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Direct preparation of unprotected aminimides (R_3N^+–NH^-) from natural aliphatic tertiary alkaloids (R_3N) by [Mn(TDCPP)Cl]-catalysed *N*-amination reaction†

Shilong Zhang, [a] Yungen Liu, *[a] Fangrong Xing[b] and Chi-Ming Che *[abc]

A panel of natural aliphatic tertiary alkaloids (R_3N) were directly converted to R_3N^+–NH^- (without the need to prepare protected aminimides R_3N^+–NR'^- followed by deprotection) by [Mn(TDCPP)Cl]-catalysed *N*-amination reaction, with *O*-(2,4-dinitrophenyl) hydroxylamine as the nitrogen source, in up to 98% yields under mild reaction conditions.

Alkaloids are a family of natural products prevalent in herbs known for its broad spectrum of biological activities and uses in traditional therapy. Pure compounds and derivatives/analogues of alkaloids can be easily found in pharmaceuticals,[1–4] examples of which include the naturally occurring tertiary alkaloid *N*-oxides (R_3N^+–O^-) that show physiological activities similar to their parent alkaloid compounds (Fig. 1).[5–8] Alkaloid *N*-oxides exhibit higher polarity than their parent alkaloid compounds and show decreased penetration rate through the membrane system resulting in a decrease in toxicity response.[9–12] This class of *N*-oxide compounds might be reduced under the hypoxic environment, which is often found in the tumor tissue.[13,14] However, many of these *N*-oxides have a poor stability.[15] As amine *N*-oxides are iso-electronic with aminimides R_3N^+–NR'^-,[16] or their deprotected forms R_3N^+–NH^-, we envisioned that aminimides of alkaloids might exhibit similar bioactivities but are more stable than their *N*-oxide counterparts due to the lower electronegativity of nitrogen. In the literature, aminimides in protected forms R_3N^+–NR'^- (R′ = *p*-tosyl, *etc.*) could be obtained from *N*-amination of amines by transition metal-catalysed nitrene (NR′) transfer reactions;[17,18] among the known R_3N^+–NR'^- compounds obtained by such nitrene transfer reaction, only that of brucine was subjected to a second, deprotection step to give the corresponding R_3N^+–NH^- compound in 21% total yield (Scheme 1).[17] To the best of our knowledge, the preparation of unprotected aminimides R_3N^+–NH^- directly from metal-catalysed nitrogen atom/group transfer to amines has not been reported in the literature.

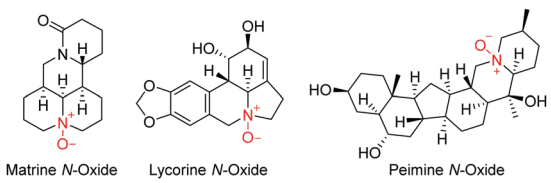
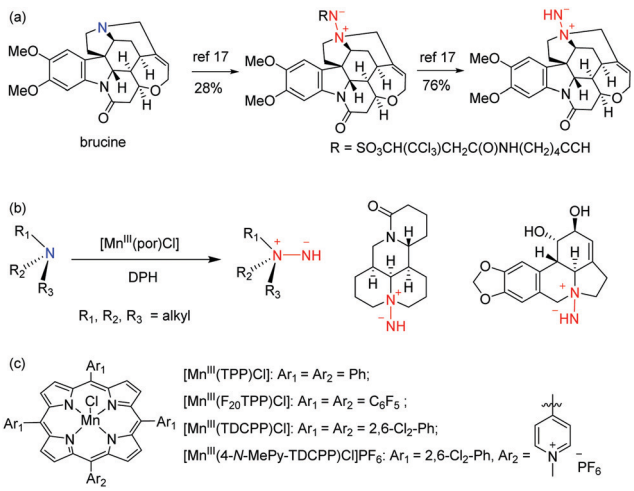


Fig. 1 Examples of naturally occurring alkaloid *N*-oxides.



Scheme 1 (a) Reported method of preparing an unprotected aminimide by two steps, *i.e.*, metal-catalysed nitrene transfer to brucine to give protected aminimide followed by deprotection; (b) method employed in this work; (c) catalysts employed in this work.

[a] *Department of Chemistry, Southern University of Science and Technology, Shenzhen, Guangdong 518055, P. R. China. E-mail: cmche@hku.hk, liuyg@sustech.edu.cn*
[b] *Department of Chemistry, State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Hong Kong, P. R. China*
[c] *HKU Shenzhen Institute of Research and Innovation, Shenzhen, Guangdong 518057, P. R. China*

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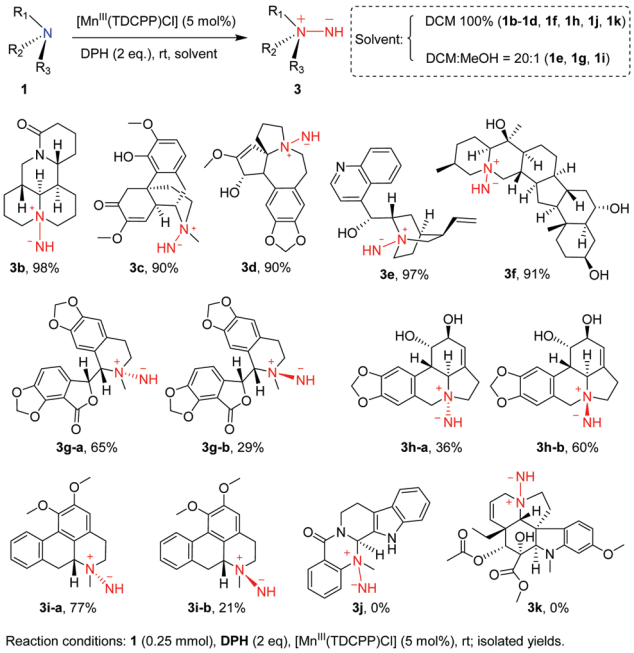
Recently, *O*-functionalized hydroxylamine derivatives (such as $RONH_2$ or $RONH_3^+$, R = strong electron-withdrawing groups) had been reported to be a versatile nitrogen source for the preparation of unprotected amine products with transition metal complex as catalyst.[19–22] Morandi and co-worker reported the preparation of 2-amino-1-phenylethanols[23] from alkenes with $PivONH_3OTf$ as the nitrogen source, and amination of aromatic C–H bonds[24] with $MsONH_3OTf$ as nitrogen source; Flack, Kürti and co-workers reported the dirhodium-catalysed amination of aromatic C–H bonds[20] with NH_2/NH(alkyl)-*O*-(sulfonyl)hydroxylamines in the presence of a Brønsted acid *via* a highly reactive protonated rhodium–nitrene intermediate. Very recently, we reported ruthenium porphyrin-catalysed intermolecular amino-oxyarylation of alkenes to give primary amines[25] using *O*-(2,4-dinitro-phenyl)hydroxylamine (DPH) as nitrogen source. Herein is described $[Mn^{III}(TDCPP)Cl]$-catalysed one-step *N*-amination reaction of the natural aliphatic tertiary alkaloids R_3N (**1**), with DPH (**2**) as the nitrogen source, to directly afford unprotected aminimides $R_3N^+–NH^-$ (**3**) in up to 98% yields under mild conditions (Scheme 1).

At the outset, we employed matrine (**1a**) as the substrate to optimize the reaction conditions. A panel of metal porphyrins and nitrogen sources were screened (see Table S4 in the ESI†). With DPH (**2a**) as the nitrogen source, the iron porphyrins $[Fe^{III}(TPP)Cl]$, $[Fe^{III}(TDCPP)Cl]$, and $[Fe^{III}(F_{20}TPP)Cl]$ exhibited low catalytic activity with no aminimide product(s) obtained (Table S4, entries 1–3, ESI†); ruthenium porphyrins such as $[Ru^{IV}(TPP)Cl_2]$, $[Ru^{IV}(TDCPP)Cl_2]$, and $[Ru^{IV}(F_{20}TPP)Cl_2]$ catalysed this reaction to give the unprotected aminimide product **3a** in 21–32% yields (Table S4, entries 7–9, ESI†). To our delight, significant improvement in product yields up to 89% was achieved with manganese porphyrins including $[Mn^{III}(TPP)Cl]$, $[Mn^{III}(TDCPP)Cl]$ and $[Mn^{III}(F_{20}TPP)Cl]$ as the catalyst (Table S4, entries 4–6, ESI†). Further screening of nitrogen source (Table S4, entries 10–13, ESI†) and solvent (Table S4, entries 14–17, ESI†) revealed that dichloromethane gave the best result and DPH was the best nitrogen source. In the absence of catalyst $[Mn^{III}(TDCPP)Cl]$, there was no substrate conversion (Table S4, entry 18, ESI†). In addition, the reaction was insensitive to air and moisture, and inert atmosphere protection was not needed.

Under the optimal reaction conditions, we examined the substrate scope of the manganese porphyrin-catalysed direct preparation of unprotected aminimides of alkaloids (Scheme 2). A panel of tertiary aliphatic alkaloids **1b-1i** could be converted to the corresponding unprotected aminimides **3b-3i** in up to 98% yield. Sophoridine (**1b**), sinomenine (**1c**), cephalotaxine (**1d**), cinchonidine (**1e**) and peimine (**1f**) were converted to **3b-3f**, respectively, in 90–98% yields. The presence of functional groups such as hydroxy (**1c**, **1e**, **1f**), quinolinyl (**1e**) and alkene (**1c**, **1d**, **1e**) had no significant effect on the substrate conversion and product yield. Bicuculline (**1g**), lycorine (**1h**), and nuciferine (**1i**) gave the corresponding products **3g-3i** each as a pair of *cis*/*trans*-isomers. Evodiamine (**1j**), a tertiary alkaloid containing l-2,3-dihydroquinazolinone moiety, could not be converted to the corresponding product **3j**. Vindoline (**1k**), in which the tertiary amine localizes deeply in the molecule, was inert under the reaction condition.



Scheme 2 Preparation of unprotected aminimides **3** directly from alkaloids **1**.

The crystal structures of the unprotected aminimides **3c** and **3h-b** have been determined by X-ray diffraction analysis (Fig. 2), which feature N–N bond distances of 1.462 Å and 1.451 Å, respectively. These N–N bond distances are similar to the corresponding N–N bond distances in the crystallographically characterized protected aminimides reported in the literature (*e.g.*, 1.463–1.471 Å[18]).

In the course of the catalytic amination reaction, a red species was observed to accumulate gradually with the consumption of $[Mn^{III}(TDCPP)Cl]$. Further characterization of this red species by UV-vis, MS and ^1H NMR spectroscopic analyses suggested it to be $[Mn^{V}(TDCPP)(N)]$,[26] the structure of which was confirmed by comparing the characterization data with that of $[Mn^{V}(TDCPP)(N)]$ independently prepared and with its structure determined by single crystal X-ray diffraction analysis (Fig. 3), which features Mn≡N bond distance of 1.508 Å. Indeed, $[Mn^{V}(TDCPP)(N)]$ could be obtained by the reaction of $[Mn^{III}(TDCPP)Cl]$, DPH and NaOH (aq., 2.5 M) in dichloromethane with nearly quantitative yield. Notably, treatment of the isolated $[Mn^{V}(TDCPP)(N)]$ with alkaloids **1** under

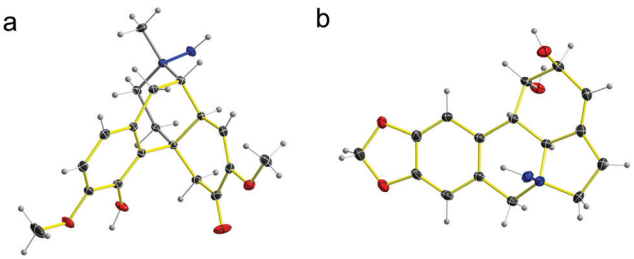


Fig. 2 ORTEP drawings of **3c** (a) and **3h-b** (b). Thermal ellipsoid probability level: 30%.

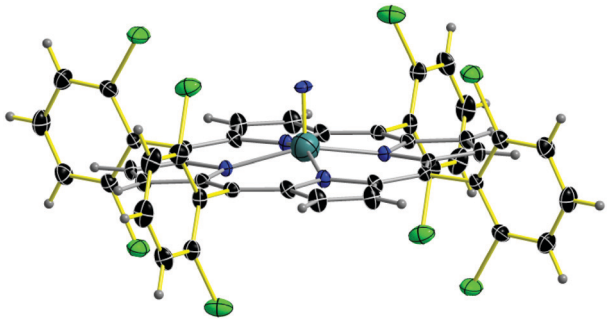


Fig. 3 ORTEP drawing of [Mn^{V}(TDCPP)(N)]. Thermal ellipsoid probability level: 30%.

stoichiometric reaction conditions did not afford the unprotected aminimides **3**.

To gain further insight into the reaction mechanism, we employed ESI-MS to follow the reaction. Unfortunately, the MS signals attributed to the [Mn(TDCPP)]-containing species were weak; presumably the species is charge neutral. Hence, we prepared a cationic manganese porphyrin, [Mn^{III}(4-*N*-MePy-TDCPP)Cl]PF_6 (Scheme 1), by replacing one of the four *meso*-2,6-dichloro phenyl moieties of [Mn^{III}(TDCPP)Cl] with an *N*-methyl pyridinium group so that the resultant manganese porphyrin species and reaction intermediate(s) there from are cationic, hence easily detected by ESI-MS. We found that [Mn^{III}(4-*N*-MePy-TDCPP)Cl]PF_6 exhibited a catalytic activity similar to that of [Mn^{III}(TDCPP)Cl]; for example, both the complexes catalysed the reaction of sinomenine (**1c**) with DPH to give **3c** in 90% yield (see the ESI†). As shown in Fig. 4a, a cluster peak at *m*/*z* 903 was immediately detected right after mixing [Mn^{III}(4-*N*-MePy-TDCPP)Cl]PF_6 and DPH (10 eq.) in dichloromethane (for assignments of the other peaks in Fig. 4, see the ESI†), the intensity of which diminished dramatically upon addition of alkaloid sinomenine (20 eq., Fig. 4b). In contrast, for the reaction mixture in which synthetic [Mn(4-*N*-MePy-TDCPP)(N)]PF_6 (*m*/*z* 903 for the cation species, 1 eq.) was added prior to catalysis (Fig. 4c), the signal at *m*/*z* 903 did not decrease significantly after addition of sinomenine (20 eq.) under similar experimental conditions (Fig. 4d). The ESI-MS analyses did not reveal signals assignable to the parent ion of $[Mn(4\text{-}N\text{-MePy-TDCPP})(NH)]^{2+}$, $[Mn(4\text{-}N\text{-MePy-TDCPP})(NH)]^{+}$ or $[Mn(4\text{-}N\text{-MePy-TDCPP})(DPH)]^{2+}$. Although the isotopic pattern of the cluster peak at *m*/*z* 903 in Fig. 4a is consistent with that of $[Mn(4\text{-}N\text{-MePy-TDCPP})(N)]^{+}$, it is more reasonable to assign the signal at *m*/*z* 903 as a fragmented daughter ion of the [Mn(4-*N*-MePy-TDCPP)(NA)]$^{+}$ (A = H or (2,4-dinitrophenyl)hydroxyl) intermediate, which could be unstable and decompose to [Mn(4-*N*-MePy-TDCPP)(N)]$^{+}$ under the ESI-MS conditions.

On the basis of the above-mentioned experimental observations, a mechanism for the formation of unprotected aminimides **3** *via* [Mn(TDCPP)(NA)]X (X = Cl or solvent) active intermediate(s) was proposed and shown in Scheme 3. The reactive [Mn(TDCPP)(NA)]X species could be trapped by the

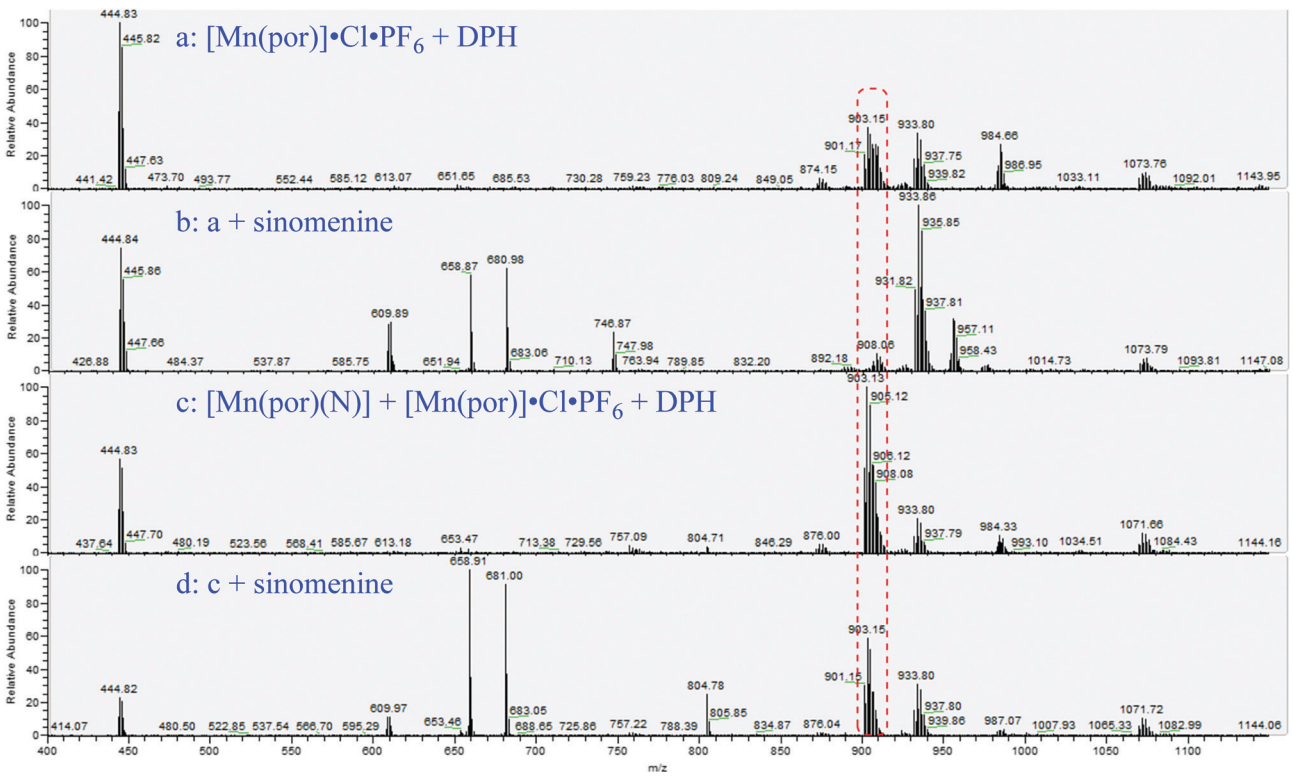
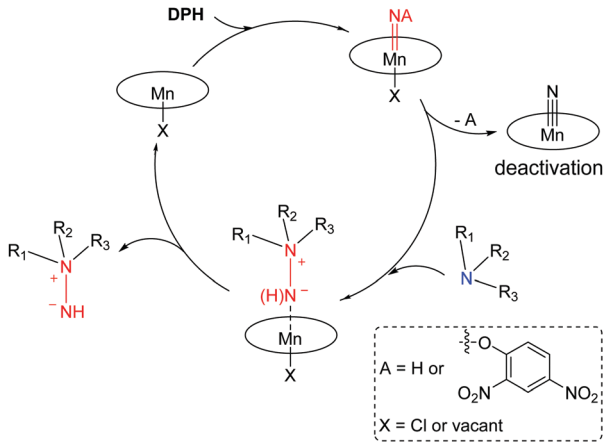


Fig. 4 ESI-MS analysis of the reaction mixtures: (a) 0.1 mM [Mn^{III}(por)Cl]PF_6 (por = 4-*N*-MePy-TDCPP) in dichloromethane solution with the addition of DPH (10 eq.); (b) sinomenine (20 eq.) was added to (a); (c) 0.1 mM [Mn^{III}(por)Cl]PF_6 and manganese-nitrido [Mn(por)(N)]PF_6 in dichloromethane solution with the addition of DPH (10 eq.); (d) sinomenine (20 eq.) was added to (c).



Scheme 3 Proposed mechanism for the formation of unprotected aminimides.

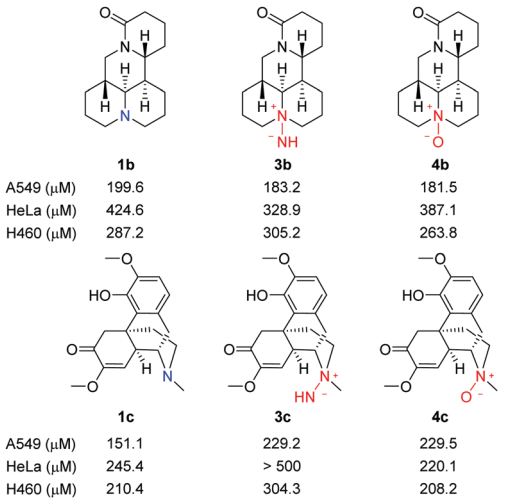


Fig. 5 Cytotoxicities of some alkaloids and their derivatives towards cancer cell lines upon 72 h treatment. A549: human lung adenocarcinoma; HeLa: cervical carcinoma; H460: human large-cell lung carcinoma.

tertiary alkaloids **1** to give the products **3** or partially underwent deactivation to give [Mn^{V}(TDCPP)(N)].

The cytotoxicity of unprotected aminimides **3b**, **3c**, **3d**, **3g-a**, **3g-b**, **3i**, as well as that of *N*-oxide derivatives **4b**, **4c**, **4d**, **4g**, **4i** and parent alkaloids **1b**, **1c**, **1d**, **1g**, **1i** towards several cancer cell lines were studied and compared. As shown in Fig. 5, the unprotected aminimides **3b** and **3c** exhibited cytotoxicity comparable to that of the parent alkaloids **1b** and **1c** and the corresponding *N*-oxides **4b** and **4c** (for the cytotoxicity of the others, see the ESI†).

In summary, under mild conditions and without protection by inert gas, the "[Mn^{III}(TDCPP)Cl] + DPH" protocol provides a simple and convenient method to prepare unprotected aminimides of alkaloids in good yields by a one-step reaction. Mechanistic studies suggested a manganese imido species to be the reactive intermediate. Cytotoxicity study indicated that the unprotected aminimides of alkaloids may provide new derivatives of alkaloids for further drug development.

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Conflicts of interest

There are no conflicts to declare.

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