NH-heterocyclic aryliodonium salts: Synthesis and Access to N1-aryl-5-iodoimidazoles

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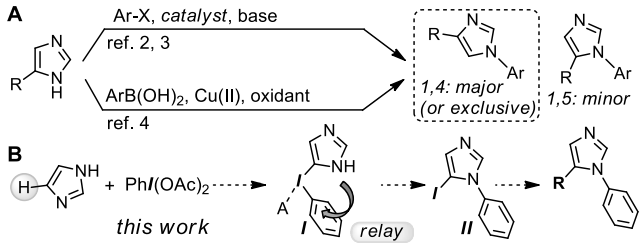
Dedication ((optional))

Abstract: The synthesis of *N*-arylimidazoles substituted at the sterically encumbered 5 position is a challenge for modern synthetic approaches. Here we report a new family of imidazolyl aryliodonium salts that serve as stepping stones *on route* to the selective formation of *N*1-aryl-5-iodoimidazoles; the iodine can now act as a "universal" placeholder to be transformed into further substituents. These new λ^3-iodanes are produced by treating the *NH*-imidazole with ArI(OAc)$_2$, and are converted to *N*1-aryl-5-iodoimidazoles by a selective Cu-catalyzed aryl migration. The method tolerates a variety of Ar fragments and is also applicable to substituted imidazoles.

Imidazole is a ubiquitous heterocyclic core present in a wide variety of biologically relevant molecules.[1] Although the synthesis of imidazole derivatives is commonly accomplished through a variety of cyclization routes, it is often desirable to obtain a particular derivative starting from a preformed heterocyclic ring. For this reason, imidazole derivatization has been the focus of attention from a number of laboratories. A particularly common challenge is the selective construction of the 1,4- and 1,5-disubstituted imidazoles. Thus, the *NH*-arylation of an imidazole substituted at the C4(5) position tends to produce a mixture of isomers favoring the sterically less encumbered *NH* position, *i.e.* that with a 1,4 substitution pattern.[2,3] This bias was recently perfected by Buchwald *et al.* through the use of highly bulky biaryl phosphine ligand in Pd-catalyzed imidazole *N*-arylation.[3b] A similar preference for the less encumbered *NH* position can also be seen in the oxidative Chan-Lam *N*-arylation of imidazole (Scheme 1A).[4]

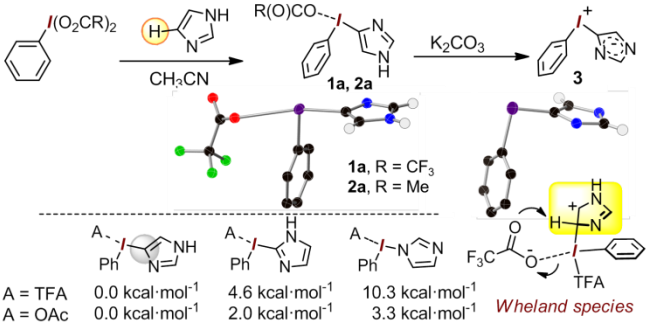


Scheme 1. Examples of common imidazole *N*-arylation strategies (**A**) and the relay arylation (**B**) proposed here.

A challenge, however, remains to access selectively the corresponding 1,5-disubstituted imidazoles. Progress made in recent years includes the usage of well-designed protection/deprotection strategies,[5] and the C5-selective *CH*-borylation[6] and *CH*-arylation[7] reactions.

Here we present a new route to a versatile class of precursors for 1,5-disubstituted imidazoles. Specifically, the *N*1-aryl-5-iodoimidazoles are produced via a relay in which a hypervalent iodoarene fragment[8] serves as a trampoline for aryl transfer to the proximal *NH* site (Scheme 1B). We reasoned that if the iodane ***I*** could be generated, it can then undergo a phenyl transfer to produce ***II***, perhaps akin the intramolecular *O*- and *N*-arylation observed in iodonium ylides.[9] Somewhat surprisingly, the *NH*-heterocyclic λ^3-iodanes have only received a limited attention beyond the early work by Neiland *et al* in the 1970's.[10,11] Recent reports, however, highlight the promise of hypervalent iodine reactivity in azole functionalization, including *via* heterocyclic λ^3-iodanes.[12]

In particular, we found only a single precedent of an imidazolyl-λ^3-iodane; the species, however, was described as containing the imidazole fragment bound to iodine through the N atom.[13] A reaction between PhI(O$_2$CCF$_3$)$_2$ and imidazole (2 equiv) in acetonitrile at room temp. produced a white precipitate identified as [PhI(Imid)]TFA salt, **1a** (58%). However, the presence of just two imidazolic resonances in ^{1}H NMR (1H each) strongly suggested a *CH* rather than *NH* functionalization of the imidazole; accordingly, X-Ray crystallography revealed a classical T-shaped diaryliodonium environment, with the imidazole bound to the iodine through the C4(5) carbon atom (Scheme 2). An analogous acetate salt **2a** was obtained by employing PhI(OAc)$_2$. A DFT analysis confirmed that both the C2 and the *N*-bound isomer are higher in energy than the observed C4(5) isomer. An *N*-bound species was found unlikely even as an intermediate *en route* to **1a**; rather, the reaction appeared to proceed through a Wheland-type intermediate (see Supporting Information).



Scheme 2. Formation and structures of the imidazole-based λ^3-iodanes and of the neutral (betaine) **3**. Gibbs Energies (kcal mol^{-1}) in CH$_3$CN.

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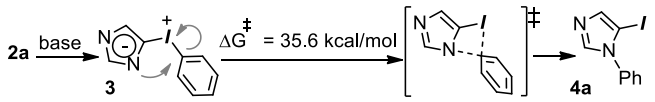
Supporting information for this article is given via a link at the end of the document.

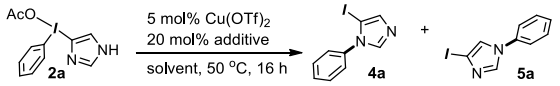
While sparingly soluble in $CDCl_3$, **1a** and **2a** dissolved well in MeOH and water. They also underwent a facile deprotonation to a zwitterionic **3**, for which both the solid state and DFT structures show an essentially "normal" single C_{imid}-I bond (2.051 and 2.076 Å, respectively, *vs* 2.091 Å observed for in **1a**). We quickly discovered that the desired *I*-to-*N* phenyl transfer does not take place upon heating **1a**, **2a** or **3** in CH_2Cl_2, with or without Cs_2CO_3. Consistently, only a high energy transition state (35.6 kcal mol^{-1}) could be identified for the direct (non-catalyzed) *I*-to-*N* 1,3 phenyl migration in **3** (Scheme 3).



Scheme 3. Reaction path modelled for uncatalyzed 1,3 phenyl migration.

Gratifyingly, the addition of 5 mol% of $Cu(OTf)_2$ did allow for the formation of two regioisomeric *N*-phenyl iodoimidazoles, with a moderate selectivity towards the more hindered **4a** achieved in fluorinated alcohols (Table 1, runs 1-3, both isomers confirmed by X-Ray diffraction). The use of Cs_2CO_3 in hexafluoroisopropanol (HFIP) led to a combined yield of 86% with a 4:1 ratio in favor of **4a** (run 4). This ratio was further improved by employing catalytic amounts of certain heterocyclic additives (runs 5-7); *e.g.* the use of 20 mol% of *N*-Me-benzimidazole (run 6) led to an 8:1 selectivity and a 93% yield.

Table 1. Cu-catalyzed *I*-to-*N* phenyl transfer in **2a**.[a]

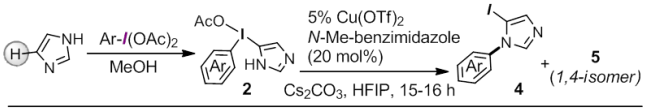


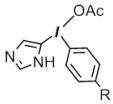
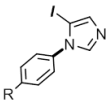
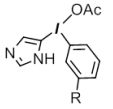
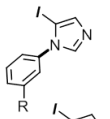
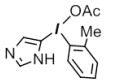
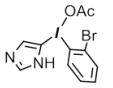
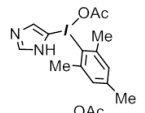
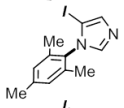
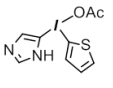
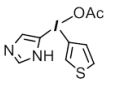
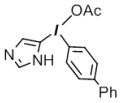
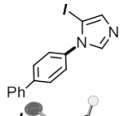
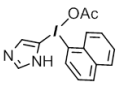
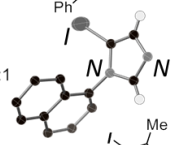
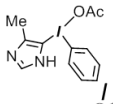
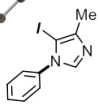
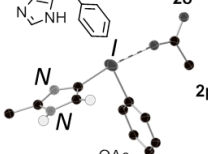
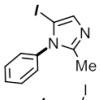
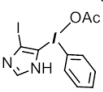
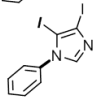
Run	Base	Solvent	Additive	Yield(%)[b]	**4a/5a**[b]
1	---	CH_2Cl_2	--	39	0.1:1
2	---	CF_3CH_2OH	--	51	1.5:1
3	---	HFIP	--	53	4.2:1
4	Cs_2CO_3	HFIP	--	86	4.1:1
5	Cs_2CO_3	HFIP	4-methylimidazole	90	7.3:1
6	Cs_2CO_3	HFIP	benzimidazole	90	8.4:1
7	Cs_2CO_3	HFIP	*N*-Me-benzimidazole	93	8.0:1

[a] Using 0.5 mmol **2a**, 5 mol% $Cu(OTf)_2$ and 1.6 equiv of base (if any) in 2.6 mL of solvent. [b] Total yield (%**4a**+**%5a)** and the ratio as determined by GC.

It was subsequently found that the highest yields of **2** were achieved in trifluoroethanol[14] and, notably, MeOH as solvents. CH_3CN, however, remained convenient for large scale applications due to product precipitation, as seen in the synthesis of a 23 g batch of **2a** (Supp. Info). All the aryl(imidazolyl)-λ^3-iodanes, **2**, exhibited the corresponding Ar-I(Imid)$^+$ cation in the HR (ESI+) mass spectra. These species were subsequently transformed into the *N1*-aryl-5-iodoimidazole, **4,** with good selectivities. As previously observed for **4a**, in all cases a characteristic ^{13}C resonance at 71-73 ppm was observed for the ^{13}C-I unit in **4**, which is approx. 10 ppm lower than in the corresponding 1,4 species **5** (82-85 ppm). Given the synthetic potential of **4a**, the method was extended to structurally diverse aryl(imidazolyl)-λ^3-iodanes (Table 2). The most robust protocol involves the use of 20 mol% of *N*-Me-benzimidazole in combination with 5 mol% of $Cu(OTf)_2$.

Table 2. Scope of the relay synthesis of *N*1-aryl-5-iodoimidazoles **4**.



structure **2**		yield **2**[a]	yield **4**[b]	**4**/**5**[c]	structure **4**
	**2a,** R = H **2b**, R = OMe **2c**, R = Me **2d**, R = Cl **2e**, R = OCF_3	87% (78%) 81% (62%) 91% (76%) 81% (68%) 91% (72%)	**4a**, 74% **4b**, 72% **4c**, 75% **4d**, 60% **4e**, 47%	8.1:1 9.8:1 8.5:1 8.4:1 11.6:1[d]	
	**2f**, R = OMe, **2g**, R = Br	81% (64%) 87% (85%)	**4f**, 77% **4g**, 62 %	9.8 :1 8.2:1[e]	
	**2h**	67% (57%)	**4h**, 85%	8.5:1	
	**2i**	96% (71%)	**4i**, 61%	13.0:1[d]	
	**2j**	90% (47%)	**4j** 51%	9.4:1	
	**2k**	75% (80%)	**4k**, 78%	11.8:1[e]	
	**2l**	74% (72%)	**4l**, 79%	13.5:1	
	**2m**	83% (79%)	**4m**, 70%	10.4:1	
	**2n**	82% (76%)	**4n**, 74%	5.6:1	
	**2o**	79% (64%)	**4o**, 87%	13.0:1[f]	
	**2p**	90% (59%)	**4p**, 31%	4.4:1	
	**2q**	(73%)	**4q,** 82%	--	

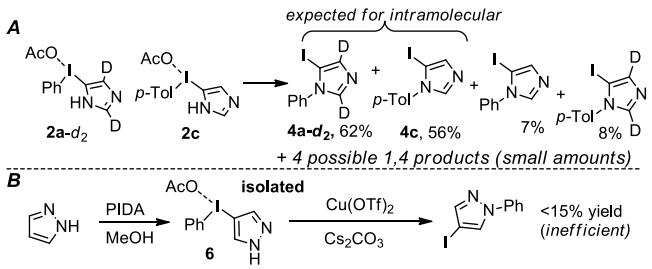
[a] ^1H NMR yield (isolated yield). [b] Isolated product. [c] **4**/**5** ratio determined by GC. [d] Benzimidazole (20 mol%) as additive. [e] 4-methylimidazole (20 mol%) as additive. [f] Ar-I(imid)$^+$$OAc^-$ was added before injection of the solvent; no additive was used.

The improved selectivity with these additives is likely due to the formation of Cu-heterocycle complexes. Indeed, best results were achieved by pre-mixing $Cu(OTf)_2$ with the additive and base for 20 min, presumably favoring complex formation. We

observed that while $Cu(OTf)_2$ alone did not dissolve in HFIP, a green solution formed upon addition of *N*-Me-benzimidazole.

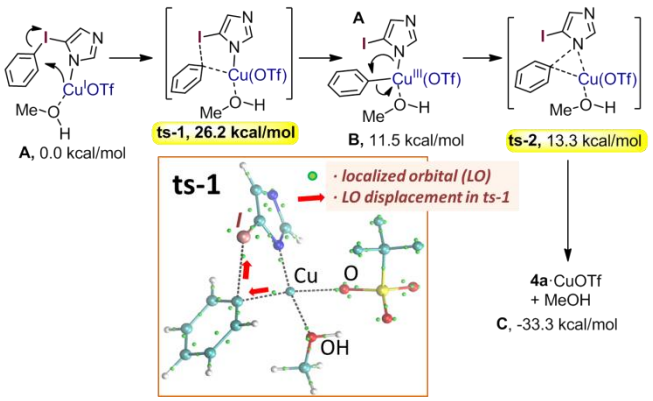
Both electron-donating and mildly electron-withdrawing substituents were well tolerated on the aryl fragment (**4b**-**i**, Table 2). In fact, even a di-*ortho* substitution was tolerated, as illustrated in the successful synthesis of the highly hindered *N*-mesityl-5-iodoimidazole, **4j**. We were particularly pleased with the successful incorporation of a second heterocycle, as in the 2- and 3-thienyl derivatives **4k** and **4l**. The 4-iodobiphenyl and 2-iodonaphthalene derivatives could also be obtained in 70% and 74% yield, respectively (**4m** and **4n**). In the case of the 4-Me-imidazolyl iodane **2o**, a 13:1 **4**/**5** selectivity was achieved, affording the target **4o** in an 87% yield, with the selectivity benefiting from hindrance at the competing *N* site. The aryl transfer in the 2-Me derivative **2p** was less efficient, providing **4p** in 31% yield. The method was also applied to produce an 82% of the 4,5-diiodo derivative **4q**. In general, separation between **4** and **5** proved rather straightforward.

As mentioned earlier (see Scheme 1), the high selectivity towards **4** would stem from an intramolecular aryl migration from iodine to the proximal nitrogen.[16] Accordingly, a cross-over experiment between **2a**-d_2 and **2c** revealed a predominant formation of **4a**-d_2 and **4c** expected for an intramolecular process (Scheme 4A).[15] Small amounts of the 1,4 isomers were also produced, and for these, full aryl/imidazole scrambling was observed, indicating their origin in a bimolecular process. Indirect support for an intramolecular manifold was also obtained from the poor performance of the pyrazole-derived iodane **6** (<15% yield, Scheme 4B) lacking a proximal *NH* site.



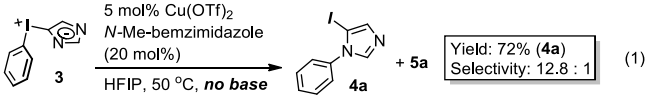
Scheme 4. Cross-over experiment (A), and the assay with pyrazol (B).

We envisaged that **3** (formed upon deprotonation of **2**), binds a Cu(I)-OTf fragment through *N1* (Scheme 5).[17,18] Indeed, despite employing a Cu(II) precatalyst, the true catalytic species is likely a Cu(I) center.[18,19] The inclusion of MeOH in the coordination sphere of Cu (as a stand-in for a solvent molecule) was found to be beneficial to properly describe the Cu intermediate, and, given that the process was already moderately selective (up to 4:1) in the absence of an additive, this initial DFT study was performed in the absence of an added heterocycle. In the first step, the Ph group in **A** is transferred from I to Cu, leading to a formal Cu(III)-phenyl intermediate **B**.[19,20] This step features an activation barrier of 26.2 kcal mol^{-1} (**ts-1**). A Localized Orbital analysis supports the change in Cu oxidation state and allows visualizing the flow of electrons (see small green spheres of **ts-1** in Scheme 5 and Supporting Information). The final C-N bond is formed through an essentially barrierless reductive elimination step (Scheme 5, **ts-2)**. Given the energetic proximity between **B** and **ts-2**, the mechanism resembles a Cu-guided concerted I-to-N phenyl migration. A preliminary investigation also revealed that the coordination of *N*-Me-benzimidazole to the Cu(I) center may disfavor the binding of two molecule of **3** to the same Cu center, hence enforcing an intramolecular Ph transfer.[21]



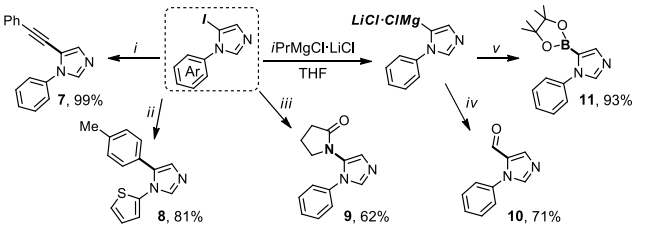
Scheme 5. A DFT profile for the Cu(I)-catalyzed aryl migration. Relative Gibbs energies in methanol (kcal mol^{-1}).

In agreement with Scheme 5, the preformed zwitterionic **3** was also an excellent substrate even in the absence of a base (Eq 1).



The reason for the poor performance of solvents such as CH_2Cl_2 is likely twofold. The deprotonation of **2** in CH_2Cl_2 appears sluggish, which negatively affects the selectivity, giving rise to by-molecular cross-over events (see Supporting Info). In addition, while the use of **3** does render the reaction moderately selective, the rate in CH_2Cl_2 remains low.

Iodine introduced at the C5 position ushers the synthesis of a wide spectrum 1,5-imidazole derivatives (Scheme 6).



i) PhCCH, $PdCl_2$/CuI, Ph_3P, Et_3N at 60 °C; *ii*) tol-$B(OH)_2$, $Pd(OAc)_2$, XanPhos, K_3PO_4, toluene, 120 °C; *iii*) pyrrolidinone, CuI, Cs_2CO_3, *N,N´*-dimethylethylenediamine in dioxane, 105 °C; *iv*) DMF in THF, -15 °C to rt (from Het-MgX); *v*) from **4a**: *i*PrMgCl·LiCl, *i*PrOBPin in THF

Scheme 6. Versatility of the 1-aryl-5-iodoimidazoles in the synthesis of 1,5-substituted imidazoles.

Thus, the 5-alkynyl and 5-aryl derivatives **7** and **8** were prepared *via* Pd-catalyzed C-C coupling reactions. In addition, a Cu-catalyzed *C-N* bond formation was readily accomplished to give **9**.[22] The 5-iodoimidazole **2a** was also readily converted to an organomagnesium species,[23] which served as precursor to the 5-formyl and the 5-borylderivatives **10** and **11**.[23b,c]

In conclusion, we have shown that the new (*NH*-imidazolyl)aryl iodonium cation, readily obtained from imidazole and aryliodine diacetate, $ArI(OAc)_2$, serves as an excellent stepping stone for the formation of *N*-arylimidazoles bearing an iodine substituent at the strategic C5 position. The method complements common existing protocols known to produce the sterically favored 1,4-derivatives. The method was tolerant of a variety of aryl substitution patterns, including mono- or bis-*ortho* substitution. Through subsequent transformation of the iodine group, the newly formed *N*1-aryl-5-iodoimidazole constitutes a valuable precursor to a wide range of products. Experimental and DFT data suggest that the selectivity is likely the result from an intramolecular copper-catalyzed iodine-to-nitrogen migration of the aryl fragments.

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Keywords: imidazoles • hypervalent iodine • CH functionalization • copper catalysis • C-N coupling • DFT

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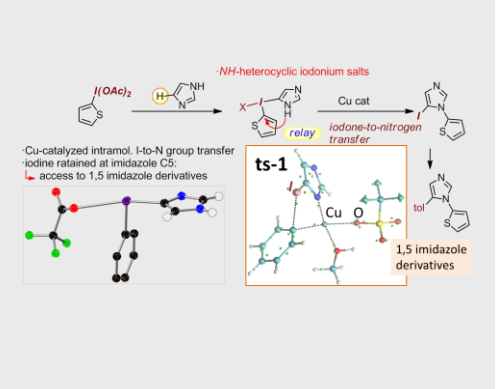
Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

A new family of imidazolyl aryliodonium salts serves as stepping stones *on route* to the *N*1-aryl-5-iodoimidazoles; the iodine substituent can now act as a “universal” placeholder to be transformed into further substituents. These new λ^3-iodanes are produced by treating the *NH*-imidazole with $ArI(OAc)_2$, and are converted to *N*1-aryl-5-iodoimidazoles by a selective Cu-catalyzed aryl migration.



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NH-heterocyclic aryliodonium salts: a stepping stone to N1-aryl-5-iodoimidazoles