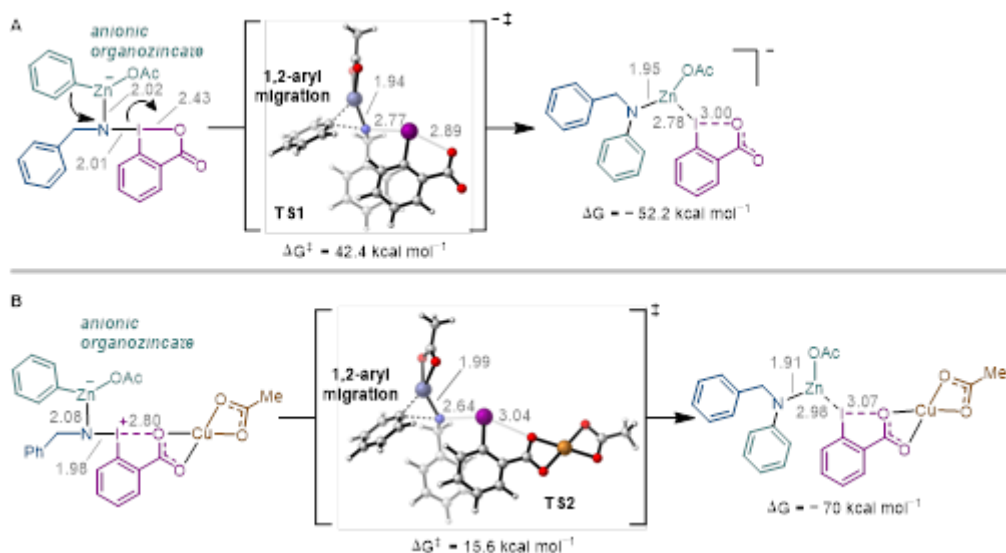
*Scheme 5: Computed transition state geometries of the 1,2–aryl migration of the (A) uncatalyzed and (B) Cu(II)-catalyzed formation of **4a**. DFT calculations performed at M06/LANL2DZ(Cu,Zn,I)/6-31G*(H,C,N,O) level of theory. Bond lengths (grey) are in Å.*

In conclusion, we have developed an efficient synthesis of novel HIR bearing a large set of transferable primary amines. The reaction of these reagents **2** with readily available organozinc pivalates allows the preparation of a wide range of polyfunctional secondary amines. This procedure allows an access to both aryl, heteroaryl and alkyl amines, showing an excellent functional group tolerance.

Acknowledgements

Conflicts of interest

The authors declare no conflict of interest.

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