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1,3-Iodo-amination of 2-methyl indoles *via* C_{sp^2}–C_{sp^3} dual functionalization with iodine reagent†

Katsuhiko Moriyama, *[ab] Tsukasa Hamada,[a] Kazuma Ishida[a] and Hideo Togo [a]

A 1,3-iodo-amination with iodine reagent that involved the C_{sp^2}–C_{sp^3} dual functionalization of 2-methyl indoles was developed to provide 2-aminomethyl-3-iodo-indole derivatives. The iodo-amination proceeded *via* a 1,4-transfer of an imide group through the formation of an indolyl(phenyl)iodonium imide using $PhI(OAc)_2$, followed by an iodination using DIH or a double iodination of indole using excess DIH.

The direct functionalization of organic compounds has attracted considerable attention recently as an exciting alternative for the installation of various heteroatoms into these compounds.[1] Among the known synthetic methods, the dual functionalization of organic compounds for the synthesis of functional organic compounds presents a challenging task.[2] We recently developed a regioselective vicinal C_{sp^2}–C_{sp^2} dual functionalization that installs two different functional groups simultaneously into N-electron-withdrawing-group (EWG)-protected indoles through bromo-amination *via* a 1,3-transfer of an imide group after the formation of indolyl(phenyl)iodonium imides.[3] To the best of our knowledge, regioselective remote C–H dual functionalization involving installation of two different functional groups by a multicomponent system has never been realized.

The emergence of a direct C_{sp^3}–H amination of 2-substituted indoles has motivated us to establish a novel C–N bond formation of an inert hydrocarbon group to provide 2-aminomethyl indole derivatives that are related to the construction of the key framework in indole alkaloids, biologically active compounds, and pharmaceuticals.[4] In general, the installation of amino groups into sp^3 carbon at the 2-position of 2-substituted indoles is achieved by radical bromination (Wohl–Ziegler reaction), followed by nucleophilic substitution with amines.[5] Regarding previous work on the direct C_{sp^3}–H amination of indoles, the C_{sp^3}–H azidation of 2,3-disubstituted indoles with iodine azide (IN_3) (Fig. 1a, eqn (1))[6] and the C_{sp^3}–H azidation of *N*-Boc-2-methyl indole with azidoiodinane using a Cu(II) photoredox catalyst under visible light conditions (Fig. 1a, eqn (2)) are available.[7] However, these practical methods are characterized by a simple amination as well as limited substrate scope and utility of the aminated products. In this context, we report herein a 1,3-iodo-amination of 2-methyl indoles *via* a regioselective C_{sp^2}–C_{sp^3} dual functionalization by a three-component reaction with iodine reagent and bis(sulfonyl)imide (Fig. 1b).

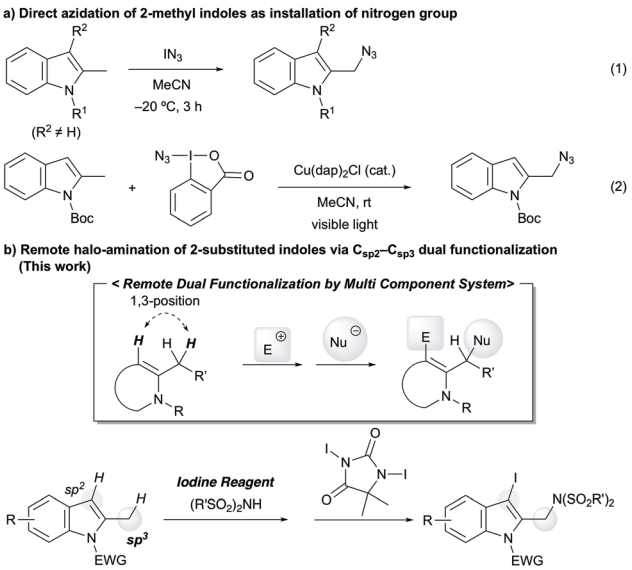

Fig. 1 Direct C_{sp^3}–H amination of 2-substituted indole derivatives.

First, we investigated the preparation of indolyl(phenyl)iodonium imide (**2a**) from *N*-pivaloyl-2-methyl indole (**1a**) based on previously reported reaction conditions[3,8] and obtained **2a** in 97% yield (88% isolated yield) by treatment of **1a** with $PhI(OAc)_2$ and

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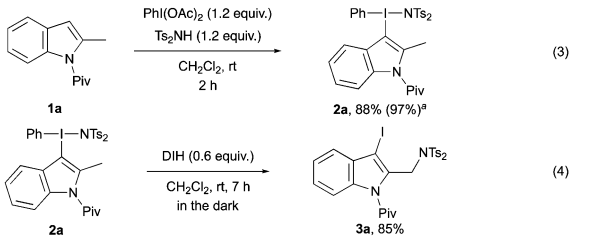
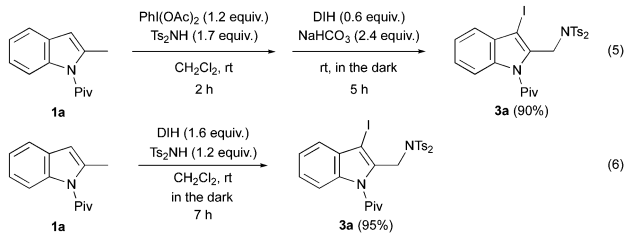


Scheme 1 Preparation of indolyl(phenyl)iodonium imide (**2a**). [a] Number in parentheses indicates the yield of **2a** determined by ^{1}H-NMR analysis based on an internal standard.



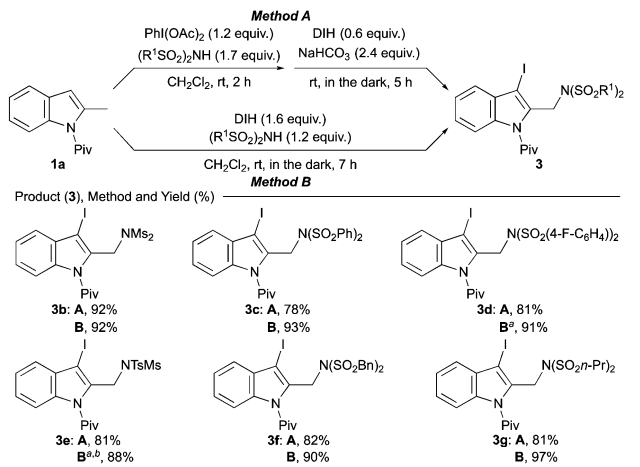
Scheme 2 Direct 1,3-iodo-amination of **1a**.

Ts_2NH in CH_2Cl_2 (Scheme 1, eqn (3)). Additionally, halogen reagents and solvents were screened for the 1,3-iodo-amination of **2a** (Table S1, ESI†) and the optimum conditions were found to include **2a** and 1,3-diiodo-5,5-dimethylhydantoin (DIH) (0.6 equiv.) in CH_2Cl_2 at room temperature under dark conditions, which afforded **3a** in 85% yield (Scheme 1, eqn (4)).

Next, we attempted to conduct a direct iodo-amination of **1a** with Ts_2NH *via* the formation of indolyl(phenyl)iodonium imide (**2a**) (Scheme 2). By using $PhI(OAc)_2$ as the oxidant in the formation of **2a** and $NaHCO_3$ as the base in the iodo-amination, this reaction proceeded to furnish **3a** in 90% yield (eqn (5)). Interestingly, use of an excess amount of DIH (substantially 3.2 equiv. as the iodination reagent) also provided **3a** in high yield (95%, eqn (6)) whereas use of 0.6 equiv. DIH (substantially 1.2 equiv. as the iodination reagent) decreased the product yield.[9]

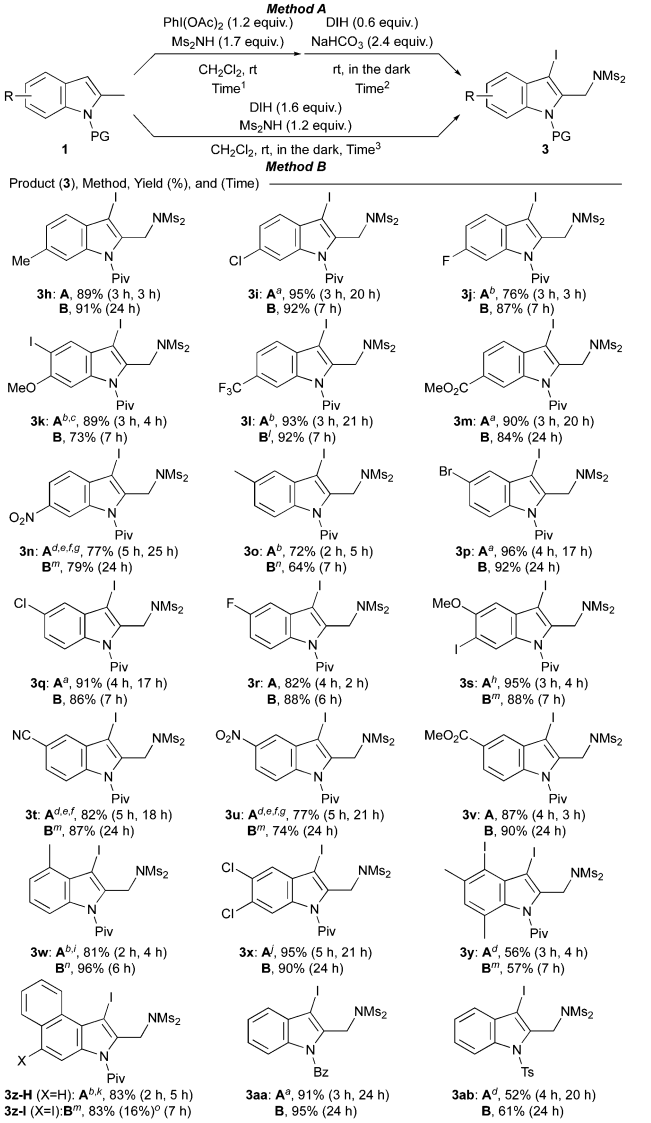
To explore the substrate scope for the direct iodo-amination using two methods (Methods A and B), the utility of various imides in the reaction with **1a** was examined under the optimum conditions (Table 1). When aliphatic, aromatic, and asymmetric bis(sulfonyl)imides were used in the reaction under both conditions, the corresponding products (**3b–3g**) were obtained in high yields (78–97%), respectively. A direct 1,3-iodo-amination of various indoles bearing useful substituents on the indole ring (**1**) with Ms_2NH was also examined by using

Table 1 1,3-Iodo-amination of **1a** with bis(sulfonyl)imides



[a] The reaction was carried out for 24 h. [b] $NaHCO_3$ (1.2 equiv.) was added.

Table 2 1,3-Iodo-amination of indoles (**1**) with Ms_2NH



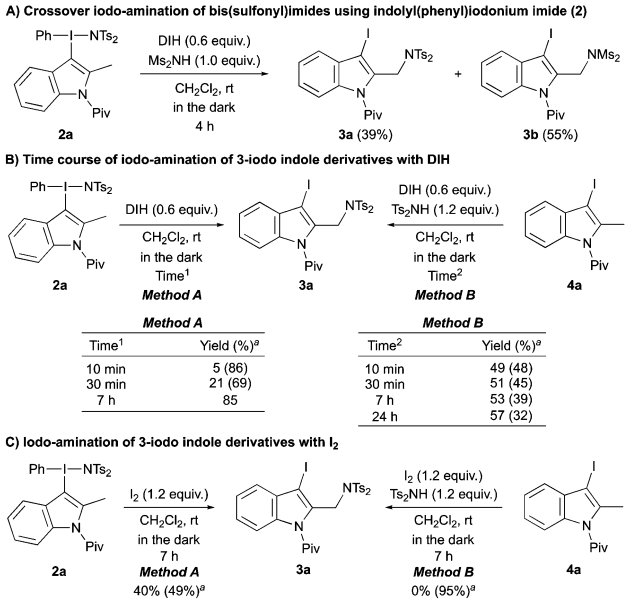
[a] NIS (2.0 equiv.) was used. [b] Ms_2NH (1.2 equiv.) was used. [c] DIH (1.0 equiv.) was used. [d] DIH (1.6 equiv.) was used. [e] Ms_2NH (2.4 equiv.) was used. [f] The reaction was carried out without $NaHCO_3$. [g] Na_2SO_4 (2.0 equiv.) was added. [h] NIS (2.4 equiv.) was used. [i] DIH (0.5 equiv.) was used. [j] NIS (3.0 equiv.) was used. [k] NIS (1.2 equiv.) was used. [l] Ms_2NH (1.7 equiv.) was used. [m] DIH (2.1 equiv.) was used. [n] Ms_2NH (1.5 equiv.) was used. [o] Number in parentheses indicates the yield of **3z-H**.

both methods (Table 2). Various indoles, including 6-, 5-, and 4-substituted indole derivatives (**1h–1n**), furnished the corresponding products (**3h–3n**) in high yields (64–96%) by both iodo-amination methods. Among them, simultaneous to the iodination of the aromatic ring, substrates bearing 6-OMe (**1k**), 5-OMe (**1s**), 5,7-diMe (**1y**), and naphthyl (**1z**) groups gave concurrently iodinated products (**3k**, **3s**, **3y**, and **3z-I** (in Method B)) in good yields (56–95%), respectively. Disubstituted indole derivatives (**1x–1z**) and indole derivatives protected with other groups instead of a pivaloyl group (**1aa** and **1ab**) were also converted into the desired products (**3x–3ab**) in 56–95% yields. For the reaction of **1z**, a divergent synthesis of a mono-iodinating product (**3z-H**) and a di-iodinating product (**3z-I**) from **1z** was enabled by these iodo-aminations with the two methods. Unfortunately, the reaction of 2-ethylindole and 2-benzylindole derivatives did not afford the desired products.

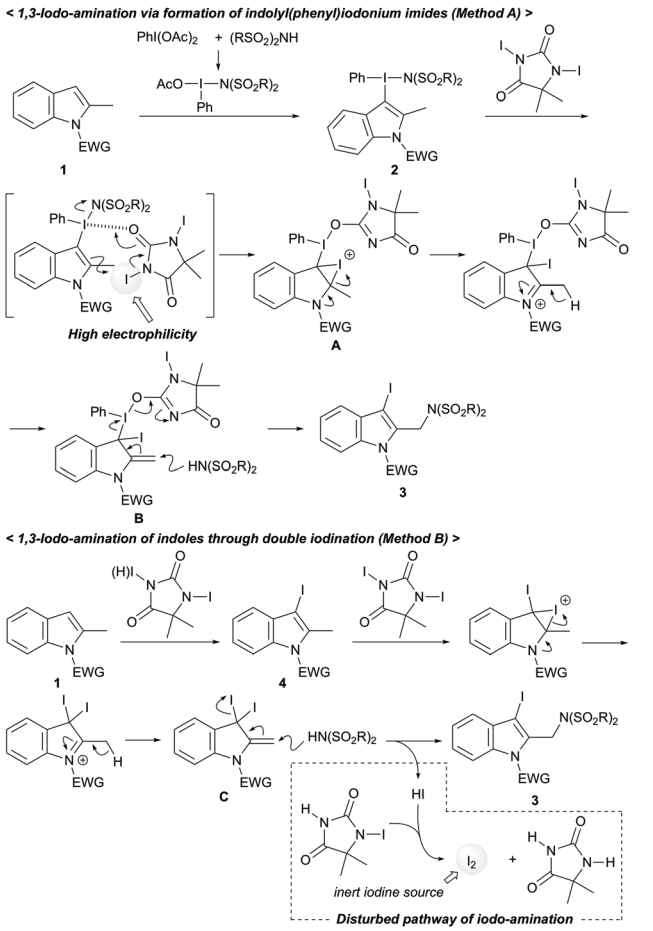
We performed mechanistic studies on the direct iodo-amination of **1** to elucidate the reaction mechanism. In Method A, the reaction of **1a** with $PhI(OAc)_2$, Ts_2NH, and DIH produced iodobenzene as the co-product together with **3a**.[10] In addition, a crossover iodo-amination of **2a** with Ms_2NH provided two iodo-amination products **3a** (39%) and **3b** (55%) (Scheme 3A). Time course experiments on the iodo-amination of 3-iodo indole derivatives **2a** and **4a** with 0.6 equiv. DIH interestingly revealed major differences in the reactivity of the substrates (Scheme 3B). The reaction of **4a** was disturbed halfway whereas the reaction of **2a** efficiently proceeded to give the desired product in high yield. Furthermore, the iodo-amination of **4a** with I_2 was inactive compared to that of **2a** with I_2 (Scheme 3C).

Based on these mechanistic experiments, we proposed a reaction mechanism, as depicted in Scheme 4. In Method A, 2-methyl indole (**1**) is converted into indolyl(phenyl)iodonium imide (**2**) by reacting with $PhI(OAc)(N(SO_2R)_2)$ generated *in situ* from $PhI(OAc)_2$ and $(RSO_2)_2NH$. Upon subsequent activation by the iodine atom in **2** as a Lewis acid, the iodo reagent promotes electrophilic addition to the enamine moiety in indole by increasing the electrophilicity of a cationic iodine atom on the iodo reagent.[3] This electrophilic addition converts **2** into an unstable iodonium cation intermediate (**A**), which subsequently forms *exo*-enamine (**B**) by ring-opening elimination. The intermolecular S_N2' nucleophilic substitution of bis(sulfonyl)imide into **B** is promoted due to the high leaving ability of the λ^3-iodanyl group to provide a 2-aminomethyl-3-iodo-indole derivative (**3**). By contrast, in Method B, after **1** is transformed into a 3-iodo indole derivative (**4**) by electrophilic iodination with the iodinating reagent,[11] a second electrophilic iodination (double iodination) induces the formation of an *exo*-enamine form of indole (**C**). Finally, **3** is obtained through an S_N2' nucleophilic substitution, similar to Method A. It is important to note that the iodide ion (I^-) released by the S_N2' nucleophilic substitution binds other cationic iodine atoms on the iodinating reagent to form molecular iodine (I_2), which is an inert iodine source for electrophilic iodination. Therefore, iodo-amination through double iodination must use an excess amount of iodine reagent to efficiently give the desired product.

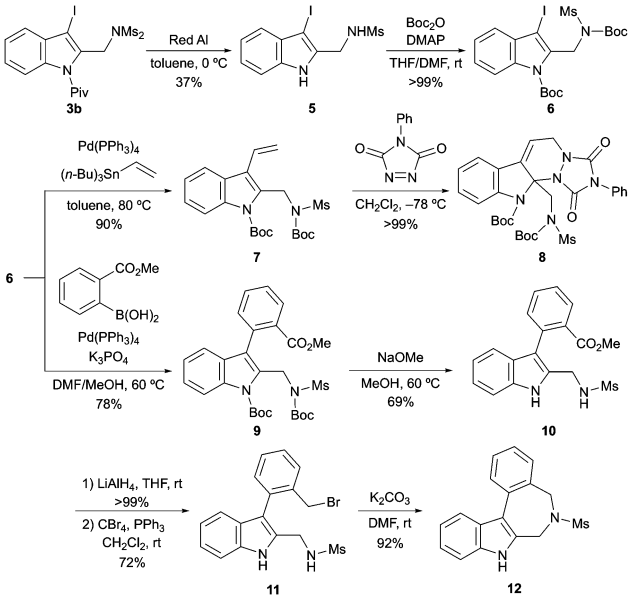
To demonstrate the utility of iodo-amination products, we synthesized a tetracyclic indole derivative (**8**) and an



Scheme 3 Comparison of the iodo-amination between the indolyl(phenyl)-iodonium imide (**2**) and the 3-iodo indole derivative (**4**). [a] Numbers in parentheses indicate recovery of substrates.



Scheme 4 Plausible reaction mechanisms for 1,3-iodo-amination of **1**.



Scheme 5 Derivatization of the 2-aminomethyl-3-iodo-indole derivative (**3b**).

indolobenzazepin derivative (**12**) (Scheme 5). Replacement of the protecting group in **3b** by reductive deprotection, which affords demesylated/depivaloylated indole (**5**), followed by protection with Boc_2O of **5** provided *N*-Boc protected indole derivatives (**6**). Vinylation of **6** by the Stille coupling reaction[12] gave a conjugated diene (**7**) in 90% yield, and a Diels–Alder reaction with 1,2,4-triazolin-3,5-dione[13] afforded a poly-nitrogen tetracyclic indole derivative containing a quaternary carbon center (**8**) in high yield. Besides, the Suzuki–Miyaura coupling reaction[14] of **6** with 2-methoxycarbonylphenylboronic acid was also effective in providing a coupling product (**9**). The following reactions of **9**, namely, cleavage of the two Boc groups under basic conditions, reduction of the ester group, bromination of the alcohol group using the Appel reaction, and 7-membered ring cyclization by the nucleophilic substitution of **11**, gave the indolobenzazepin derivative (**12**) in high yield.

In conclusion, we developed a 1,3-iodo-amination of 2-methyl indoles (**1**) using plural iodine compounds, including hypervalent iodine(III) compounds and iodinating reagents, as a novel method for C_{sp^2}–C_{sp^3} dual functionalization. This process is characterized by the formation of indolyl(phenyl)iodonium imide (**2**) using $PhI(OAc)_2$ and the double iodination of excess DIH as an iodine reagent to afford the 2-aminomethyl-3-iodo-indole derivative (**3**). The economical and efficient installation of plural functional groups into an organic molecule by a dual functionalization process is underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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9 When DIH (0.6 equiv.) was used in the reaction of **1a** with Ts_2NH, **3a** was obtained in 7% yield together with **4a** (84%).
10 The reaction of **1a** under the optimum conditions of Method A (Scheme 2, eqn (5)) gave iodobenzene (87%) together with **3a** (90%).
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