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(Diacetoxyiodo)benzene-Mediated Transition-Metal-Free Amination of C(sp^3)–H Bonds Adjacent to Heteroatoms with Azoles: Synthesis of N-Alkylated Azoles

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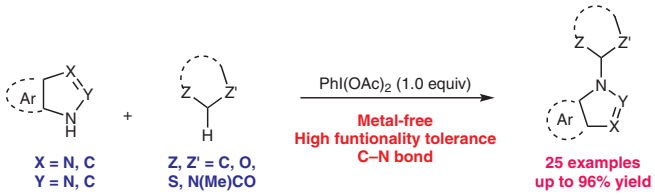

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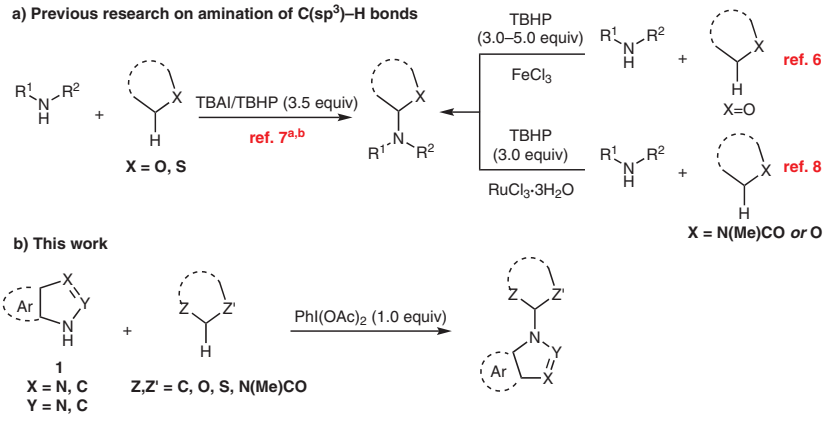
Abstract A novel PhI(OAc)$_2$-mediated cross-dehydrogenative coupling reaction of α-C(sp^3)–H bonds adjacent to a hetero atom with various azoles has been developed, which provides an alternative method for constructing C–N bonds with high atom efficiency. This new protocol requires no metal catalyst and it provides ready access to a wide range of N-alkylated azole derivatives in moderate to excellent yields by using commercially available PhI(OAc)$_2$ as the sole oxidant. Furthermore, the method is effective on a gram scale, which highlights the practicality of this transformation. The result of radical-captured experiments indicated that the transformation might involve a free-radical pathway.

Key words diacetoxyiodo benzene, C–H functionalization, C–N bond, azoles, metal-free, amination

Azoles and their derivatives are widely used in pharmaceuticals because of their broad spectrum of biological activities, including antimicrobial, antiinfection, antiinflammatory, DNA-cleavage, and antitubercular properties.[1] In addition, azole derivatives have also been frequently used as precursors of N-heterocyclic carbenes[2] and ionic liquids.[3] The N-alkylation of azoles is the most common method for the synthesis of azole derivatives because of the large number of N–H bonds present in azoles. The conventional method for the alkylation of azoles involves nucleophilic substitution with an electrophile such as an alkyl halide.[4] However, this strategy suffers from significant limitations such as harsh conditions, the need for a strong base, overalkylation, and a lack of commercially available cyclic ether halides. Nowadays, direct C–H functionalization through a dehydrogenative pathway has emerged as an attractive method for constructing C–C or C–X bonds.[5] This versatile strategy avoids the prefunctionalization of substrates and it has advantages in terms of atom economy. By applying this protocol, much progress has been made in syntheses of N-alkylated azole derivatives through oxidative C–N coupling reactions. For example, Li and co-workers reported a novel and efficient method for the synthesis of azole derivatives through iron-catalyzed oxidation of ethers.[6] Subsequently, Aruri and co-workers developed a metal-free method for the N-alkylation of azoles catalyzed by tetrabutylammonium iodide and *tert*-butyl hydroperoxide (TBHP) through the α-C(sp^3)–H activation of ethers (Scheme 1).[7] Recently, Lakshman's group described another Ru-catalyzed method for the functionalization of C(sp^3)–H bonds adjacent to oxygen atoms of ethers with various azoles.[8] Although there have been many achievements relating to the N-alkylation of azoles through oxidative coupling reactions, several drawbacks still remain; for example, these transformations invariable require reflux temperatures for prolonged periods and they suffer from the need for large excesses of oxidants such as TBHP or di-*tert*-butyl peroxide (DTBP). Consequently, the development of environmentally friendly and highly efficient methods for activating C(sp^3)–H bonds for the synthesis of functional azoles is still of great interest.

In the past decade, with the growing demand for the development of environmentally conscious synthetic approaches, hypervalent iodine compounds have been extensively used in C–H functionalization reactions, due to their low toxicity, environmental friendliness, and ready availability.[9] For example, Maruoka's group developed a novel method for the direct esterification of benzylic C–H bonds of alkylbenzenes by a combination of a hypervalent iodine compound and visible-light irradiation.[10] Here, we report a transition-metal-free oxidative coupling reaction of a variety of azoles with ethers, tetrahydrothiophene, or NMP to give a series of N-alkylated azoles by employing inexpensive PhI(OAc)$_2$as the sole an oxidant (Scheme 1).

To begin our study, we chose 1*H*-benzimidazole (**1a**) and isochroman (**2a**) as model reactants to explore and optimize the cross-dehydrogenative reaction. The reaction

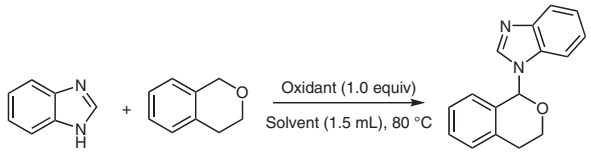


Scheme 1 Syntheses of N-alkylated azole derivatives

was initially studied with Dess-Martin periodinane (DMP) as the oxidant in DCE at 80 °C without any metal or additive. Fortunately, the coupling product **3aa** was successfully obtained, even though the yield was only 65% (Table 1, entry 1). Encouraged by this result, we investigated other commercially available oxidants such as 2-iodoxybenzoic acid (IBX), $PhI(OAc)_2$, [bis(trifluoroacetoxy)iodo]benzene (PIFA), TBHP, DTBP, $K_2S_2O_8$, and O_2 (entries 2–8), but only $PhI(OAc)_2$ promoted this direct amination (entry 2). Among the various oxidants surveyed, IBX and PIFA proved to be effective for this transformation, but gave lower yields than $PhI(OAc)_2$, whereas the other oxidants were ineffective (entries 3–8). Subsequently, various commonly used solvents, including EtOAc, MeCN, acetone, and CH_2Cl_2 were examined, but none of these gave a better result (entries 9–12). Increasing the amount of $PhI(OAc)_2$ to 1.5 equivalents did not increase the yield of **3aa** (entry 13), and when the amount of $PhI(OAc)_2$ was reduced to 0.5 equivalents, the expected decrease in yield was observed (entry 14). Increasing the temperature to 100 °C or decreasing the temperature to 60 °C led to a decrease in the yield of the coupled product (entries 15 and 16). On the basis of our screening of the reaction conditions, we concluded that this oxidative cross-coupling reaction should be performed in DCE at 80 °C for six hours with $PhI(OAc)_2$(1.0 equiv) as an oxidant.

Next, various sets of experiments were carried out to investigate the scope and limitations of this reaction under the optimized conditions. First, the success of the direct amination of isochroman (**2a**) with 1*H*-benzimidazole (**1a**) prompted us to extend our protocol to other ether derivatives (Scheme 2). The method was found to be applicable to a wide range of ethers, giving the desired coupled products in moderate to excellent yields. For example, 1,3-dihydro-2-benzofuran reacted with 1*H*-benzimidazole (**1a**) to afford product **3ab** in 88% yield. Next, the reactions of a range of cyclic ether derivatives that contained no phenyl moiety were examined. Gratifyingly, this transformation showed excellent tolerance to aliphatic cyclic ethers such as tetrahydrofuran, tetrahydropyran, 1,4-dioxane, or 1,3-dioxolane, giving the corresponding coupled products **3ac–af** in mod-

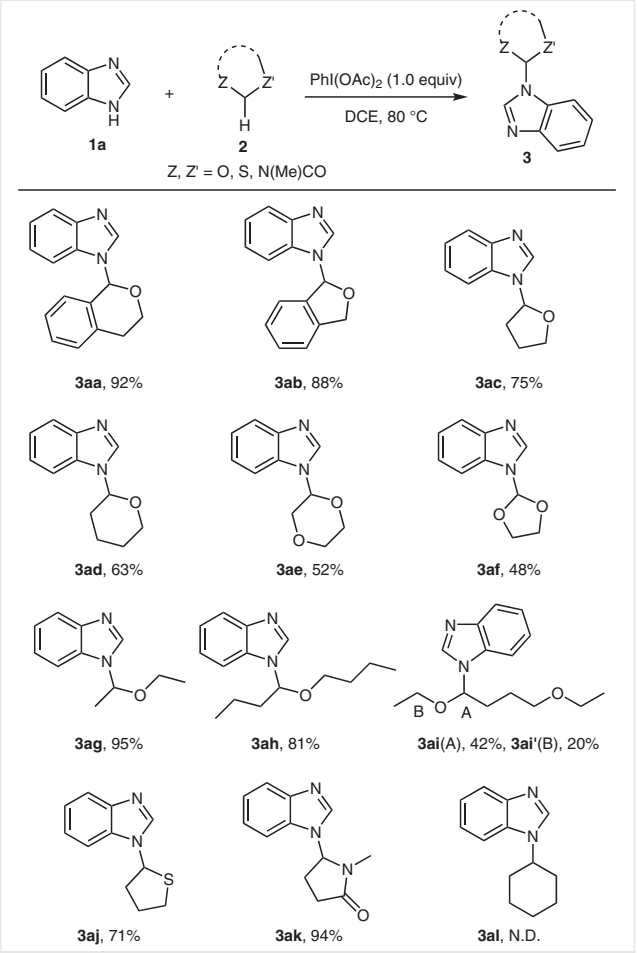
Table 1 Screening for Optimal Reaction Conditions[a]



1a 2a 3aa

Entry	Oxidant	Solvent	Yield[b] (%)
1	DMP	DCE	65
2	$PhI(OAc)_2$	DCE	92
3	IBX	DCE	60
4	PIFA	DCE	81
5	TBHP	DCE	N.D.
6	DTBP	DCE	N.D.
7	$K_2S_2O_8$	DCE	N.D.
8	O_2	DCE	N.D.
9	$PhI(OAc)_2$	EtOAc	70
10	$PhI(OAc)_2$	MeCN	75
11	$PhI(OAc)_2$	acetone	59
12	$PhI(OAc)_2$	CH_2Cl_2	82
13[c]	$PhI(OAc)_2$	DCE	91
14[d]	$PhI(OAc)_2$	DCE	46
15[e]	$PhI(OAc)_2$	DCE	85
16[f]	$PhI(OAc)_2$	DCE	55

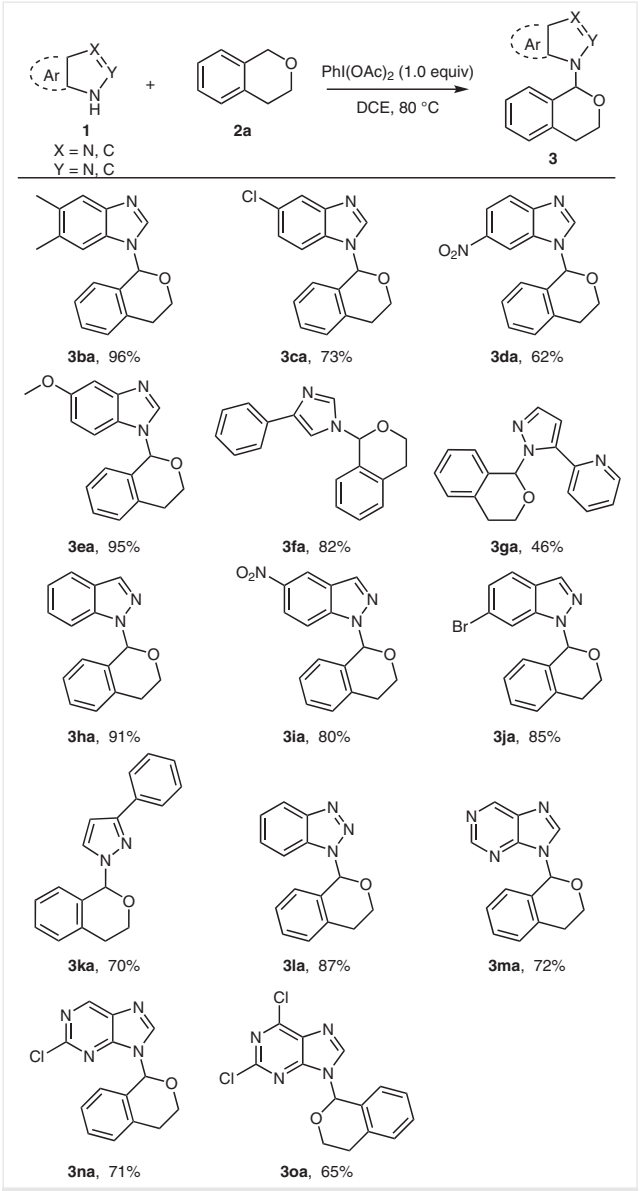
[a] Reaction conditions: **1a** (0.5 mmoL), **2a** (2.0 mmol), oxidant (0.5 mmol), solvent (2.0 mL), 80 °C, 6 h.
[b] Isolated yield based on **1a**.
[c] $PhI(OAc)_2$ (1.5 equiv).
[d] $PhI(OAc)_2$ (0.5 equiv).
[e] At 100 °C.
[f] At 60 °C.



Scheme 2 Direct alkylation reactions of 1*H*-benzimidazole: *Reaction conditions*: **1a** (0.5 mmoL), **2** (2.0 mmol), $PhI(OAc)_2$, (0.5 mmol), DCE (2.0 mL), 80 °C, 6 h.

erate to excellent yields. Next, the reactivity of the straight-chain ether derivatives diethyl ether, dibutyl ether, and 1,4-diethoxybutane were investigated. All these straight-chain ethers gave the corresponding C–N coupled products, although the yield decreased markedly with increasing length of the carbon chain of the ethers. For example, diethyl ether (**2g**) reacted readily with 1*H*-benzimidazole (**1a**) to give the coupled product **3ag** in an excellent yield of 95%, whereas 1,4-diethoxybutane (**2i**) gave a mixture of **3ai** and **3ai'** in yields of 42% and 20%, respectively. Subsequently, other categories of α-C(sp^3)–H bonds adjacent to a hetero atom were also investigated for this transformation. Tetrahydrothiophene and NMP also underwent the transformation and gave the corresponding oxidative coupled products **3aj** and **3ak** in 71% and 94% yield, respectively. It should be pointed out that the regioisomeric product was not obtained from the reaction of NMP with 1*H*-benzimidazole, possibly because the secondary carbon might be more reactive than the primary carbon. In addition, we also attempted to extend the reaction to cyclohexane as a substrate, but this failed to give the desired product **3al**.

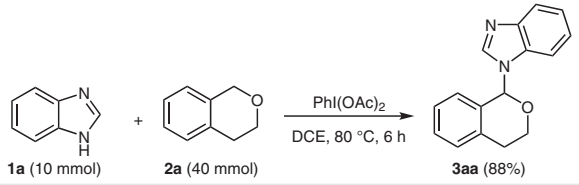
Having examined the scope of the C(sp^3)–H species, we then examined the corresponding reactions of a series of azoles with isochroman (**2a**) as a standard substrate (Scheme 3). Various substituted benzimidazoles containing electron-donating groups, such as 5,6-dimethyl-1*H*-benzimidazole and 5-methoxy-1*H*-benzimidazole, or those containing electron-withdrawing groups, such as 5-chloro-1*H*-benzimidazole and 6-nitro-1*H*-benzimidazole, participated in the oxidative coupling reaction with isochroman (**2a**) to



Scheme 3 Direct amination of isochroman **2a** with various azoles. *Reaction conditions*: **1** (0.5 mmoL), **2a** (2.0 mmol), $PhI(OAc)_2$ (0.5 mmol), DCE (2.0 mL), 80 °C, 6 h.

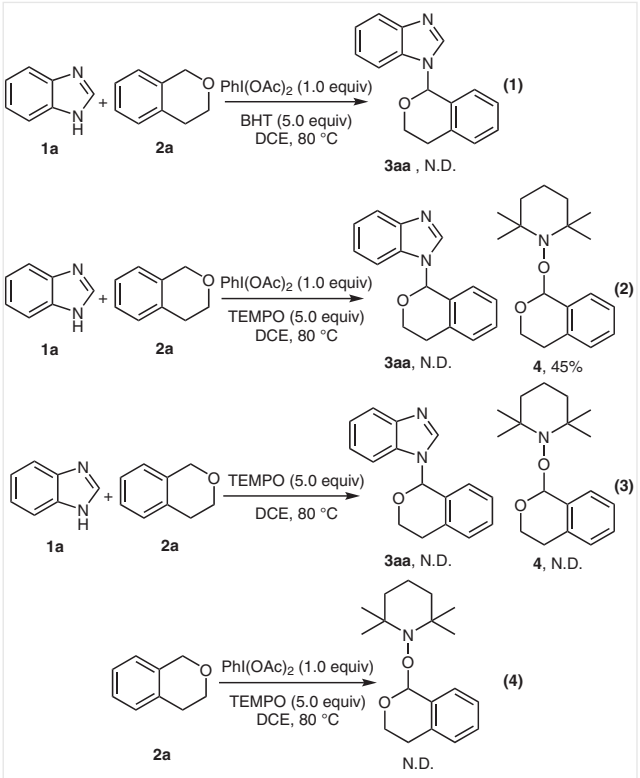
afford the corresponding C–N adducts **3ba–ea** in 62–96% yield. In addition, 4-phenyl-1*H*-imidazole also coupled to give **3fa** in 82% yield. Next, we expanded the scope of the azole substrate to include indazoles and pyrazoles. To our delight, our reaction protocol was efficient with these azoles and it provided the corresponding coupled products **3ga–ka** in synthetically useful yields of 46–91%. For example, 5-nitro-1*H*-indazole, which contains a strongly electron-withdrawing group, gave **3ia** in a remarkably high yield of 80%. On extending the azole substrate to benzotriazole, we obtained the desired C–N coupling product **3la** in an excellent yield of 87%. Finally, we examined the reactivities of purine, 2-chloropurine, and 2,6-dichloropurine, and we found that all three were well tolerated under the standard conditions, affording the oxidative coupled products **3ma–oa** in satisfactory yields.

To evaluate the potential synthetic utility of this C–N bond formation strategy, we carried out the reaction 1*H*-benzimidazole (**1a**) and isochroman (**2a**) on a preparative scale under the optimized conditions, and we obtained the desired product **3aa** in 88% yield (Scheme 4).



Scheme 4 Large-scale experiment

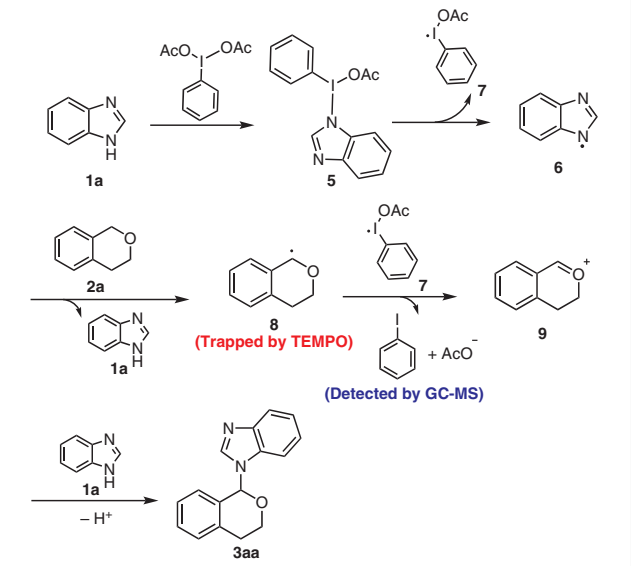
To explore the possible mechanism of our transformation, we carried out several control experiments, as shown in Scheme 5. First, the addition of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) to the model reaction system completely inhibited the oxidative coupling reaction (Scheme 5, Equation 1); however, no BHT–isochroman coupled product was obtained. Next, we observed that the model reaction was also inhibited by TEMPO, another radical scavenger and, fortunately, the TEMPO–isochroman coupled product **4** was obtained as a major product (Scheme 5, Equation 2). This result tends to confirm that a radical process is involved in this transformation. Note that neither **3aa** nor **4** was observed in the absence of $PhI(OAc)_2$ (Scheme 5, Equation 3). Finally, we treated isochroman (**2a**) with $PhI(OAc)_2$ and TEMPO under the standard conditions without adding benzimidazole (**1a**); however, the TEMPO–isochroman coupled product **4** was not observed (Scheme 5, Equation 4). This result suggested that 1*H*-benzimidazole not only acts as a substrate, but also plays an important role in initiating the radical transformation. A GC/MS experiment showed that PhI is formed during the transformation (see Supporting Information).



Scheme 5 Control experiments (N.D. = not detected)

On the basis of the above experimental results, we propose the plausible mechanism for our oxidative C–N coupling reaction that is shown in Scheme 6. Initially, the nitrogen-centered radical **6** and the iodine radical **7** are formed through a substitution reaction of 1*H*-benzimidazole (**1a**) with $PhI(OAc)_2$, followed by homolysis of the I–N bond. The resulting N-radical **6** then undergoes α-hydrogen abstraction with isochroman (**2a**) to afford the isochroman radical **8** (captured by TEMPO). Next, through further oxidation by **7**, radical **8** is transformed into the cationic intermediate **9**. Finally, the desired product **3aa** is obtained through a cross-dehydrogenative coupling reaction of **1a** and **9**.

In conclusion, we have succeeded in developing a novel $PhI(OAc)_2$-mediated metal-free method for construction of C–N bonds through an oxidative cross-coupling reaction between an α-C(sp^3)–H bond adjacent to a heteroatom and various azoles, without adding any base or additive.[11] This transformation proved to be effective for the amination of various C(sp^3)–H bonds, including those of ethers, tetrahydrothiophene, and NMP, with a wide range of azoles bearing various functional groups, and it gave the corresponding compounds in moderate to good yields. Owing to its broad substrate scope and high efficiency, this method should be of great synthetic potential.



Scheme 6 Proposed mechanism of our C–N coupling reaction

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610293.

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(11) **1-(3,4-Dihydro-1*H*-isochromen-1-yl)-1*H*-benzimidazole (3aa; Ref. 6); Typical Procedure**

PhI(OAc)$_2$ (0.5 mmol) was added to a mixture of 1*H*-benzimidazole (**1a**; 0.5 mmol), isochroman (**2a**; 2.0 mmol), and DCE (2.0 mL) in a Schlenk tube at r.t. The mixture was stirred at 80 °C for 6 h then cooled. H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residues were purified by flash column chromatography (silica gel, hexane–EtOAc) to give a colorless oil; yield: 115 mg (92%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86–7.83 (m, 1 H), 7.65 (s, 1 H), 7.48–7.46 (m, 1 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.35–7.31 (m, 3 H), 7.27 (t, *J* = 7.2 Hz, 1 H), 7.09 (d, *J* = 7.8 Hz, 1 H), 6.94 (s, 1 H), 4.02–3.98 (m, 1 H), 3.87–3.83 (m, 1 H), 3.17–3.12 (m, 1 H), 2.91–2.87 (m, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.2, 142.7, 135.0, 133.8, 130.3, 129.4, 129.2, 127.1, 127.0, 123.4, 122.8, 120.4, 111.1, 80.2, 60.1, 27.7. MS (ESI): *m/z* = 251.1 [M + H]$^+$.