Photocatalytic N-Methylation of Amines over Pd/TiO_2 for the Functionalization of Heterocycles and Pharmaceutical Intermediates

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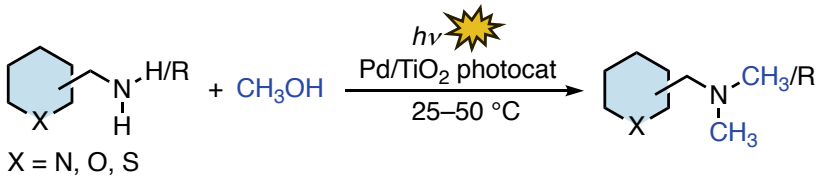
Supporting Information Placeholder

ABSTRACT: Amines in heteroaromatic systems and pharmaceutical intermediates were functionalized through N-methylation with methanol using a palladium-loaded titanium dioxide (Pd/TiO_2) photocatalyst. This method provides access to a series of tertiary *N*-methylamines bearing N-, O-, and/or S-containing heteroaromatic functionalities from primary/secondary amines and methanol under mild reaction conditions. Facile syntheses of several pharmaceuticals containing *N*-methyl or ethyl groups, as well as related deuterated drugs, was achieved through the late-stage functionalization of amines.

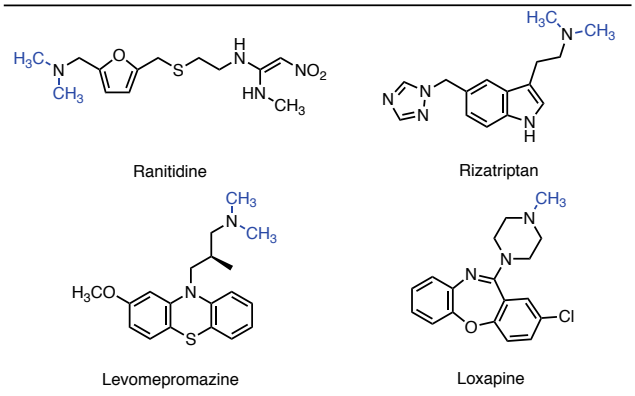


KEYWORDS: *Green Chemistry, Photocatalysis, Methylation, Methanol, Pharmaceuticals*

INTRODUCTION

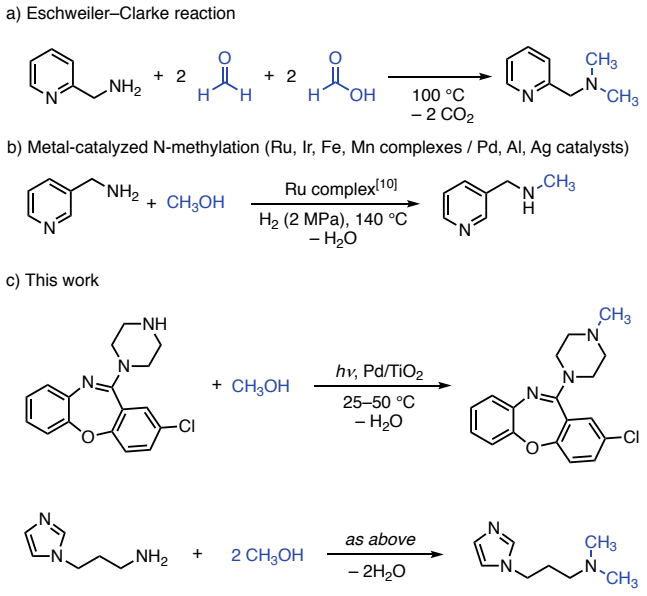
N-Methylamines are among the most important classes of chemicals in pharmaceutical science and technology.[1,2] Molecular modification of drugs at primary or secondary amino groups into tertiary methylamine analogues is a widely used strategy in drug design for improving the oil-water partition coefficient (log *P*), reducing their toxicity, and increasing their drug efficacy.[3] This makes the N-methylation of amines to tertiary amines an indispensable methodology in the synthesis of pharmaceuticals. Because N-methyl drugs often contain heteroaryls in their structures (Scheme 1), the compatibility of N-methylation with the presence of various O-, N-, and S-containing heteroaromatic skeletons is highly important.

Scheme 1. Examples of Pharmaceuticals Incorporating N-Methylamines with Heteroaromatic Skeletons



The most reliable traditional method for N-methylation of amines bearing heteroaromatic functionalities is the Eschweiler–Clarke reaction. This protocol, which uses formaldehyde and formic acid (Scheme 2a),[4,5] is free from stoichiometric salt-waste formation and over-methylation into quaternary ammonium salts, both of which are inevitable in the conventional nucleophilic substitution using methyl halides or dimethyl sulfate.[6] However, the Eschweiler–Clarke method requires heating (typically 100 °C) under acidic conditions, which is detrimental when the substrate is thermally unstable or acid/redox-sensitive.

Scheme 2. Approaches for C–N Bond Formation in N-Methylated Amines-Bearing Heteroaryls



As green and sustainable synthesis has become a crucial part of the industrial production of pharmaceuticals, N-methylation of amines with methanol (CH_3OH) has been recently recognized as a better methylation technology with its advantages of the near-neutral reaction conditions and clean reaction scheme (water is the only byproduct).[7] Because of such importance, the catalytic N-methylation of amines employing methanol as a methylation agent has been extensively explored.[8] Examples of recently developed catalysts include ruthenium,[9,10] iridium,[11–13] iron[14] and manganese[15,16] complexes, and heterogeneous catalysts (Scheme 2b).[17–19] These catalysts could be used for the efficient synthesis of secondary aromatic or tertiary aliphatic methylamines bearing heteroaryls such as pyridine, pyrimidine, and thiophene.[7,8a,8b,8d,10,11c] Whereas most of these methods are effective for methylation of (hetero)aromatic amines, however, methylation of aliphatic amines with heteroaryl functionalities has been rare (Scheme 2b).[10] Furthermore, these reactions have generally required harsh reaction conditions (typically ≥ 100 °C) and the presence of strongly basic additives (e.g. *t*-BuOLi, *t*-BuOK, NaOH). Thus, a general method for N-methylation of heterocyclic amines with methanol at ambient temperature under near-neutral conditions is in high demand.

We have recently demonstrated that the chemoselective N-methylation of various amines with CH_3OH is promoted at room temperature by a Ag/TiO_2 photocatalyst.[20] More recently, we reported the first late-stage photocatalytic N-alkylation to provide pharmaceuticals (namely, rivastigmine) by a mixed photocatalytic system comprising Cu/TiO_2 and Au/TiO_2 or by the sole use of Cu/TiO_2.[21] These methods allowed access to functionalized tertiary amines under mild conditions (25–50 °C, 1 atm, acidic or basic additive not required) and showed better scalability (gram-scale) over the prototype Pt/TiO_2 photocatalyst[22] and other reported photocatalysts (*e.g.* Au/TiO_2,[23] Pd/TiO_2,[24,25] and $Cu\text{-}Mo/TiO_2$[26]). Therefore, we envisaged that photocatalytic methylation with CH_3OH would also be effective for solving the challenge of N-methylating amines bearing heteroaromatic functionalities under mild conditions.

Herein, we disclose that a Pd-loaded TiO_2 photocatalyst effectively promotes the N-methylation of primary and secondary amines bearing pharmaceutically relevant heteroaromatic rings under mild reaction conditions (Scheme 2c). We also extended this approach to the synthesis of several (deuterated) pharmaceuticals through photocatalytic N-methylation/ethylation using (deuterated) methanol/ethanol.

EXPERIMENTAL SECTION

Preparation of Photocatalysts. Pd (5 wt %)/TiO_2 was prepared as previously reported.[27] To a 500-mL round-bottom flask wrapped in aluminum foil, TiO_2 (2.85 g) and deionized H_2O (75 mL) were added, followed by $PdCl_2(CH_3CN)_2$ (365.6 mg, 1.41 mmol) dissolved in THF (45 mL). After the resulting suspension was rotated for 30 min at 50 °C with a rotary evaporator under ambient pressure, the solvent was removed (20 mmHg). After the flask was successively evacuated and refilled with N_2, deoxygenated, deionized H_2O (75 mL) was added to the solid residue. The resulting slurry was stirred for 20 min, treated with CH_3CO_2Na (1.0 M aq, 85 mL, 85 mmol, 60 equiv), and stirred for 15 min. To the suspension, a mixture of $NaBH_4$ (9.9 mmol, 7 equiv) and degassed H_2O (90 mL) was added dropwise, and the resulting suspension stirred for 3.5 h at 25 °C. The stirring was stopped, the solid allowed to settle and the supernate roughly removed using a cannula. The remaining suspension was transferred to a 50-mL Falcon tube and centrifuged (3500 rpm, 5 min). The supernate was removed by decantation, the solid residue suspended in deionized H_2O (30 mL) and stirred overnight under N_2. Centrifugation of the mixture (3500 rpm, 5 min), removal of the supernate by decantation, and drying in vacuum

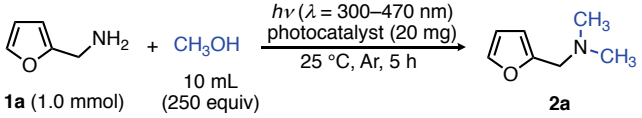
(0.01 mm Hg) at 25 °C for 10 h yielded Pd (5 wt %)/TiO_2 as a dark-grey solid (2.84 g, 95% yield). Mean particle size of the supported Pd nanoparticles was 3.3 ± 0.6 nm (N = 100) as determined by high-resolution transmission electron microscopy (HRTEM). For further details of characterization, see the Supporting Information (HRTEM and XRD) and Ref 27 (ICP-AES and DRS). Preparation and characterization of other photocatalysts are described elsewhere (Ag,[20,27] Cu,[21] Au,[21,27] Pt[27]).

General Procedure for Photocatalytic N-Methylation/Ethylation of Amines (Schemes 3 and 4). Amine (1.00 mmol), dehydrated alcohol (10 mL), and Pd (5 wt %)/TiO_2 (20 mg, 0.9 mol % Pd) were added successively to a cylindrical Pyrex glass reaction vessel (diameter: 50 mm, height: 130 mm with a top window made of Pyrex) connected to a balloon. After the resulting mixture was sonicated for 30 sec and deaerated by Ar bubbling through a cannula for 5 min, the vessel was immersed in a water bath (kept at 25 ºC using a cooling circulator), and stirred with irradiation [300 W Xe lamp (λ = 300–470 nm)]. Reaction progress was analyzed by GC/MS. After reaction, the mixture was filtered through a 0.45 μm membrane filter and the photocatalyst was washed with CH_3OH (10 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (Kanto Chemical) or 50NH_2 silica gel (Wako Chemical) to afford the desired product as a free amine. See the Supporting Information for characterization of products.

RESULTS AND DISCUSSION

Photocatalyst Screening and Optimization. In order to identify a suitable photocatalytic system for the N-methylation of amines bearing heteroaromatic cores, we selected the N,N-dimethylation of furfurylamine **1a** with methanol to a tertiary amine **2a** as a model reaction (Table 1). The structure of **2a** is an important pharmacophore in a variety of medicines (*e.g.* ranitidine in Scheme 1). Among the photocatalysts tested, Pd (5 wt %)/TiO_2, proved to be the best, affording **2a** in 96% yield under irradiation (Xe lamp, λ = 300–470 nm) for 5 h (Table 1, entry 1). This reaction also proceeded well under irradiation with a UV-LED (λ_0 = 365 nm, entry 2). Reaction hardly proceeded in the dark, indicating it to be driven by light irradiation (entry 3). The Pd/TiO_2 photocatalyst was recyclable at least 5 times (entries 4–7). Other photocatalysts, such as Ag (4 wt %)/TiO_2,[20] Cu (5 wt %)/TiO_2,[21] and the Cu–Au mixed photocatalytic system[21] promoted reaction of **1a** less efficiently than Pd/TiO_2 (entries 8–10 vs entry 1). Only marginal or trace amounts of desired product were formed by employing Au (5 wt %)/TiO_2,[27] Pt (5 wt %)/TiO_2,[22] or pristine TiO_2 (entries 11–13).

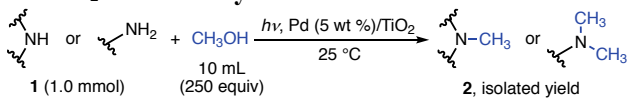
Table 1. Photocatalytic N,N-Dimethylation of Furfurylamine[a]

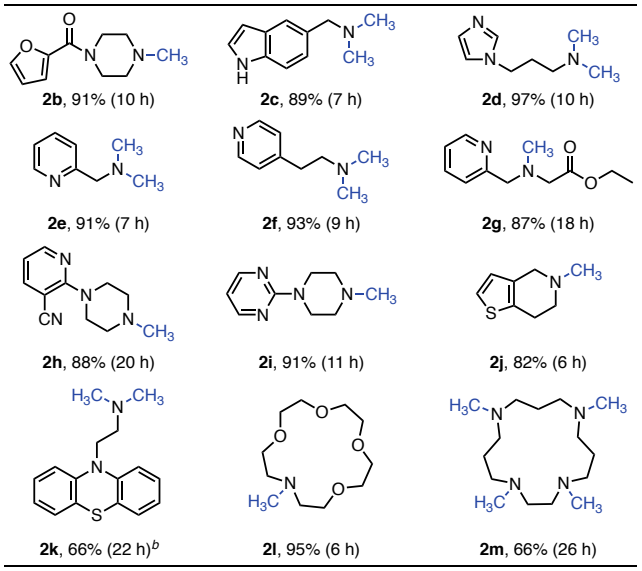


entry	metal/TiO_2	metal (mol %)	yield (%)[b]
1	Pd/TiO_2	Pd (0.9)	96
2	Pd/TiO_2	Pd (0.9)	93[c]
3	Pd/TiO_2	Pd (0.9)	< 1[d]
4	Pd/TiO_2	Pd (0.9)	94 (2nd run)[e]
5	Pd/TiO_2	Pd (0.9)	90 (3rd run)[e]
6	Pd/TiO_2	Pd (0.9)	89 (4th run)[e]
7	Pd/TiO_2	Pd (0.9)	89 (5th run)[e]
8	Ag/TiO_2	Ag (0.8)	64
9	Cu/TiO_2	Cu (1.4)	71
10	Cu/TiO_2 + Au/TiO_2	Cu (0.7), Au (0.2)	51
11	Au/TiO_2	Au (0.5)	5
12	Pt/TiO_2	Pt (0.5)	1
13	TiO_2	–	< 1

[a]300 W Xe lamp with a UV-cold mirror. Metal content (Pd: 5 wt %; Pt: 5 wt %; Cu: 5 wt %; Ag: 4 wt %; Au: 5 wt %) was determined by ICP-AES. [b]^{1}H NMR yields using 2,2-dimethylpropan-1-ol as an internal standard. [c]**1a** (0.1 mmol), CH_3OH (250 equiv, 1.0 mL), 32W UV-LED lamp λ_0 = 365 nm. [d]Without light irradiation. [e]Recovered photocatalyst was used.

Scheme 3. Methylation of Amines by Alcohols Using Pd/TiO_2 Photocatalysis[a]

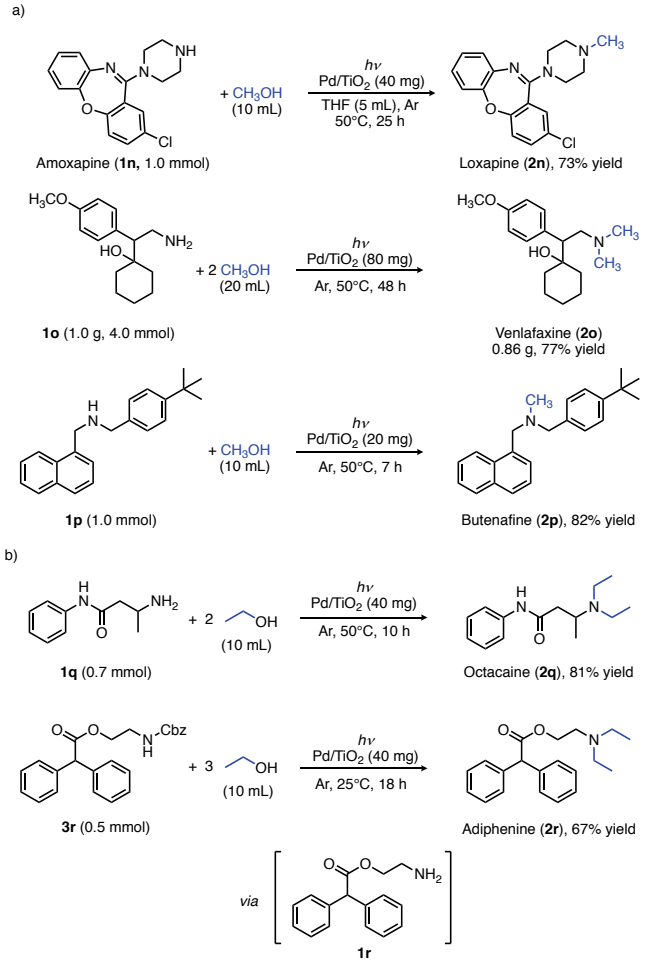




[a]Conditions analogous to Table 1, entry 1. [b]0.5 mmol scale, amine HCl salt as starting material.

Substrate Scope. With the optimized reaction conditions in hand, Pd/TiO_2-mediated photocatalytic N-methylation was tested on a variety of heteroaromatic and saturated heterocyclic amines (Scheme 3). The present method proved to be effective in the synthesis of amines bearing heteroaromatic structural motifs such as furan (**2b**), indole (**2c**), imidazole (**2d**), pyridine (**2e–h**), pyramidine (**2i**), and thiophene (**2j**). The desired products **2b–2j** were obtained in good to excellent yields. The presence of reducible functional groups such as an ester in **2g** and a nitrile in **2h** was well tolerated. Interestingly, the primary amino group in a phenothiazine derivative was also N,N-dimethylated to give tertiary amine **2k** in 66% yield despite the large absorbance of phenothiazine in the UV region (300–350 nm) that potentially competes with light absorption by Pd/TiO_2. It should be noted that the products **2c** and **2k** share structural motifs with the medicines rizatriptan and levomepromazine, respectively (Scheme 1). The present method also enabled the (tetra-)methylation of aza-crown ethers to give **2l** and **2m** without involving any neutralization procedure so far requested (Scheme 3).[28]

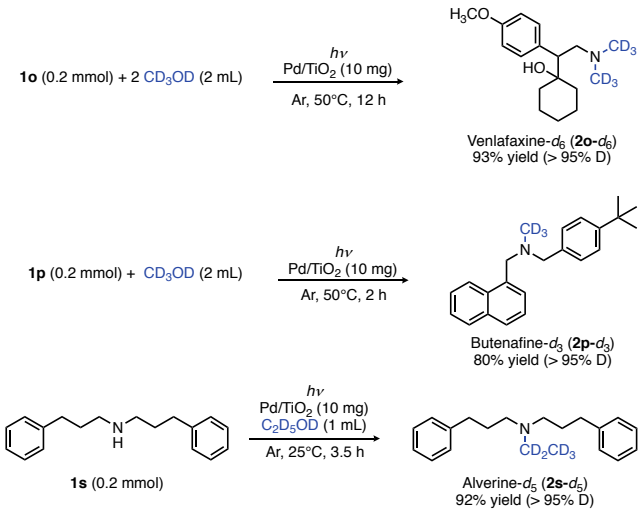
Scheme 4. Synthesis of Pharmaceuticals Using Pd/TiO_2 Photocatalysis



Late-Stage N-Methylation Leading to Pharmaceuticals. Its compatibility with various pharmaceutically relevant functional groups being established, this method was extended to the synthesis of several pharmaceuticals (Scheme 4a). The photocatalytic reaction at 50 °C using methanol and Pd/TiO_2, efficiently produced loxapine (**2n**, a drug used for treating schizophrenia) in 73% isolated yield from its metabolite amoxapine (**1n**), where the presence of a dibenzoxazepine system was well tolerated. This photocatalytic method was also effective in the synthesis of other pharmaceuticals such as venlafaxine (**2o**, a drug used for major depressive disorders) and butenafine (**2p**, a drug used for treating tinea). The results for **2o** (sub-gram scale, 0.86 g) proved the good scalability of this method in pharmaceutical synthesis. The photocatalytic N-methylation of **1p** to **2p** selectively proceeded without the cleavage of benzylic C–N bonds.

Photocatalytic Ethylation for Pharmaceutical Synthesis. The synthesis of octacaine (**2q**, a local anesthetic) was achieved through the direct N,N-diethylation of primary amine **1q** using ethanol as an alkylating reagent. This protocol was further extended to a one-pot deprotection–diethylation sequence on a Cbz-protected amine **3r** by using ethanol as a deprotecting and alkylating agent, producing adiphenine (**2r**, a drug used in spasmolysis) in moderate yield (Scheme 4b). This one-pot strategy is advantageous over a stepwise method because the intermediate **1r** is thermally unstable.[29]

Scheme 5. Synthesis of Deuterated Drugs



Synthesis of Deuterated Drugs Using Deuterated Alcohols. Regio-specifically deuterated drugs have begun receiving significant attention, because deuterium-labeled drugs show longer half-life and better drug efficacy than their non-deuterated analogues.[30–32] The current photocatalytic method enabled the facile synthesis

of site-specifically-labeled deuterated drugs using CD_3OD. Deuterated venlafaxine-d_6 (**2o**-d_6) and butenafine-d_3 (**2p**-d_3) were successfully synthesized in 93% and 80% yields, respectively (Scheme 5). Alverine-d_5 (**2f**-d_5) was also synthesized in 92% isolated yield employing C_2D_5OD as an alkylation reagent.[33] In these products, only the installed alkyl groups were specifically labeled with deuterium. The degree of deuteration was unambiguously confirmed by MS and NMR analyses (see Supporting Information).

Methylation of Colistin. To further test the utility of our new photocatalyst, the direct functionalization of colistin (composed of a mixture of colistin A [**1t-A**] and B [**1t-B**]) was tested (Figures 1). Colistin is a cationic lipopeptide antibiotic used for the treatment of Gram-negative bacterial infection, and *N*-methylation of cationic antibiotics is expected to broaden the spectrum of their activity.[33] A mixture of **1t-A** and **1t-B** was *in situ* generated by the treatment of colistin sulfate with sodium carbonate, and was irradiated for 2 h in aqueous methanol with a UV–vis light in the presence of Pd/TiO_2 (Figure 1a). The LC/ESI-MS analysis of the reaction mixture indicated the formation of free amines **1t-A** and **1t-B** before irradiation (Figure 1b, t = 0 h). Upon irradiation, the mono-, di-, and trimethylation of **1t** and **1u** proceeded to give products **2t-A**$^{1–3}$ and **2t-B**$^{1–3}$ as indicated by the ion chromatograms (Figure 1b, reaction time t = 1 and 2 h). Further improvement of this reaction system and more detailed analysis of the products are currently under way.

Mechanistic Considerations. A possible mechanism for photocatalytic N-alkylation is shown in Scheme 6. This scheme is analogous to those previously proposed for Pd/TiO_2.[24,25] The reaction starts with the irradiation of TiO_2 producing an electron (e^-)-hole (h^+) pair at Pd/TiO_2 (Scheme 6a). The electron is transferred to palladium nanoparticles ($[Pd]_n$) on TiO_2 and reacts with a proton to form a palladium hydride species ($[Pd]_n$–H). The hole is quenched by adsorbed methanol to give formaldehyde and a proton. Methylation of primary amines starts with reaction of the primary amine with formaldehyde to give an imine and water (Scheme 6b). The imine is then reduced by $[Pd]_n$–H to a secondary amine. Methylation of secondary amines proceeds analogously (Scheme 6c). Secondary amine reacts with formaldehyde and a proton to give an iminium cation and water. The iminium cation is reduced to tertiary amine by $[Pd]_n$–H. The overall stoichiometry for either alkylation is shown in Scheme 6d. The formation of water as a by-product is supported by the fact that more than stoichiometric amounts of water (4.2 mmol) were formed in the photocatalytic N-methylation of **2a** (1.0 mmol), as determined by the Karl–Fischer method.

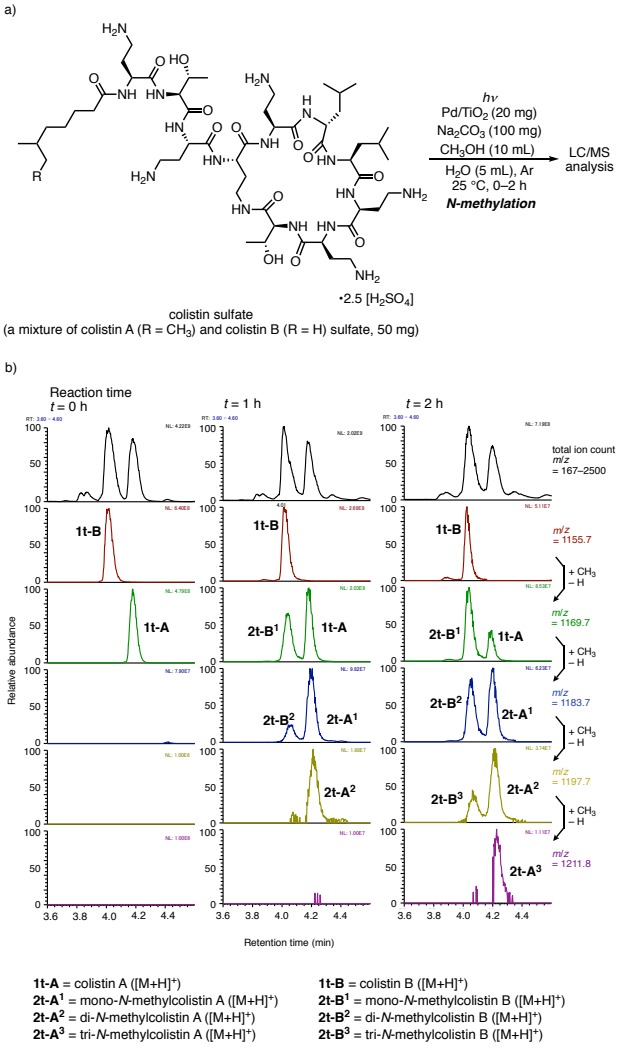
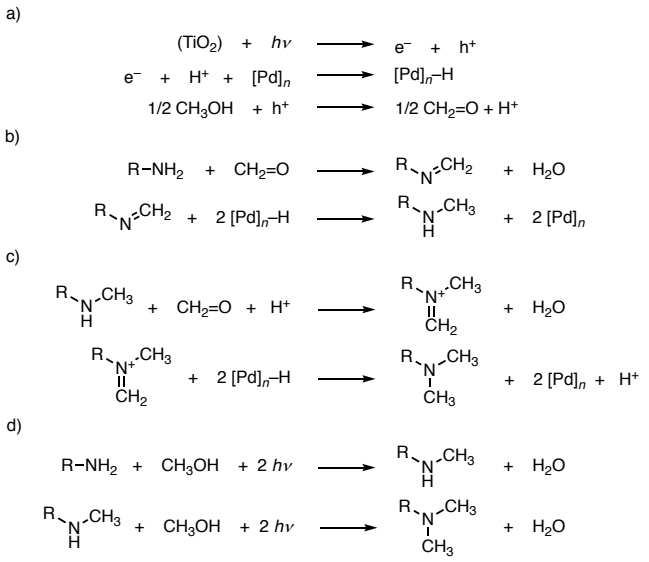


Figure 1. a) Photocatalytic N-methylation of colistin by a Pd/TiO_2 photocatalyst. b) LC/ESI-MS chromatograms of the reaction mixture irradiated for 0, 1, and 2 h showing total ion count, ion chromatograms of m/z = 1155.7, 1169.7, 1183.7, 1197.7, and 1211.8. Full-size chromatograms are shown in Figures S6–S8 in the Supporting Information.

The presented view of the mechanism is complicated by the possibility that electrophilic formaldehyde, imine, or iminium salt could react with methanol or amines to give an equilibrium mixture of hemiacetal, hemiaminal, or aminal species. These species may compete with formaldehyde, imine, and iminium salt for reaction with amine or palladium hydride (Scheme 6b and 6c). Furthermore, a known side-reaction is the production of H_2 gas and formaldehyde from methanol.[24,27] H_2 presumably dissociates from the palladium hydride shown in Scheme 6a. The amount of H_2 in the gas phase after photocatalytic N-methylation of **2a** (1.0 mmol) using 10-mL methanol was 0.82 mmol as determined by μ-GC analysis (Figure S9). Reaction of the resulting formaldehyde with 2 equivalents of methanol to give dimethoxymethane and water would partially account for the ex-

cess formation of water produced in the present photocatalytic experiments.

Scheme 6. A Proposed Mechanism for Photocatalytic N-methylation over Pd/TiO_2



The origin of the higher reactivity of Pd over its metallic analogues shown in Table 1 remains unclear, but we presume it originates from the high affinity of hydrogen for the Pd nanoparticles[35–37] and the high reactivity of Pd hydride species ([Pd]$_n$–H) for the reduction of imines and iminium intermediates (Schemes 6b and 6c). The presence of Pd nanoparticles with a mean particle size of 3.3 ± 0.6 nm supported on TiO_2 in the Pd/TiO_2 photocatalyst was established by HRTEM analysis (Figures S1–S3). Lattice fringes (Figure S2) agree with the [111] reflection of face-centered cubic (*fcc*) Pd, indicating the presence of standard metallic Pd nanoparticles. The hydrogenation of an imine (*N*-benzylidenebenzylamine) to the corresponding secondary amine (dibenzylamine) spontaneously occurred in the presence of Pd/TiO_2 under atmospheric H_2 gas both with and without light irradiation (see Supporting Information for details).

CONCLUSION

In summary, we have developed an efficient photocatalytic method for the N-methylation of heterocyclic amines and pharmaceutical intermediates using methanol with Pd/TiO_2 under mild reaction conditions. This methodology provides an economical and environment-friendly way for the synthesis of complex *N*-methyl heterocyclic amines and several medicines by late-stage N-methylation. Comparable late-stage ethylation and deuterium labeling are also demonstrated. We believe that this work will contribute to the green and sustainable production of pharmaceuticals.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, Figures and Tables. This material is available free of charge via the Internet at http://pubs.acs.org. Detailed data are available at the University of Cambridge data repository (http://dx.doi.org/xx.yyyyy/CAM.zzz).

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Author Contributions

L.-M.W. selected the pharmaceutical targets, conducted all synthetic experiments, and wrote the manuscript. K.J. and A.E.H.W. characterized the photocatalyst by means of HRTEM and XRD and edited the manuscript. K.K. conducted the LC/MS analyses. S.S. guided the research. H.N. designed the project, guided the research, and wrote the manuscript.

Funding Sources

This work was supported by JSPS KAKENHI Grant Number JP26410115 (H.N.), the Tobe Maki Scholarship Foundation (H.N.), the JGC-S Scholarship Foundation (H.N.), Fusion Emergent Research Program from Integrated Research Consortium on Chemical Sciences (IRCCS, H.N. and A.E.H.W.), the JST ACT-C program (S.S.), and the UK EPSRC (EP/J500380/1, K.J.).

Notes

The authors declare no competing interest.

ACKNOWLEDGMENTS

The authors wish to thank Professors R. Noyori (NU), A. Mitsuhiro (Osaka University), and A. Kudo (Tokyo University of Science) for fruitful discussions. Constructive comments for revision raised by referees are gratefully acknowledged.

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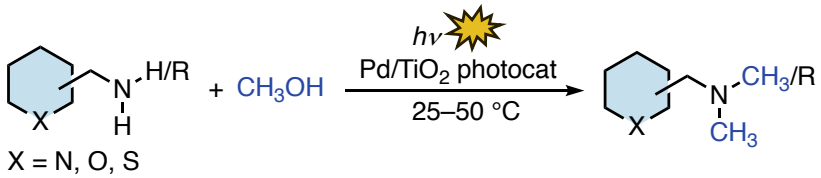
TOC graphic



Brief synopsis

Photocatalytic N-(m)ethylation of amines with (m)ethanol at ambient temperature has enabled the sustainable synthesis of pharmaceuticals and complex molecules.