C–H Amination

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The Multiple Facets of Iodine(III) Compounds in an Unprecedented Catalytic Auto-amination for Chiral Amine Synthesis

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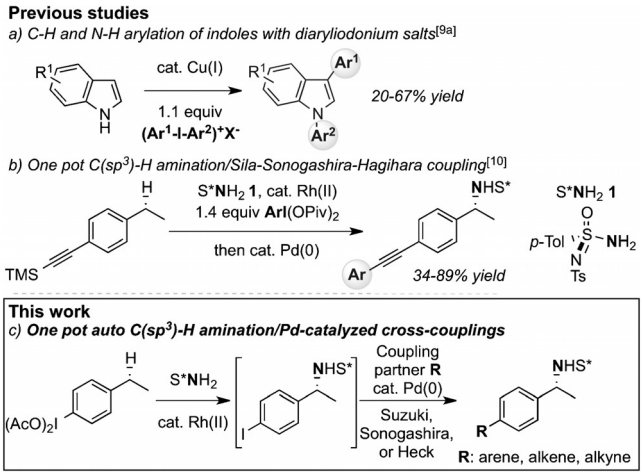
Abstract: *Iodine(III) reagents are used in catalytic one-pot reactions, first as both oxidants and substrates, then as cross-coupling partners, to afford chiral polyfunctionalized amines. The strategy relies on an initial catalytic auto C(sp³)–H amination of the iodine(III) oxidant, which delivers an amine-derived iodine(I) product that is subsequently used in palladium-catalyzed cross-couplings to afford a variety of useful building blocks with high yields and excellent stereoselectivities. This study demonstrates the concept of self-amination of the hypervalent iodine reagents, which increases the value of the aryl moiety.*

Catalytic sequential reactions for the synthesis of complex products are invaluable in modern organic chemistry.[1,2] Equally important is the chemistry of hypervalent iodine compounds, which has expanded in the last two decades.[3,4] Accordingly, the design of new synthetic methods merging these two research domains is a source of inspiration for the organic chemists to address the issues of diversity and sustainability. Trivalent iodine oxidants have become the reagents of choice to perform selective transformations under mild conditions. However, because they are often derived from iodoarenes, their use in synthesis raises the problem of the production of stoichiometric amount of aryl iodides. The design of processes catalytic in iodine[5] and recyclable iodine reagents[5a,6] has allowed this issue to be addressed. More recently, an alternate solution has emerged with the report of synthetic strategies valuing the ArI group. The latter has been used as a building block in condensation reactions,[7] or for the α-arylation of carbonyl compounds.[8] More significantly, Greaney has reported the tandem C–H/N–H arylation of indoles based on the coupling of both aryl groups of diaryliodonium salts (Scheme 1 a).[9a] At the same time, we designed a sequence of Rh^{II}-catalyzed C(sp³)–H amination/sila-Sonogashira–Hagihara coupling that recycled the ArI moiety of iodine(III) oxidants generated in the first step of the nitrene addition (Scheme 1 b).[10]



Scheme 1. Background for the design of the self-amination of iodine(III) reagents.

These transformations highlight the value of the iodoarene side-product that has been previously considered as waste. However, they rely on the use of an excess of the iodine(III) reagent, thereby limiting their atom-economy and efficiency. Moreover, with the aim to increase the molecular diversity accessible through one-pot reactions, we sought to improve the variety of sequences combined with the C(sp³)–H amination from a unique precursor. We hypothesized that the iodine(III) oxidant could be used as both the oxidant and the substrate for the C(sp³)–H amination reaction. This would deliver a functionalized iodo compound that could, then, be used for further cross-couplings. Such an unprecedented self-reaction of iodine(III) oxidants should be optimal in terms of sustainability and versatility, and increase the synthetic potential of these reagents. Herein, we wish to report the details of our investigations that have provided a proof of concept and the application to the successful design of several sequences of auto C(sp³)–H amination/Pd-catalyzed couplings (Scheme 1 c).

Our first aim was to demonstrate the ability of iodine(III) oxidants to undergo a catalytic auto C(sp³)–H amination under the conditions reported for the stereoselective amination of hydrocarbons.[10–12] This required the preparation of (diacetoxyiodo)arenes that were obtained in good to excellent yields after oxidation of the corresponding aryl iodides with sodium perborate (Table 1).[13,14] A screening of the stoichiometry of the reagents then led us to find that the sulfonimidamide **1** (1.0 equiv), in the presence of the chiral Rh^{II} complex **2**, reacts with a slight excess (1.1 equiv) of the hypervalent reagent **3a** to afford the self-aminated product at

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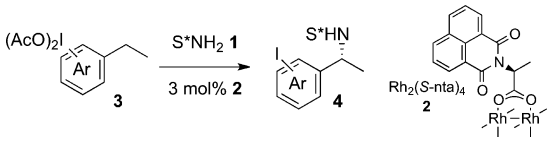
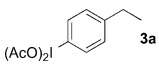
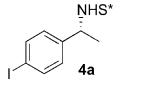
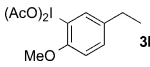
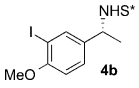
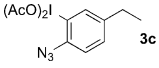
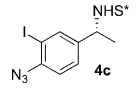
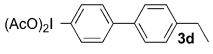
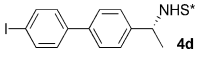
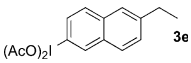
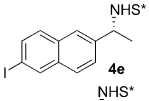
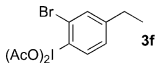
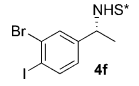
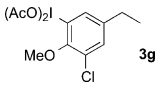
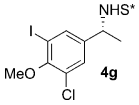
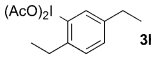
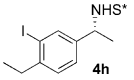
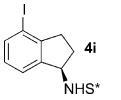
Table 1: Catalytic auto-C(sp^3)–H amination of iodine(III) oxidants **3**.[a]



Entry	3	Yields of 3 [%]	4	Yield of 4 [%][b]
1	 **3a**	86 (87)[c]	 **4a**	90
2	 **3b**	63	 **4b**	88
3	 **3c**	76	 **4c**	91
4	 **3d**	82	 **4d**	70 (75)[d]
5	 **3e**	75	 **4e**	75
6	 **3f**	86	 **4f**	85
7	 **3g**	70	 **4g**	64[e]
8	 **3h**	74	 **4h**	34
9	 **3i**	78	 **4i**	90[f]

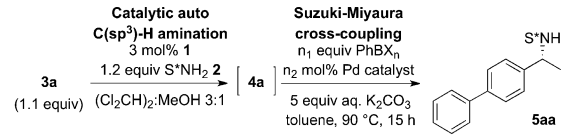
[a] Reaction conditions: A mixture of **3** (0.22 mmol), **1** (0.2 mmol), and the catalyst **2** (3 mol%) in 1,1,2,2-tetrachloroethane/MeOH 3:1 (1 mL) is stirred at −35 °C for 72 h. [b] Isolated after chromatography with a d.r. > 98:2. [c] On a 8 mmol scale. [d] After of 96 h of reaction. [e] Isolated with a d.r. = 9:1. [f] 4:1 mixture of regioisomers.

the benzylic position. Compound **4a** was thus isolated in 90% yield as a single diastereoisomer (entry 1).[15,16]

The self-amination was successfully extended to other aromatic iodine(III) oxidants bearing a methoxy, an azido, a phenyl, and a halo substituent (entries 2–7). The expected products **4b–g** were isolated with yields in the 64–91% range. We also investigated the reactions with compounds **3h** and **3i** that raise the issue of regioselectivity. While product **4h** resulting from the auto C(sp^3)–H amination at the *meta*-ethyl group was exclusively obtained albeit with a modest yield of 34% (entry 8), indan derivative **3i** led to a 4:1 mixture of regioisomers with compound **4i** isolated as the major product (entry 9), a ratio that is in line with our previous results.[10]

We next turned our attention to combining this reaction with one-pot metal-catalyzed cross-couplings. We first decided to study the auto C(sp^3)–H amination/Suzuki–Miyaura reaction.[17] Early attempts with phenylpinacol boronic ester in the presence of $Pd(PPh_3)_4$ generated the expected product **5aa** with a low yield of 10% (Table 2, entry 1). This result was improved by screening the palladium

Table 2: Screening of conditions for the catalytic one-pot auto-C(sp^3)–H amination/Suzuki–Miyaura cross-coupling.[a]



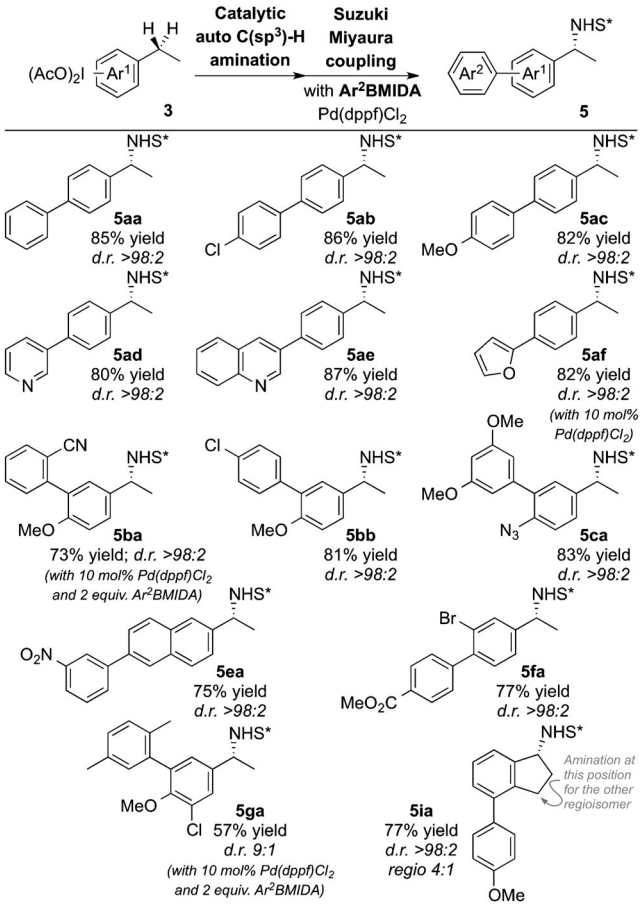
Entry	$PhBX_n$ (n_1 equiv)	Pd Catalyst (n_2 mol%)	Yield[%][b]
1	PhBPin (2.0)	$Pd(PPh_3)_4$ (10)	10
2	PhBPin (2.0)	$Pd(dppf)_2Cl_2$ (10)	37
3	$PhBF_3K$ (2.0)	$Pd(dppf)_2Cl_2$ (10)	70
4	PhBMIDA (2.0)	$Pd(dppf)_2Cl_2$ (10)	86
5	PhBMIDA (2.0)	$Pd(dppf)_2Cl_2$ (5)	85
6	**PhBMIDA (1.5)**	**$Pd(dppf)_2Cl_2$ (5)**	**85**
7	PhBMIDA (1.5)	$Pd(dppf)_2Cl_2$ (3)	82
8	PhBMIDA (1.2)	$Pd(dppf)_2Cl_2$ (5)	75

[a] Reaction conditions: A mixture of **3a** (0.22 mmol), **1** (0.2 mmol), and **2** (3 mol%) in 1,1,2,2-tetrachloroethane/MeOH 3:1 (1 mL) is stirred at −35 °C for 72 h. The palladium complex (3 to 10 mol%), aqueous K_2CO_3 (5 equiv), and the boron reagent (0.24 to 0.4 mmol) in toluene (1 mL) are added. The mixture is stirred at 90 °C for 15 h. [b] Isolated after chromatography with a d.r. > 98:2.

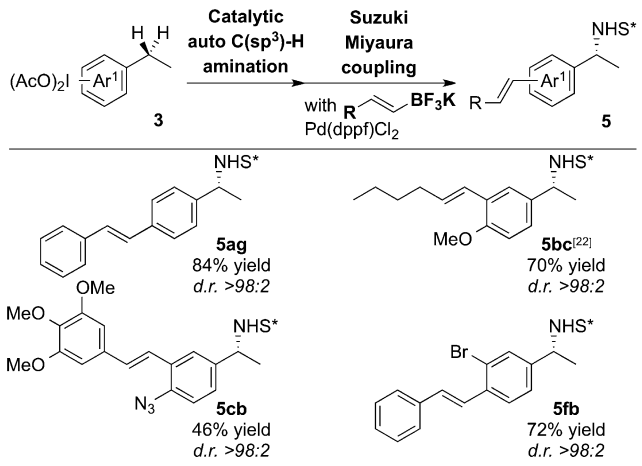
complex (entry 2), the base, the solvent (Supporting Information, Table S1), and the boron reagent[18] (entries 3 and 4). We found that use of 2 equiv of the phenylboronic acid MIDA ester[19] in the presence of 10 mol% $Pd(dppf)_2Cl_2$ in toluene affords **5aa** in 86% yield. Pleasingly, lowering the amount of both the boron reagent and $Pd(dppf)_2Cl_2$ did not modify significantly the yield (entries 5–8) and the product **5aa** was obtained in 85% yield using only 1.5 equiv of the MIDA boronate ester and 5 mol% $Pd(dppf)_2Cl_2$ (entry 6).

The one-pot auto C(sp^3)–H amination/Suzuki–Miyaura reaction was then applied to several iodine oxidants (**3**) to afford a small library of optically pure substituted benzylic amines (Scheme 2). The yields were very good, being generally greater than 75% over the two steps. The reaction is compatible with various aromatic rings substituted at the *para*, *meta*, or *ortho* position either by a chloro, an ether, a cyano, an ester, or a nitro group. Moreover, the one-pot reaction can be applied to the introduction of heterocycles such as pyridine, quinoline, and furan ring, a result that highlights the synthetic potential of the sequence. Compounds **5ad** and **5ae** are indeed not accessible through the application of the catalytic C(sp^3)–H amination reaction to the biaryl precursor, as the presence of a basic nitrogen induces the deactivation of the Lewis acid dirhodium(II) complex, while the presence of a furan (compound **5af**)[20] is not compatible with the oxidizing conditions. Furthermore, products **5fa** and to a lesser extent **5ga** demonstrates that a chemoselective coupling of the iodoarene can be performed in the presence of other halogen substituents.

Finally, we found that the auto C(sp^3)–H amination/Suzuki–Miyaura reaction allows the efficient coupling of vinyl groups in the presence of potassium vinyltrifluoroborate salts and of $Pd(dppf)_2Cl_2$ (Scheme 3).[21] This led to the introduction of either a styrenyl side chain or a linear alken-2-yl substituent.[22] The one-pot reaction with vinyl boron reagents provides a relevant solution to the issue of chemoselectivity



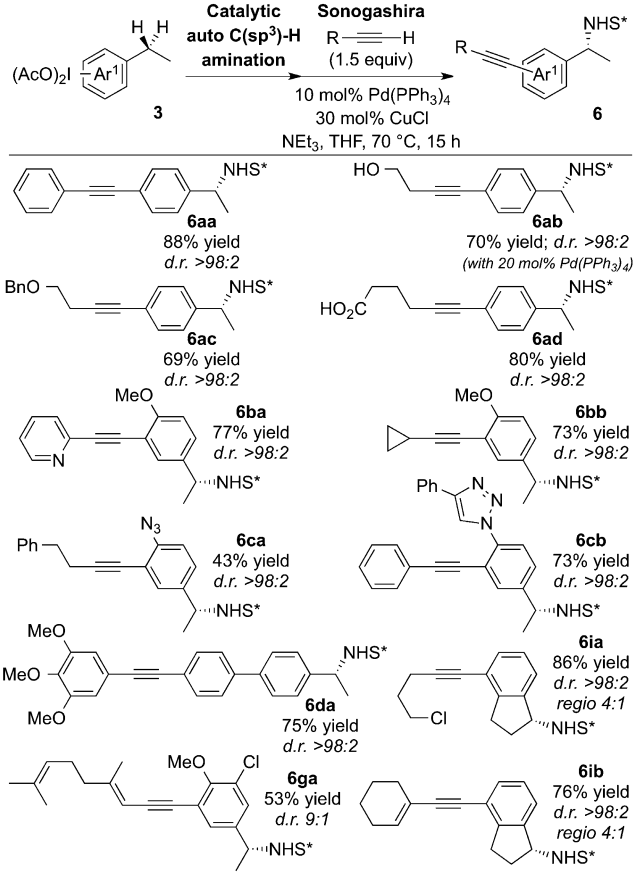
Scheme 2. Scope of the catalytic one-pot auto-C(sp^3)–H amination/ Suzuki cross-coupling with aryl boron reagents.



Scheme 3. Scope of the catalytic one-pot auto-C(sp^3)–H amination/ Suzuki cross-coupling with vinyl boron reagents.

that would be faced with a substrate bearing a benzylic site and an alkene both likely to undergo the addition of the rhodium-bound nitrene.

We, then decided to combine the catalytic auto C(sp^3)–H amination with other catalytic couplings to explore the molecular diversity accessible with the self-oxidation of iodine(III) reagents. Inspired by our previous study,[10] the one-pot auto C(sp^3)–H amination/Sonogashira reaction was

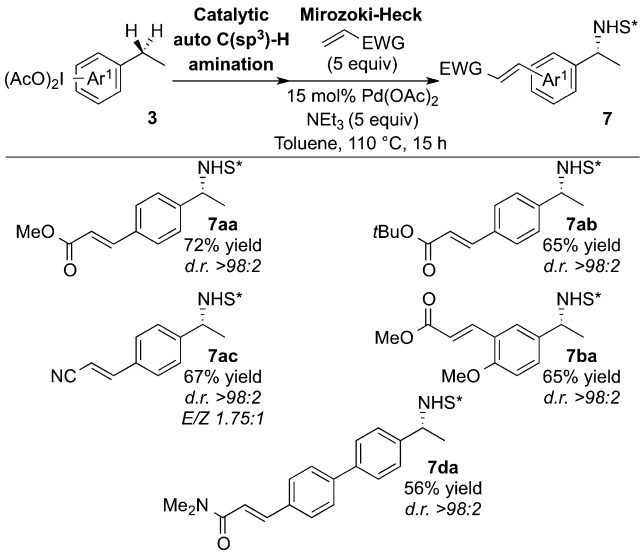


Scheme 4. Scope of the catalytic one-pot auto-C(sp^3)–H amination/ Sonogashira cross-coupling.

successfully developed (Scheme 4). A rapid screening led us to determine the optimal conditions for the coupling that include the use of 1.5 equiv of the alkyne, 10 mol% $Pd(PPh_3)_4$, 30 mol% of CuCl, and 5 equiv of Et_3N (Supporting Information, Table S2). These were applied to various substrates **3** and alkynes to afford the expected products **6**, generally as a single isomer with yields in the 43–88% range. A broad range of functional groups is again well-tolerated by the sequential reaction. The overall process also helps to address the issue of chemoselectivity, for example in the case of the 3,4,5-trimethoxyarene derivative **6da**. Such an electron-rich aromatic substrate would indeed be oxidized by the iodine-(III) reagent. Also worth mentioning is the sequence of auto C(sp^3)–H amination/Cu-catalyzed azide–alkyne cycloaddition/ Sonogashira reaction with phenylacetylene that leads to the formation of compound **6cb** in 73% yield over three steps.

Finally, we demonstrated that the auto C(sp^3)–H amination can be combined with a Mirozoki–Heck coupling (Scheme 5). Application of the optimal conditions (see Table S3), thus, provides the functionalized cinnamoyl derivatives **7** in good yields. This was compatible with the presence of an ester, a cyano, and an amide functionality.

In conclusion, this study reveals the multiple facets of iodine(III) reagents $ArI(OAc)_2$, which can be used as oxidants, substrates, and coupling partners in multistep sequences to afford optically pure amines with yields of up to 88%. We have demonstrated that the hypervalent iodine



Scheme 5. Scope of the catalytic one-pot auto-C(sp^3)–H amination/ Mizoroki-Heck cross-coupling.

reagent can undergo an efficient catalytic auto C(sp^3)–H amination that delivers a functionalized iodoarene. The latter can be subsequently engaged in one-pot palladium-catalyzed cross-couplings. Importantly, some of these compounds could not be easily accessible through a reversed sequence of Pd-catalyzed cross-couplings/auto C(sp^3)–H amination for chemoselectivity reasons. The overall strategy accordingly highlights the value of hypervalent iodine reagents as hitherto underestimated useful building blocks in synthesis.

Acknowledgements

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Keywords: C–H amination · cross-coupling · homogeneous catalysis · hypervalent iodine · tandem synthesis

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[14] The iodine(III) oxidants are stable over months, except compounds **3d** and **3e**, which should be used freshly prepared in the one-pot reactions to ensure the best yields.

[15] This auto C(sp^3)–H amination compares favorably with the C(sp^3)–H amination of 4-iodo-ethylbenzene. In the presence of 1.2 equiv of S^*NH_2 **1**, 3 mol% of the Rh-complex **2**, and 1.4 equiv of the iodine(III) oxidant $PhI(OPiv)_2$, compound **4a** was obtained in 84% yield.

[16] Running the auto C(sp^3)–H amination with stoichiometric amounts of the sulfonimidamide **2** and the iodine(III) reagent **3a** generated compound **4a** with a slightly lower yield of 86%.

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