Efficient and Selective N-Methylation of Nitroarenes under Mild Reaction Conditions

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Direct and mild $N$-methylation: Nitroarenes have been smoothly methylated using formic acid as a C1 source and phenylsilane as reducing agent. In the presence of cubane-type complexes (see scheme) tertiary amines have been obtained at mild conditions with good functional group tolerance.
Abstract

Herein, we report a straightforward protocol for the preparation of \( \text{N,\text{-dimethylated}} \) amines from readily available nitro starting materials using formic acid as a renewable \( \text{C}_1 \) source and silanes as reducing agents. This tandem process is efficiently accomplished in the presence of a cubane-type \( \text{Mo}_3\text{PtS}_4 \) catalyst. For the preparation of the novel \( [\text{Mo}_3\text{Pt(PPh}_3\text{)S}_4\text{Cl}_3\text{(dmen)}_3]^{3+} \) (dmen: \( \text{N,N'}\text{-dimethylethylenediamine} \)) compound we have followed a \([3 + 1]\) building block strategy starting from the trinuclear \( [\text{Mo}_3\text{S}_4\text{Cl}_3\text{(dmen)}_3]^{1+} \) and \( \text{Pt(PPh}_3\text{)}_4 \) complexes. The heterobimetallic \( 3^+ \) cation preserves the main structural features of its \( 1^+ \) cluster precursor. Interestingly, this catalytic protocol operates at room temperature with high chemoselectivity when the \( 3^+ \) catalysts co-exists with its trinuclear \( 1^+ \) precursor. \( \text{N-heterocyclic arenes, double bonds, ketones, cyanides and esters functional groups are well retained after} \) \( \text{N-methylation reaction of the corresponding functionalized nitroarenes. In addition, benzylic-type nitro compounds can also be methylated following this protocol.} \)

Introduction

\( \text{N-methylated amines are widely used as platform chemicals for the preparation of medicines, pesticides, dyes and perfumes.}^{[1]} \) Traditional procedures for \( \text{N-methylation of amines in fine chemical manufacture rely on reductive amination reactions using toxic formaldehyde as} \text{C}_1 \) source,\(^{[2]} \) whereas carcinogenic methylation reagents, such as methyl iodide, methyl trifluoromethanesulfonate, dimethyl sulfate or diazomethane are still popular at laboratory scale.\(^{[3]} \) Hence, there exists growing interest in the search for greener and safer \( \text{C}_1 \) feedstocks for \( \text{N-methylations in industry and academia. In recent years, great progress has been made by using} \text{CO}_2,\(^{[4]} \) dimethyl carbonate,\(^{[5]} \) formic acid (FA),\(^{[6]} \) methanol\(^{[7]} \) or dimethylsulfoxide\(^{[8]} \) as methylaing reagents. Among them, FA is an attractive reagent to introduce carbon into amines.\(^{[9]} \) FA is a non-toxic and biodegradable liquid produced industrially by
hydrolysis of methyl formate or by CO$_2$ hydrogenation, and is one of the major by-products of lignocellulosic biomass processing.$^{[10]}$ Furthermore, FA represents an ideal liquid hydrogen carrier for renewable energy storage,$^{[11]}$ and has been thoroughly investigated as a liquid surrogate of molecular hydrogen for the well-established transfer hydrogenation reactions.$^{[12]}$

Pioneering work on N-methylation of amines with FA as a C$_1$ building block was reported by some of us using silanes as reducing agents in the presence of an in situ combination of the commercially available Karstedt’s catalyst and dppp (1,3-bis(diphenylphosphino)propane) as ligand.$^{[6a]}$ Notably, by using a related Pt/diphosphine-based catalyst the protocol was also extended to higher carboxylic acids (RCO$_2$H; R ≠ H) to give a broad range of secondary and tertiary amines.$^{[13]}$ This work was followed by others who have expanded the range of homogeneous catalysts available to Ir,$^{[14]}$ Rh,$^{[4s]}$ Ru,$^{[15]}$ and Cu,$^{[6h]}$ as well as to a heterogeneous Pt/C catalyst for the construction of the C-N bond employing hydroxilanes as reductants.$^{[6g]}$ In this context, the metal-free amine alkylation reaction using B(C$_6$F$_5$)$_3$ as catalyst is also noteworthy.$^{[6c, 6f]}$ Cantat et al. first,$^{[6b]}$ and Kim et al.$^{[6c]}$ reported the N-methylation of amines applying FA as a unique carbon and hydrogen source catalyzed by a Ru/Triphos [Triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane] complex or a heterogeneous PdAg alloy catalyst, respectively. Furthermore, the Ru/Triphos system has also proven to be an excellent catalyst for the N-alkylation of amines with a variety of carboxylic acids using molecular hydrogen as reducing agent.$^{[16]}$

Although tremendous success has been achieved in the search for greener methylating reagents, the development of new strategies to access N-methylated amines from readily available feedstocks in a safe, compact and energy-efficient manner still remains as a major challenge. Typically, their preparation involves synthesis and isolation of the amine, followed by N-methylation in two separated
individual stages. In this respect, the design of a domino or tandem process that avoids the synthesis and isolation of the amine intermediate is clearly advantageous.

Currently, one of the most common methodologies to access (aromatic) amines is the reduction of nitro compounds,\cite{17} and thus the development of a straightforward reductive methylation of nitroarenes is of great practical significance. However, only a few examples, mostly using heterogeneous catalysts, dealing with this convenient and direct strategy have been reported to date (Scheme 1). In 2009, Li et al. achieved the synthesis of N,N-dimethylaniline from nitrobenzene and methanol over a pretreated Raney-Ni® catalyst under high temperature and N₂ pressure (170 °C; 30 bar N₂).\cite{7c} In 2013, Rong et al. reported the use of a skeletal Cu (also known as Raney-Cu®) catalyst for the direct N-methylation from nitroarenes, but toxic and carcinogenic formaldehyde was employed as C₁ source in the presence of molecular hydrogen.\cite{18} Notably, Shi et al. described the synthesis of a limited number of N-methylated anilines from nitroarenes employing CO₂/H₂ and CuAlOₓ or Pd/CuZrOₓ as catalysts under harsh conditions and long reaction times (150-170 °C, 35-100 bar; 30-48 h).\cite{4j, 4k} Soon after, the same group accomplished the direct N-methylation of nitroarenes using methanol and TiO₂-supported nanopalladium catalysts (Pd/TiO₂) at room temperature, albeit photoactivation under intense UV irradiation was required.\cite{7g} Later, Cao et al. utilized a Au/rutile catalyst that allowed the preparation of N,N-dimethylanilines from nitroarenes using formic acid (FA) as benign C₁ source, but high pressure of H₂ (40 bar) and high temperature (140 °C) were required to avoid accumulation of intermediate products.\cite{6d} Unfortunately, the application of all these methods, especially at laboratory scale, is constrained by the needs of high temperatures, special high-pressure equipment and/or hazardous UV irradiation. In addition, they present a limited substrate scope and their functional-group tolerance to other reducible functionalities has been scarcely investigated.
In this regard, homogeneous catalysis should provide a more convenient approach to obtain a broad functional group tolerance and high activity under mild conditions. Wang and Xiao et al. have recently reported a Fe-catalyzed N-methylation of nitroarenes under transfer hydrogenation conditions using dimethylsulfoxide (DMSO) and a mixture of FA/Et$_3$N as methylating and reducing agents, respectively (Scheme 1).\textsuperscript{[8]} However, the required temperature (150 ºC) is still too high and the functional-group tolerance to sensitive moieties, such as double bonds, ketones or carboxylic acid derivatives, has not been demonstrated. Hence, the development of a chemoselective catalytic protocol for N-methylation of nitroarenes that operates under mild conditions is still highly desirable. A key prerequisite for such pursuit lies in the proper choice of a catalyst able to lead to the direct one-pot C-N bond construction in a domino or tandem sequence. In this sense, the design of heterobimetallic complexes with several active sites acting individually or in a cooperative manner to catalyze the individual steps of the overall catalytic process is an attractive approach.
Since many years, one of our groups has been involved in the preparation of heterobimetallic cuboidal Mo₃M’S₄ clusters by incorporation of a second transition metal atom (M’) into trinuclear Mo₃S₄ complexes.[19] The resulting Mo₃M’S₄ cluster unit displays a cubane-type structure where the metals and sulfur atoms occupy adjacent vertices in a cube (Figure 1). In general, their application as catalysts for organic synthesis is quite limited and most of their reported activity relies on the heterometal (M’ = Pd,[20] Ni,[21] Ru,[22] and Cu[19c, 19h]).[23]

![Figure 1. Cubane-type Mo₃M’S₄ clusters.](image)

In the last few years, we have demonstrated that incomplete cubane-type Mo₃S₄ complexes functionalized with diphosphine, diamine or diimine ligands are excellent chemoselective catalysts for the reduction of nitroarenes using different reducing agents.[12c, 24] In addition, some of us have also recently applied Pt-based catalysts to establish new efficient synthetic routes for N-alkylation of amines.[5g, 6a, 13] This experience inspired us to prepare a heterobimetallic Mo₃PtS₄ cluster and explore its performance as catalyst for the direct one-pot reductive methylation of nitroarenes under mild conditions using FA as C₁ source and silanes as reducing agents.
Results and Discussion

Synthesis and characterization of the catalyst

Incomplete cubane-type Mo$_3$S$_4$ clusters are known to act as metalloligands towards a second transition or post-transition metal to form a large family of heterobimetallic cuboidal Mo$_3$M’S$_4$ complexes both in aqueous and organic media.[19b, 23, 25] This synthetic approach, so-called [3 + 1] building block strategy, has proven to be an efficient route to construct Mo$_3$PtS$_4$ clusters by reaction of the preassembled Mo$_3$S$_4$ complex containing aqua, diphosphine or methylcyclopentadienyl ligands with either Pt(0) complexes or Pt(II) salts, the latest in the presence of a strong reducing agent.[26] In this work, this synthetic strategy has been extended to the diamino Mo$_3$PtS$_4$ system. Reaction of the [Mo$_3$S$_4$Cl$_3$(dmen)]$^+$ (1+) cation with the mononuclear complex Pt(PPh$_3$)$_4$ (2) at room temperature in THF, readily affords the heterobimetallic complex [Mo$_3$Pt(PPh$_3$)S$_4$Cl$_3$(dmen)$_3$]$^+$ (3+) as represented in Scheme 2.

![Scheme 2. Synthetic procedure for the preparation of [Mo$_3$Pt(PPh$_3$)S$_4$Cl$_3$(dmen)$_3$]$^+$ (3+).](image)

Tetrafluoroborate salts of 3+ were isolated as a brown air-stable solid in 52% yield. Single crystals were obtained by slow diffusion of diethyl ether into dichloromethane sample solutions. The structure of 3(BF$_4$) was determined by single crystal X-ray diffraction methods and its ORTEP representation with the most relevant bond distances is depicted in Figure 2. The cluster is formed by a single cubane-like Mo$_3$PtS$_4$ array, in which the metal atoms occupy the vertices of a slightly
distorted tetrahedron and each tetrahedron face is capped by a \( \mu_3 \)-coordinated sulfur atom. Each molybdenum atom presents an octahedral coordination environment with the outer position occupied by one chlorine and two nitrogen atoms of the diamine ligand while platinum possess a tetrahedral coordination with the outer position occupied by the phosphorous atom of the triphenylphosphine ligand. In general, cation 3\(^+\) shares the main geometric features with other cubane-type Mo\(_3\)PtS\(_4\) complexes reported to date.[26]

**Figure 2.** ORTEP representation (50% probability level ellipsoids) of the cationic cluster 3\(^+\). Hydrogen atoms are omitted for clarity. Selected averaged bond lengths (Å): Mo-Mo 2.775[6], Mo-Pt 2.836[4], Mo-(\( \mu_3 \)-S(1)) 2.333[1], Mo-(\( \mu_3 \)-S\(^\text{trans} \)-Cl) 2.352[2], Mo-(\( \mu_3 \)-S\(^\text{trans} \)-N) 2.352[7], Mo-N\(^\text{trans} \)-(S(1)) 2.278[8], Mo-N\(^\text{cis} \)-(S(1)) 2.291[3], Mo-Cl 2.517[10], Pt-P 2.262(2) and Pt-(\( \mu_3 \)-S) 2.354[4].

Cationic cluster 3\(^+\) preserves the idealized C\(_3\) symmetry of its 1\(^+\) precursor and it is conveniently identified in solution by \(^1\)H and \(^{13}\)C\(^{\{1\}H}\) NMR spectroscopy region (Figures SI1 and SI2 in the Supporting Information) Further support on the integrity of complex 3(BF\(_4\)) in solution is provided by ESI mass spectrometry where a peak centred at \( m/z = 1244.8 \) is associated to the pseudomolecular 3\(^+\) cation on the basis of the \( m/z \) value and its characteristic isotopic pattern (Figure SI3 in the Supporting Information).
Upon Pt insertion, the electron precise Mo$_3$S$_4^{4+}$ unit with six metal cluster skeletal electrons (CSE) to form three metal-metal bonds, becomes a Mo$_3$PtS$_4^{4+}$ cluster containing sixteen CSE, and so some changes in their redox properties are expected. The electronic delocalization in the resulting heterobimetallic systems makes inconclusive all schemes directed towards the metal oxidation states assignment.[19] Electrochemical properties of the incomplete 1$^+$ and cubane-type 3$^+$ complexes have been investigated by cyclic voltammetry (see Table 1 and Figure S14 in the Supporting Information). Complex 3$^+$ undergoes one reduction and one oxidation quasireversible processes of similar intensity at -1.02 and 1.10 V, respectively, a redox behavior similar to that reported for the [Mo$_3$PtS$_4$(η$_5$-Cp')$_3$(PPh$_3$)$_3$]$^+$ (Cp' = methylcyclopentadienyl) ion complex.[27] The cyclic voltamogram of the trinuclear 1$^+$ precursor shows a unique quasireversible reduction wave at -0.45 V while no oxidation process is observed within the solvent window. Therefore, incorporation of the Pt-PPh$_3$ fragment into the Mo$_3$S$_4$ core to give the heterobimetallic complex 3$^+$ exerts an important electronic effect, making the heterobimetallic cluster more difficult to reduce and easier to oxidize than its trinuclear precursor, as observed for the Pt insertion into the cyclopentadienyl Mo$_3$S$_4$ complex.[27]

| Table 1. Redox potentials of 1$^+$ and 3$^+$ clusters in dichloromethane$^a$ |
|-----------------------------|-----------------|-----------------|
| Compound          | Oxidation $E_{1/2}^{b}[|\Delta E|^{d}]$ (V) | Reduction $E_{1/2}^{b}[|\Delta E|^{d}]$ (V) |
|-------------------|-----------------|-----------------|
| 1(BF$_4$)         | -               | -0.45(0.13)     |
| 3(BF$_4$)         | 1.15(0.06)      | -1.02(0.08)     |

[a] $E_{1/2}$ (Fc/Fc$^+$) = 0.44 V (vs Ag/AgCl). [b] Potentials measured at 100 mV/s. [c] $\Delta E = |E_a - E_c|$
Catalytic results

The catalytic activity of the heterobimetallic 3(BF₄) cluster in the direct N-methylation of nitroarenes was investigated in the model reaction of p-nitrotoluene (1a) with formic acid and using phenylsilane as reductant. Initial experiments were conducted in tetrahydrofuran at 70 ºC in the presence of different catalyst loadings. Almost full conversion with formation of the desired N,N-dimethyl-p-toluidine (5a) as main product was achieved with 1 mol% of the heterobimetallic 3(BF₄) cluster (Table 2, entry 1). In addition, small amounts of p-toluidine (2a) and the monomethylated N-methyl-p-toluidine (4a) were also detected. To our delight, an increase of catalyst loading up to 3 mol% affords almost a quantitative yield of 5a (97%) after 18 h (Table 2, entry 2). At shorter reaction times (8 h), 1a was partially converted and the dimethylated amine 5a was obtained in a 33% yield (Table 2, entry 3). Incidentally, the 3⁺ cluster still remains in the reaction mixture as evidenced by electrospray ionization mass spectrometry (ESI-MS) measurements (Figure SI5 in the Supporting Information). No reaction took place in the absence of phenylsilane even when a large excess of formic acid (Table 2, entry 4) or formic acid and triethylamine mixtures (Table 2, entries 4-5) were employed. Likewise, the use of other hydrosilanes or solvents led to much lower reactivity towards the formation of the desired dimethylated product 5a (Tables SI1 and SI2 in the Supporting Information).
Next, we explored the catalytic activity of the precursor complexes, Pt(PPh$_3$)$_4$ (2) and the trinuclear 1(BF$_4$), used for the preparation of the heterobimetallic 3(BF$_4$) cluster. These complexes are known to be effective catalysts for the N-methylation of amines as well as for the reduction of nitroarenes, respectively,$^{[6a, 24a]}$ so direct N-methylation of nitroarenes catalyzed by any of these precursors should not be discarded. However, complexes 1(BF$_4$) and 2 resulted to be less efficient catalysts.

### Table 2. Optimization conditions of the N-methylation of nitroarenes.$^{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading (mol%)</th>
<th>Conv. [%]$^{[b]}$</th>
<th>2a</th>
<th>3a</th>
<th>4a</th>
<th>5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3(BF$_4$)</td>
<td>1</td>
<td>90</td>
<td>15</td>
<td>0</td>
<td>16</td>
<td>40</td>
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<tr>
<td>2</td>
<td>3(BF$_4$)</td>
<td>3</td>
<td>&gt;99</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>97</td>
</tr>
<tr>
<td>3$^{[c]}$</td>
<td>3(BF$_4$)</td>
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<td>83</td>
<td>19</td>
<td>0</td>
<td>14</td>
<td>33</td>
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<tr>
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<td>3(BF$_4$)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5$^{[e]}$</td>
<td>3(BF$_4$)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1(BF$_4$)</td>
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<td>&gt;99</td>
<td>1</td>
<td>51</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
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<td>5</td>
<td>89</td>
<td>30</td>
<td>0</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>8$^{[e]}$</td>
<td>1(BF$_4$):2</td>
<td>3:3</td>
<td>&gt;99</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>9$^{[e]}$</td>
<td>1(BF$_4$):2</td>
<td>3:1</td>
<td>&gt;99</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>10$^{[f]}$</td>
<td>1(BF$_4$):2</td>
<td>3:1</td>
<td>&gt;99</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>89</td>
</tr>
<tr>
<td>11$^{[f]}$</td>
<td>3(BF$_4$)</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
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</table>

[a] Reaction conditions: 1a (0.1 mmol), HCO$_2$H (8.5 equiv.), PhSiH$_3$ (10 equiv.), THF (2 mL). [b] Determined by GC using $n$-hexadecane as an internal standard. [c] 8 h. [d] Without silane; 26 equiv. HCO$_2$H. [e] Without silane; HCO$_2$H/Et$_3$N (26/21 equiv.). [f] 25 ºC.
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than the heterobimetallic $3(BF_4)$ cluster affording low yields of the dimethylated amine $5a$ (Table 2, entries 6-7).

Then, we decided to explore the catalytic activity of the $in situ$ generated $3^+$ cluster using different ratios between the trinuclear $1(BF_4)$ cluster and the mononuclear Pt($PPh_3)_4$ ($2$) complex. When the direct $N$-methylation of $1a$ was carried out in the presence of equimolecular mixtures of $1(BF_4)$ (3 mol%) and $2$ (3 mol%) an excellent yield of $5a$ was achieved after 8 h (Table 2, entry 8). Interestingly, the platinum complex loading could be decreased up to 1 mol% without any loss in conversion and yield (Table 2, entry 9). It should be noted that in the presence of a 3-fold excess of the trinuclear complex $1(BF_4)$ with respect to $2$, platinum is fully incorporated into the $Mo_3S_4$ cluster core thus producing a mixture of cluster complexes $3(BF_4)$ and $1(BF_4)$ as evidenced by ESI-MS (Figure SI6 in the Supporting Information). After completion of the catalytic reaction (8 h), the peaks associated to the tri- and tetranuclear clusters are still present in the ESI-MS spectrum. Unfortunately, all efforts to detect any potential silylated species generated during the catalytic reaction were unsuccessful, likely due to strong ion-suppression effects.[28]

Remarkably, the presence of the trinuclear $1^+$ cluster has a positive effect on the process not only lowering reaction times but also allowing the reaction to proceed at room temperature. (Table 2, entry 10) In fact, direct $N$-methylation of the nitroarene $1a$ is successfully accomplished at room temperature when both clusters $1^+$ and $3^+$ are present while complex $3^+$ alone is inactive under these conditions (Table 2, entries 10 and 11, respectively). However, the aniline $2a$ is efficiently methylated at room temperature in the presence of the heterobimetallic $3^+$ complex to afford the dimethylated product $5a$ in 94% yield. These results suggest that the trinuclear $1^+$ complex is more efficient catalyst than $3^+$ for the nitroarene to aniline conversion, that is the first step of this tandem process.
With respect to the reaction mechanism, in order to clarify the elementary steps involved in the direct $N$-methylation of nitroarenes, we performed the reduction of the intermediate $p$-methylformanilide (3a) with phenylsilane in the absence of formic acid. As shown in Scheme 3, the expected monomethylated aniline 4a was afforded as major product (76%), but also 2a and the dimethylated aniline 5a were formed in 12% yield. As it has been already reported, a rational route for the formation of 5a in the absence of formic acid should involve condensation of the initially formed 4a and the starting formamide 3a to produce the corresponding urea derivate, followed by reduction of this intermediate.\[6a\] Hence, the direct $N$-methylation of nitroarenes under our reaction conditions involves formation of the primary aniline by reduction of the starting nitroarene and methylation reaction with formic acid, which proceeds through the formation of formamide and urea derivatives as reaction intermediates (Scheme SI1 in the Supporting Information).

Scheme 3. Control experiment: reduction of $p$-methylformanilide (3a)

Next, the potential of this catalytic protocol for the direct $N$-methylation of nitroarenes was further investigated. For convenience, the mixture of the trinuclear 1(BF$_4$) (3 mol\%) and the mononuclear 2 (1 mol\%) complexes combined \textit{in situ} was used as catalyst. Apart from the benchmark substrate, 1a, two nitroarenes containing electron-donating substituents, such as methoxy or thiomethyl groups, were also smoothly methylated affording the corresponding dimethylated anilines in 74 and 94% yield, respectively (Table 3, entries 1-2). In the absence of any substituent on the aromatic ring, the $N$-methylation reaction also proceeded efficiently under otherwise the same reaction conditions (Table 3, entry 3). Notably, halide-containing nitroarenes were also fully converted to the corresponding halogen-substituted
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dimethylated products in 80-99% yields. It should be noted that no dehalogenation processes were observed in any case (Table 3, entries 4-8).

**Table 3.** Direct $N$-methylation of nitroarenes with formic acid.[a]

$$
\begin{array}{ccc}
\text{Entry} & \text{Substrate} & \text{Conv.}[b] & \text{Yield}[b] \\
1 & R = 3-\text{OMe} & >99 & 74 \\
2 & R = 4-\text{SMe} & >99 & (94) \\
3 & R = \text{H} & >99 & 91 \\
4 & R = 4-\text{F} & >99 & 86 \\
5 & R = 3-\text{Cl} & >99 & 96 (88) \\
6 & R = 2-\text{Cl} & >99 & >99 \\
7 & R = 4-\text{Br} & >99 & 97 \\
8 & R = 3-\text{I} & >99 & 80 \\
9[c] & \begin{array}{c}
\text{R} \\
\text{R}
\end{array} & >99 & (72) \\
10[d,e,f] & R = 3-\text{CHCH}_2 & >99 & (73) \\
11[g] & \begin{array}{c}
\text{R} \\
\text{R}
\end{array} & >99 & 96 \\
12[e,h] & R = 4-\text{CN} & >99 & 66 \\
13[g] & R = 4-\text{CO}_2\text{Me} & >99 & (89) \\
14[c,g] & \begin{array}{c}
\text{R} \\
\text{R}
\end{array} & >99 & (83)
\end{array}
$$

More interestingly, \( N \)-methylation of more challenging nitroarenes containing other easily reducible functional groups was also successfully accomplished (Table 3, entries 10-14). \( N \)-heterocyclic arenes, double bonds, ketones as well as carboxylic acid derivatives, such as cyanides and esters functional groups were well retained in the final dimethylated anilines which were obtained in good to excellent yields. In some of these cases, room temperature (Table 3, entry 10), increased amounts of formic acid and/or reaction time (Table 3, entries 11,13-14) were required to get optimal yields.

With good reactivity for \( N \)-methylation of aromatic nitroarenes, we became interested in exploring the ability of this catalytic system to methylate benzylic-type nitro compounds. As shown in Scheme 3, phenylnitromethane (6a) was used as substrate under optimized reaction conditions affording \( N,N \)-dimethylbenzylamine (7a) in 62% yield without detection of any other by-products.

![Scheme 4. \( N \)-methylation of phenylnitromethane.](image)

**Conclusions**

In summary, we have developed a convenient and straightforward catalytic protocol for the preparation of \( N,N \)-dimethylated amines from readily available nitroarenes using formic acid as a renewable \( C_1 \) source and silanes as reducing agents. As catalyst to accomplish this domino reaction, we have designed a heterobimetallic cubane-type \( Mo_3PtS_4 \) cluster. By applying the heterobimetallic \( 3(BF_4) \) complex the direct \( N \)-methylation of nitroarenes has been smoothly accomplished under mild conditions (70 °C, ambient pressure). Interestingly, we have demonstrated that in this reaction sequence the presence of the trinuclear complex \( 1(BF_4) \) favors the first step, that is
the nitroarene to aniline transformation, so almost quantitative yields of the N,N-methylated amine can be achieved even at room temperature and/or lowering the reaction times. Notably, the catalytic protocol has been applied to nitroarenes containing easily reducible functionalities, such as N-heterocyclic arenes, double bonds, ketones, cyanides and esters functional groups that are well retained in the final dimethylated anilines. Furthermore, benzylic-type nitro compounds are potential candidates to be directly methylated under this protocol.

In general, its operational simplicity with no need to use any special high-pressure equipment, the mild reaction conditions (room temperature), the use of readily available feedstocks and its high chemoselectivity make this protocol an attractive and useful methodology for organic synthesis.

**Experimental Section**

**General remarks**

All reactions were carried out under a nitrogen atmosphere using standard Schlenck techniques. The trinuclear complex $[\text{Mo}_3\text{S}_4\text{Cl}_5(\text{dmen})_3]\text{BF}_4$ (1(BF$_4$)) was prepared according to the literature procedure.$^{[24b]}$ Pt(PPh$_3$)$_4$ (2) was pursued from commercial sources and used as received.

**Physical measurements**

Elemental analyses were carried out on a EuroEA3000 Eurovector Analyser. Electrospray mass spectra were recorded with a Quattro LC (quadrupole-hexapole-quadrupole) mass spectrometer with an orthogonal Z-spray electrospray interface (Micromass, Manchester, UK). The cone voltage was set at 20 V unless otherwise stated using CH$_3$CN as the mobile phase solvent. Sample solutions have been infused via syringe pump directly connected to the ESI source at a flow rate of 10 µL/min.
and a capillary voltage of 3.5 kV was used in the positive scan mode. Nitrogen was employed as drying and nebulizing gas. Isotope experimental patterns were compared with theoretical patterns obtained using the MassLynx 4.1 program.[20] $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III HD 400 MHz or 300 MHz spectrometers using CD$_2$Cl$_2$ or CDCl$_3$ as solvents. Gas chromatography analyses were performed on an Agilent 7820A GC System equipped with a FID and a capillary column Agilent (HP-5, 30m x 0.32mm x 0.25 µm). Mass determination was carried out on a GC-Mass Agilent 5977E network equipped with a mass-selective detector. Cyclic voltammetry experiments were performed with an Echochemie Pgstat 20 electrochemical analyzer. All measurements were carried out with a conventional three-electrode configuration consisting of glassy carbon working and platinum auxiliary electrodes and an Ag/AgCl reference electrode. The solvent used was dichloromethane (HPLC grade) which was deoxygenated before used and tetrabutylammonium hexafluorophosphate (0.1 M solution) was used as supporting electrolyte.

Catalyst preparation

**Synthesis of [Mo$_3$Pt(PPh$_3$)$_4$Cl$_3$(dmen)$_3$]BF$_4$ (3(BF$_4$)):** To a green solution of the trinuclear complex 1(BF$_4$) (100 mg, 0.114 mmol) in dry THF (10 mL) was added a two-fold excess of the mononuclear Pt complex 2 (285 mg, 0.229 mmol) under inert atmosphere. The reaction occurs with an immediate colour change to brown and the formation of a precipitate. After stirring the reaction mixture for 24 h at room temperature, the solid was separated by filtration, washed with cold THF and dissolved in dichloromethane. Finally, the product was crystallized from dichloromethane/ether mixtures to afford a dark-brown solid characterized as [Mo$_3$Pt(PPh$_3$)$_4$Cl$_3$(dmen)$_3$]BF$_4$ (3(BF$_4$)) (80 mg, 52 % yield). Elemental analysis for 3(BF$_4$)·Et$_2$O: calc. (%) for Mo$_3$PtPS$_4$Cl$_3$N$_6$C$_{34}$H$_{61}$OBF$_4$: C 29.06, H 4.38, N 5.98, S
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9.13; found (%): C 29.20, H 4.42, N 5.9, S 9.13. ¹H NMR (400 MHz, CD₂Cl₂) δ 7.77 – 7.18 (m, 15H, CH), 4.25 (br s, 3H, NH), 4.15 (br s, 3H, NH), 3.30 – 3.12 (m, 6H, CH₂), 2.98 (d, J = 5.6 Hz, 9H, CH₃), 2.93 – 2.70 (m, 6H, CH₂), 2.14 (d, J = 6.1 Hz, 9H, CH₃); ¹³C NMR (101 MHz, CD₂Cl₂) δ [134.31, 134.18 (C, d, ¹J_C-P = 12.34 Hz)], [132.54, 132.44 (CH, d, ³J_C-P = 9.41 Hz )], [131.69, 131.67 (CH, d, ⁴J_C-P = 2.47 Hz)], [129.27, 129.15 (CH, d, ²J_C-P = 11.37 Hz)], 56.69 (s, CH₂), 52.49 (s, CH₂), 47.52 (s, CH₃), 43.82 (s, CH₃); ESI-MS (CH₃CN, 20 V): m/z 1244.8 [M⁺].

Catalytic activity tests

General procedure for the direct N-methylation of p-nitrotoluene (1a): Under a nitrogen atmosphere, PhSiH₃ (123 µL, 1 mmol), 1a (13.7 mg, 0.1 mmol), hexadecane (15 µL; added as an internal standard) and HCO₂H (32 µL, 0.85 mmol) were added to a brown solution of 3(BF₄) (4 mg, 0.003 mmol) in dry THF. After the reaction mixture was stirred for 18 h at 70 ºC, ethyl acetate (5 mL) was added and a sample for GC was taken after slow addition of NaOH solution (3 M (aq.), 2 mL) and vigorous stirring for 3 h at room temperature. All catalytic reactions were performed at least twice to ensure reproducibility. To determine the isolated yield of the methylated amines, no internal standard was added. After completion, dilution with ethyl acetate and stirred for 3 h with the aqueous solution of NaOH, the mixture was extracted with ethyl acetate (three times) and the combined organic layers were dried over MgSO₄ anhydrous. Finally, the organic phase was filtered, concentrated and purified by preparative thin layer chromatography (n-hexane/ethyl acetate mixtures) to give the corresponding dimethylated amines.

When a mixture of the trinuclear 1(BF₄) and the mononuclear 2 complexes mixed in situ was used as catalyst, the procedure for N-methylation of nitroarenes was as follows: Under a nitrogen atmosphere, complex 2 (1.3 mg, 0.001 mmol) was added to a green solution of 1(BF₄) (2.6 mg, 0.003 mmol). Immediately, the solution
colour changed to brown greenish. After stirring for 10 min at room temperature, the general procedure described above was applied.

**X-ray data collection and structure refinement**

Slow vapor diffusion of diethyl ether into a sample solution of $3$(BF$_4$) in CH$_2$Cl$_2$ afforded brown needle-shaped crystals suitable for X-ray studies. Diffraction data collection was performed at 200 K on an Agilent Supernova diffractometer equipped with an Atlas CCD detector using Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ Å). No instrument or crystal instabilities were observed during data collection. Absorption correction based on the Multi-scan method was applied.$^{[30-31]}$ The structure was solved by direct methods and refined by the full-matrix methods based on F$^2$ with the program SHELXL-13 using the Olex2 software package.$^{[32-33]}$ The structural figure was drawn using the Diamond visual crystal structure information system software.$^{[34]}$ Crystal data for $3$(BF$_4$)·O(CH$_2$CH$_3$); C$_{34}$H$_{51}$BCl$_3$F$_4$Mo$_3$N$_6$OPPtS$_4$; $M = 1395.08$; monoclinic; space group $P2_1/c$; $a = 12.3842(4)$, $b = 17.7628(6)$, $c = 22.6052(13)$ Å; $\beta = 91.909(4)^\circ$; $V = 4969.9(4)$ Å$^3$; $T = 200(14)$ K; $Z = 4$; $\mu$(Mo$_{K\alpha}$) = 3.956 mm$^{-1}$; $D_{calc} = 1.865$ g/cm$^3$. Reflections collected/unique = 40770/9758 ($R_{int} = 0.058$). The non-hydrogen atoms of the cluster and the counter anion were refined anisotropically whereas the hydrogen atoms were included at their idealized positions and refined as riders with isotropic displacement parameters assigned as 1.2 times the Ueq value of the corresponding bonding partner for CH, CH$_2$ and NH groups and 1.5 times for methyl groups. In the last Fourier map a highly disordered diethyl ether molecule was found. To model this disorder, the O-C and C-C bond distances were constrained to a fix value and isotropic thermal parameters for the C32, C33 and C34 ether atoms were fixed at 0.1. The hydrogen atoms of the disordered solvent molecule were not included in the model. The final refinement converged with $R_1 = 0.0525$ and $wR_2 = 0.1414$ for all reflections, GOF=1.065 and max./min. residual electron density =
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2.32/-1.79 e·Å$^3$. CCDC 1554979 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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References


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[28] Ion-suppression effects are due mainly to the competition between matrix components and the analytes to be ionized.

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