Polonovski-Type N-Demethylation of *N*-Methyl Alkaloids Using Substituted Ferrocene Redox Catalysts

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Abstract: Various substituted ferrocenes have been trialed as catalysts in the nonclassical Polonovski reaction for N-demethylation of *N*-methyl alkaloids. Earlier studies suggest that conditions facilitating a higher ferrocenium ion concentration lead to superior outcomes. In this regard, the bifunctional ferrocene $FcCH_2CO_2H$, with electron donor and acceptor moieties in the same molecule, has been shown to be advantageous for use as a catalyst in the N-demethylation of a number of tertiary *N*-methylamines such as codeine, thebaine, and oripavine. These substrates are readily N-demethylated under mild conditions, employing sub-stoichiometric amounts of the substituted ferrocene at ambient temperature. These reactions are equally efficient in air and may also be carried out in one pot.

Key words: N-demethylation, Polonovski reaction, substituted ferrocene, alkaloid

The efficient synthesis of N-substituted opioids such as naltrexone (**1**), naloxone (**2**), and buprenorphine (**3**) (Figure 1) is an important area of research relevant to therapeutics for pain management and opioid and alcohol addiction.[1] It is estimated that the annual sales for the treatment of opioid addiction alone is in the vicinity of US $1 billion.[2] Compounds such as **1**–**3** are semi-synthetic analogues of morphine in which the naturally occurring *N*-methyl group has been replaced with an *N*-alkyl group in addition to C-ring modification. The problematic step in the synthesis of such compounds is typically the removal of the *N*-methyl group prior to N-substitution. From the patent literature in particular, it is apparent that N-demethylation, even for common opiates remains a challenging task especially for large scale operations.

For a number of years, we have been interested in the use of the nonclassical Polonovski reaction for N-demethylation of *N*-methyl alkaloids such as opiates and tropanes. This was carried out via a two-step process: N-oxidation of the *N*-methyl alkaloid **a** and subsequent treatment of the *N*-oxide **b** with a redox catalyst, affording the *N*-nor product **c** (Scheme 1). A number of Fe(II) reagents such as $FeSO_4 \cdot 7H_2O$[3,4] and the ferrous porphyrin Fe(II)TPPS[5] and, more recently, zero valent iron such as iron powder and stainless steel[6–8] have been found to be effective catalysts.

Recently, we have also explored the ferrocene/ferrocenium (Fc/Fc^+) redox system in Polonovski-type N-demethylation of *N*-methyl alkaloids such as opiates and tropanes with some success.[9] It was found that yields of the N-nor products obtained were highly sensitive to substrate structural effects. Thus, whilst high yields were obtained for substrates such as dextromethorphan, codeine methyl ether, and thebaine (>80%), only modest to low yields (<40%) were obtained for others such as oripavine and thevinone. For these latter substrates, significant amounts of the corresponding *N*-methylamine by-product were also obtained. Moreover, elevated temperatures (typically, at or above 40 °C) were also found to be necessary for a favorable outcome, with essentially no reaction observed at room temperature.

As shown in Scheme 2, N-demethylation under Polonovski-type conditions has been postulated to proceed via a series of one-electron transfers, implicating a Fe^{2+}/Fe^{3+} redox couple.[10] From our earlier studies with zerovalent iron catalysts,[7,8] it was apparent to us that tuning an appropriate balance of the primary catalyst and its oxidized form would be highly desirable for process optimization.

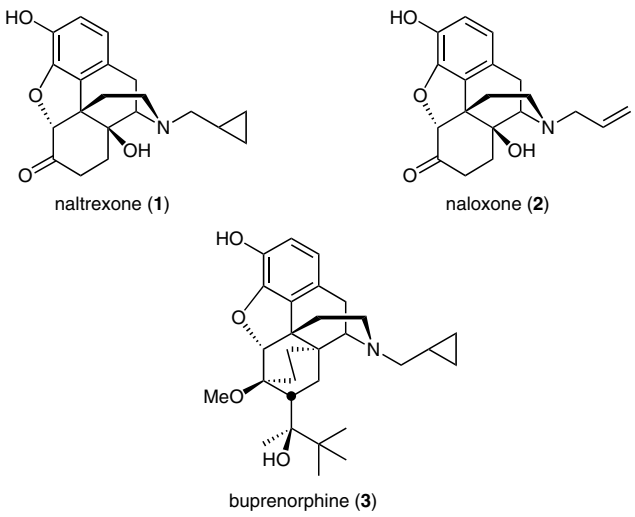
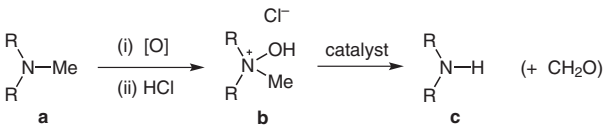


Figure 1 N-Substituted opioids **1**–**3**



Scheme 1 N-Demethylation under Polonovski-type conditions

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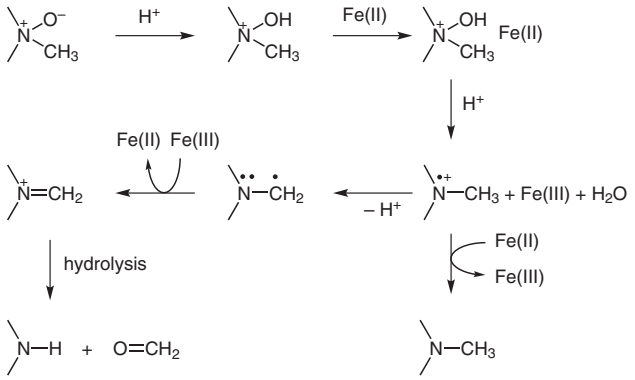
For example, we found that conducting these reactions in the presence of molecular oxygen markedly accelerates the rate of N-demethylation, suggesting that the crucial balance between the reduced and the higher oxidized iron species is important for a favorable outcome.[8] In the Fc/Fc^+-mediated N-demethylations, we have found that different solvents (namely $CHCl_3$, CH_2Cl_2, MeCN, MeOH, and *i*-PrOH) play a major role, with reaction outcomes generally better in halogenated solvents.[9] The latter solvent effects may be attributed to the relative ease of formation of the Fc^+ species in such solvents. In this regard, others have found that oxidation of Fc to Fc^+ is facilitated in halogenated alkanes, including chloroform.[11] Indeed, in photooxidation studies of ferrocene in halocarbon–ethanol solvents, there is an increase in the charge-transfer-to-solvent absorption with increasing acceptor (halocarbon) solvent concentration.[12] However, Fc/Fc^+-catalyzed N-demethylation was found not to be facilitated by molecular oxygen, with the reaction taking a significantly longer time to reach completion than the corresponding reaction under N_2.[9] This result is consistent with literature findings, which suggest that although ferrocene itself is known to be very resistant to oxygen, there may be a slow decomposition of the oxidized species in air.[13,14]



Scheme 2 Proposed mechanism for Polonovski-type N-demethylation[10]

Moreover, there have been numerous reports on the reactivity of ferrocenium ions towards molecular oxygen in organic solvents.[15–18] Hence, molecular oxygen itself could not be relied upon to tune the balance of Fc/Fc^+ for these reactions.

Notably, the Fc/Fc^+ redox couple is well suited for the study of tunable redox properties, particularly in regard to conditions that facilitate ferrocenium ion formation since its donor-acceptor ability may be modulated via the choice of an appropriate substituent(s) on the cyclopentadienyl ring(s). Indeed, numerous studies have shown that the oxidation potentials of ferrocenes depend on the electronic effects of the substituent groups.[19] We now present new data on the effects of ferrocene substituent(s) on Polonovski-type N-demethylation.

To investigate the effects of electron donor groups on N-demethylation, dimethylferrocene (Me_2Fc) and decamethylferrocene ($Me_{10}Fc$) were selected (Figure 2). It was anticipated that by employing both Me_2Fc and $Me_{10}Fc$, some insight into the effects of redox potentials on both the reaction rate and product yield, via progressive addition of electron donor groups, would be provided. These results are benchmarked to ferrocene itself and are also compared to ferrocenecarboxylic acid ($FcCO_2H$) and ferroceneacetic acid ($FcCH_2CO_2H$). Oxidation potentials for these ferrocenes are well documented in the literature,[20] albeit not under identical conditions. However, qualitative relationships can still be discerned, for example, it is reasonably expected that oxidation potential increases in the order $Me_{10}Fc > Me_2Fc > Fc > FcCH_2CO_2H > FcCO_2H$.[20] Substrate structural effects have been studied using dextromethorphan (**4a**), codeine (**5a**), thebaine (**6a**), oripavine (**7a**), and thevinone (**8a**) (Figure 2).

N-Demethylation reactions were typically conducted in chloroform whilst for chloroform-insoluble substrates, reactions were conducted in a binary solvent system: $CHCl_3$–propan-2-ol (3:1). To avoid complications due to the reactivity of certain ferrocenium ions towards molecular oxygen (vide supra), our initial studies were conduct-

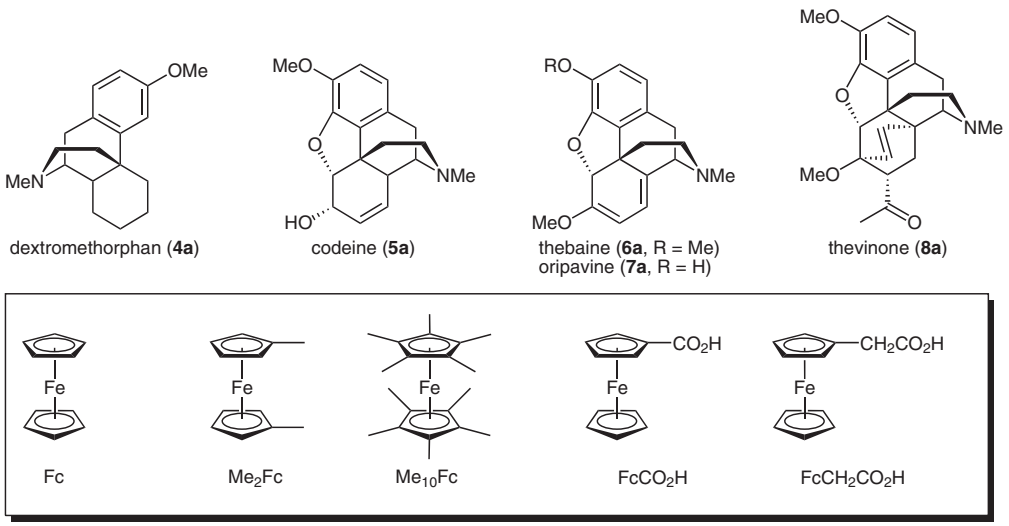
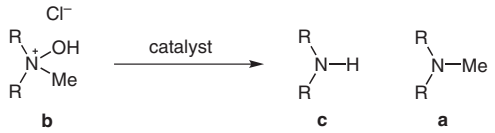


Figure 2 Test substrates and ferrocene catalysts employed in this study

Table 1 N-Demethylation of Various Opiate-*N*-oxide Hydrochlorides with Ferrocenes[a]



Entry	Substrate (*N*-oxide·HCl)	Catalyst[b]	Solvent[c]	Temp (°C)	Time (h)	NH **c** (%)[d]	NMe **a** (%)[d]
1[e]	dextromethorphan	Fc	$CHCl_3$	40	40	92	8
2[e]	dextromethorphan	Me_2Fc	$CHCl_3$	40	20	86	12
3[e]	dextromethorphan	$Me_{10}Fc$	$CHCl_3$	40	6	84	12
4[e]	dextromethorphan	$FcCO_2H$	$CHCl_3$	40	24	77	15
5[e]	dextromethorphan	$FcCH_2CO_2H$	$CHCl_3$	40	1	84	15
6[e]	dextromethorphan	$FcCH_2CO_2H$	$CHCl_3$	r.t.	4	85	15
7	codeine	Fc	$CHCl_3$	50	24	80	12
8	codeine	Me_2Fc	$CHCl_3$	50	16	85	11
9	codeine	$Me_{10}Fc$	$CHCl_3$	50	4	86	8
10	codeine	$FcCO_2H$	$CHCl_3$	50	5	72	21
11	codeine	$FcCH_2CO_2H$	$CHCl_3$	50	2	86	9
12	codeine	$FcCH_2CO_2H$	$CHCl_3$–*i*-PrOH (3:1)	r.t.[f]	2	86	11
13	thebaine	Fc	$CHCl_3$	50	30	83	8
14	thebaine	Me_2Fc	$CHCl_3$	50	16	83	7
15	thebaine	$Me_{10}Fc$	$CHCl_3$	50	3	79	12
16	thebaine	$FcCO_2H$	$CHCl_3$	50	16	73	15
17	thebaine	$FcCH_2CO_2H$	$CHCl_3$	50	1.5	83	8
18	thebaine	$FcCH_2CO_2H$	$CHCl_3$	r.t.	4.5	81	12
19	oripavine	Fc	$CHCl_3$–*i*-PrOH (3:1)	50	120	71	26
20	oripavine	Me_2Fc	$CHCl_3$–*i*-PrOH (3:1)	50	48	80	17
21	oripavine	$Me_{10}Fc$	$CHCl_3$–*i*-PrOH (3:1)	50	30	81	16
22	oripavine	$FcCO_2H$	$CHCl_3$–*i*-PrOH (3:1)	50	24	77	20
23	oripavine	$FcCH_2CO_2H$	$CHCl_3$–*i*-PrOH (3:1)	50	3	80	13
24	oripavine	$FcCH_2CO_2H$	$CHCl_3$–*i*-PrOH (3:1)	r.t.	16	81	14
25	thevinone	Fc	$CHCl_3$	r.t.	24	NR[g]	
26	thevinone	Fc	$CHCl_3$	35	24	37	62
27	thevinone	Me_2Fc	$CHCl_3$	r.t.	24	39	56
28	thevinone	$Me_{10}Fc$	$CHCl_3$	r.t.	20	19	69
29	thevinone	$FcCO_2H$	$CHCl_3$	r.t.	48	39	48
30	thevinone	$FcCH_2CO_2H$	$CHCl_3$	r.t.	2.5	56	43

[a] Reactions were conducted under N_2 with degassed solvents.
[b] Amount used: 25 mol%.
[c] Concentration: 10 mL of solvent per 100 mg of substrate.
[d] Isolated via column chromatography.
[e] Concentration: 5 mL per 100 mg of substrate.
[f] Due to limited solubility of the substrate in $CHCl_3$ at r.t., the reaction at r.t. was conducted in $CHCl_3$–*i*-PrOH (3:1).
[g] No reaction.

ed under a nitrogen atmosphere using degassed solvents. Thus, the *N*-methylamine **a**, oxidized to the corresponding *N*-oxide hydrochloride **b**,[3,9] was stirred with the redox catalyst in solvent until complete consumption of starting material (via TLC analysis). After standard workup, the N-demethylated product **c** was isolated from the tertiary *N*-methylamine **a** via column chromatography. These results are shown in Table 1.

The reactions involving Fc, Me_2Fc, and $Me_{10}Fc$ gave comparable yields of *N*-nordetromethorphan (**4c**), *N*-norcodeine (**5c**), *N*-northebaine (**6c**), and *N*-nororipavine (**7c**) ranging between 70–92%. In all cases, the N-demethylation of thevinone-*N*-oxide (**8b**) proceeded in much lower yield (19–39%), which may result from steric factors associated with the significantly bulkier C-ring structure of this substrate. The other substrates (dextromethorphan-*N*-oxide, codeine-*N*-oxide, thebaine-*N*-oxide, and oripavine-*N*-oxide as HCl salts) gave consistent yields for a given catalyst, with the variation typically less than 5% of the average. In contrast, the reaction rates differed markedly with the different ferrocene catalysts, with rate enhancement in the order of $Me_{10}Fc > Me_2Fc > Fc$. The observed kinetics of these reactions was consistent with the ease of oxidation of the ferrocene, with oxidation rates reported to be much higher for permethylferrocenes than for the parent compound.[21] Although the N-demethylation rate is enhanced by the increasing electron donor effects of the substituents, with the notable exceptions of codeine and oripavine, the rate enhancement appears to compromise the yield of the N-demethylated product. In the case of codeine and oripavine, $Me_{10}Fc$ performed the best, delivering the *N*-nor product in high yield after only a relatively short reaction time at 50 °C.

The N-demethylation reactions, which employed $FcCO_2H$ as a catalyst, also afforded similar isolated yields to the previous examples. However, the reactions involving $FcCO_2H$ generally proceed faster than for ferrocene itself. Superficially, this might appear to be counter-intuitive since electron-withdrawing moieties might be expected to retard the reaction. For $FcCO_2H$, the electronic effects of the substituent may be complicated by other secondary considerations. Thus, previous studies have found that, whilst the directly bound CO_2H group exerts quite a strong electron-withdrawing effect, the rate of oxidation or ease of ferrocenium ion formation of ferrocene derivatives containing such strong electron-withdrawing substituents (e.g., formylferrocene, acetylferrocene, and $FcCO_2H$) can significantly exceed that of unsubstituted ferrocene, depending on the pH.[22] Moreover, it has been reported that in $FcCO_2H$, the oxidation state of the ferrocene subunit can greatly influence the relative proportions of the acid and its conjugate base, $FcCO_2^-$.[23] Furthermore, voltammetry studies carried out on unbuffered solutions containing $FcCO_2H$ have shown that this acid and its conjugate base undergo independent oxidation processes over a pH range of 4–8, with increasing pH resulting in a decrease in the oxidation of the $FcCO_2H$ form and a concomitant increase in the oxidation of the $FcCO_2^-$ form. Hence, the electronic effect of the substituent is dependent on pH in a complex way.

We envisaged that further rate and/or product yield enhancement may be possible by a more considered choice of the nature of the appended group on ferrocene. In particular, it is well known that a number of ferrocene derivatives are bifunctional reagents, with the electron-donor reaction site at the metal center and the electron-acceptor site on the substituent. Indeed, previous studies have found that, whilst ferrocene itself is stable to autooxidation, some derivatives of ferrocene, such as ferroceneacetic acid ($FcCH_2CO_2H$), readily undergo autoxidation.[24] Thus, ferroceneacetic acid readily oxidizes at 20–50 °C forming the 'inner' ferrocenium salt $Fc^+CH_2CO_2^-$ as the main oxidation product.[22,25,26] For this bifunctional ferrocene, having both reaction sites present in the same molecule, with the cation and anion stabilizing each other via intramolecular charge-transfer, can be expected to result in a decrease in the activation free energy due to a gain in activation entropy compared to an intermolecular process (e.g., charge-transfer to solvent), facilitating the charge-transfer process.[24,27]

On this basis, as an initial proof of concept, ferroceneacetic acid was chosen as a suitable redox candidate for further study. Preliminary investigations were also conducted at room temperature in chloroform, using 25 mol% of $FcCH_2CO_2H$. However, in the cases of codeine (**5a**) and oripavine (**7a**), reactions were performed in $CHCl_3$–propan-2-ol (3:1) rather than chloroform alone, since the respective *N*-oxide hydrochloride has only limited solubility in chloroform at ambient temperature. Results are also summarized in Table 1.

Using ferroceneacetic acid as redox catalyst, the N-demethylation rate was found to be significantly enhanced, with reactions being complete within 16 hours, even at room temperature. Also noteworthy is a significant improvement in the yield of *N*-northevinone (**8c**) to 56% (compared with 37% when ferrocene was used as the catalyst).

The N-demethylation rate enhancement using ferroceneacetic acid as catalyst prompted further investigations into the effect of stoichiometry and the influence of molecular oxygen on N-demethylation for the substrates thebaine (**6a**) and oripavine (**7a**). Results are summarized in Table 2. Relevant results from earlier experiments conducted under a nitrogen atmosphere have been included in Table 2 for reference. In both cases, lowering the catalyst loading from 25 to 6 mol% afforded a similar yield of the *N*-nor product. However, the lower catalyst loading increased the time it took for the reaction to proceed to completion. This was most notable in the case of oripavine-*N*-oxide hydrochloride (**7b**), where the reactions took approximately three times longer to reach completion.

With respect to the influence of molecular oxygen, in the case of thebaine (**6a**), the reaction outcome proved to be sensitive to the catalyst loading. At a catalyst loading of 25 mol%, there appears to be no significant benefit in con-

ducting the reaction under an inert atmosphere (cf. Table 2, entries 1 and 3). At a lower catalyst loading of 6 mol%, the yield of the *N*-nor product **7c** was slightly compromised for the air experiment (cf. entries 2 and 4). In the case of oripavine, both catalyst loadings gave lower yields of *N*-nororipavine (**7c**) for the air experiments. Recent studies have found that oxidation of ferroceneacetic acid with molecular oxygen gave other ferrocene derivatives such as hydroxymethylferrocene, formylferrocene, and ferrocenylpyruvic acid as main products.[27] It is conceivable that these ferrocene derivatives can themselves perform redox chemistry similar to the primary $FcCH_2CO_2H$ catalyst and thus may explain the slight difference in yields for the reactions conducted in the presence and absence of molecular oxygen.

Since ferroceneacetic acid has an inherent acidic group, we have also investigated reactions using the *N*-oxide free base. For these experiments, dextromethorphan-*N*-oxide was used as substrate. Unlike the situation with the hydrochloride salt **4b**, essentially no conversion into product was observed after 24 hours at room temperature when the *N*-oxide free base was used. However, N-demethylation was achieved when the temperature was increased to 50 °C, though the isolated yield of *N*-nordextromethorphan (**4c**) was poor (25%) and the major product of this reaction was the parent amine, dextromethorphan (36%). It should be noted that the *N*-oxide-free base failed to N-demethylate when treated with ferrocene itself, even at elevated temperatures. The latter result is perhaps not surprising given the requirement for the initial protonation of the substrate *N*-oxide (Scheme 2) and that oxidation of

Table 2 Further Investigations on N-Demethylation with Ferroceneacetic Acid[a]

Entry	Substrate (*N*-oxide·HCl)	Catalyst (mol%)	Solvent[b]	Atm[c]	Time (h)	NH **c** (%)[d]	NMe **a** (%)[d]
1	thebaine	25	$CHCl_3$	N_2	4.5	81	12
2	thebaine	6	$CHCl_3$	N_2	8	87	7
3	thebaine	25	$CHCl_3$	air	4.5	80	9
4	thebaine	6	$CHCl_3$	air	8	81	11
5	oripavine	25	$CHCl_3$–*i*-PrOH (3:1)	N_2	16	81	14
6	oripavine	6	$CHCl_3$–*i*-PrOH (3:1)	N_2	48	82	12
7	oripavine	25	$CHCl_3$–*i*-PrOH (3:1)	air	16	77	17
8	oripavine	6	$CHCl_3$–*i*-PrOH (3:1)	air	48	75	18

[a] Reactions were conducted at r.t.
[b] Concentration: 10 mL of solvent per 100 mg of substrate.
[c] Reactions in N_2 were conducted in degassed solvents.
[d] Isolated yields following column chromatography.

Table 3 One-Pot N-Oxidation and N-Demethylation with Ferrocene and Ferroceneacetic Acid[a]

Entry	Substrate (0.67 mmol)	Catalyst[b]	Solvent: $CHCl_3$–*i*-PrOH[c]	Atm[d]	Time (h)[e]	NH **c** (%)[f]	NMe **a** (%)[f]
1	thebaine	Fc	20:1	N_2	48	76	16
2	thebaine	Fc	20:1	air	48	75	15
3	thebaine	$FcCH_2CO_2H$	20:1	N_2	6	85	13
4	thebaine	$FcCH_2CO_2H$	20:1	air	6	86	13
5	oripavine	Fc (12 mol%)	3:1	N_2	120	72	20
6	oripavine	Fc (12 mol%)	3:1	air	72	72	19
7	oripavine	$FcCH_2CO_2H$	3:1	N_2	16	82	17
8	oripavine	$FcCH_2CO_2H$	3:1	air	8	76	17

[a] N-Oxidation was performed at –5 °C whilst subsequent N-demethylation was conducted at 50 °C.
[b] Unless otherwise specified, 6 mol% of the catalyst was used.
[c] Concentration: 10 mL of solvent per 100 mg of substrate.
[d] Reaction conducted under N_2 used degassed solvents.
[e] Reaction time after addition of catalyst.
[f] Isolated yield following column chromatography.

ferrocene itself with molecular oxygen only occurs in the presence of strong Brønsted acids.[21,28,29]

Finally, to demonstrate the feasibility of reducing the current two-step protocol to one pot, a number of experiments were conducted using $FcCH_2CO_2H$ on thebaine (**6a**) and oripavine (**7a**). Results are summarized in Table 3. For comparison, reactions were also conducted using ferrocene itself for these substrates. Since some ferrocenium ions have been reported to be highly sensitive to certain conditions and additives,[11,30] it was gratifying that the presence of the by-product *m*-chlorobenzoic acid from the N-oxidation did not adversely interfere with these reactions, with respect to yield and total product recovery. Interestingly, with respect to reaction kinetics, depending upon the catalyst employed, the presence of molecular oxygen may prove to be beneficial in these one-pot reactions (cf. Table 3, entries 5 and 6). Indeed, a range of acids such as benzoic acids has been reported to catalyze the oxidation of certain ferrocenes with molecular oxygen.[24,29]

In summary, we have found that the ferrocene-mediated N-demethylation of the *N*-methylamines, dextromethorphan, codeine, thebaine, oripavine, and thevinone under Polonovski-type conditions is sensitive to the electronic effects of the substituent(s) on ferrocene. The reactivity of ferrocene and its methyl derivatives (Me_2Fc, $Me_{10}Fc$) was observed to increase in the order $Me_{10}Fc > Me_2Fc > Fc$, which reflects the relative electron-donor capability of these ferrocenes. However, for certain substrates, rate enhancement compromised the yield of the N-demethylated product obtained. On the other hand, under the same conditions, bifunctional ferroceneacetic acid was found to enhance the rate without compromising the yield. Thus, employing this redox catalyst, the *N*-methylamines were readily N-demethylated under mild conditions, requiring only sub-stoichiometric amounts of catalyst (6 mol%) for reactions to complete within a practical time period, even at room temperature, providing the corresponding *N*-nor product in high yields.

m-Chloroperbenzoic acid (*m*-CPBA, max 77% reagent), 1,1′-dimethylferrocene, decamethylferrocene, ferrocenecarboxylic acid, and ferroceneacetic acid were purchased from Sigma-Aldrich. Ferrocene was from BDH. Reactions, unless otherwise indicated, were conducted under an atmosphere of N_2. For these reactions, solvents were degassed before use: sonicated under vacuum for 10 min and back-filled with N_2. TLC was performed with 0.25 μm TLC silica gel 60F aluminum plates with 254 nm fluorescent indicator and plates were visualized using both UV light and molybdate stain. Unless otherwise indicated, ^1H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively. Chemical shifts (δ ppm) were referenced with solvent residual peaks. High-resolution mass spectra were obtained using a Waters LCT Premier XE time-of-flight mass spectrometer fitted with an electrospray (ESI) ion source and controlled with MassLynx software (version 4.5). All substrate *N*-oxides, isolated as the corresponding hydrochloride salt, were prepared via N-oxidation with *m*-CPBA according to the procedure previously described.[3,9]

N-Demethylation Using Ferrocene; General Procedure

To a solution of the *N*-oxide hydrochloride **4b**, **5b**, **6b**, **7b**, or **8b** (100 mg) in a solvent such as $CHCl_3$ or $CHCl_3$–*i*-PrOH (3:1) (typically, 10 mL per 100 mg), under a N_2 atmosphere, was added ferrocene (6–25 mol%). The resulting solution was left to stir at the specified temperature for the specified length of time or until complete consumption of starting material [via TLC analysis, eluent: $CHCl_3$–MeOH–NH_4OH (85:15:1) for **4b**, **6b**, **7b** and **8b** and CH_3Cl–MeOH (4:1) for **5b**]. Reactions were processed according to either Method A or B.

Method A: The reaction mixture was diluted with $CHCl_3$ (30 mL) and the solution was washed with either concentrated ammonia in brine (5 mL) or 10% aq NaOH (1 mL), dried (Na_2SO_4), filtered, and concentrated. The remaining residue was purified via column chromatography on SiO_2 using a $CHCl_3$–MeOH–NH_4OH gradient which isolated the *N*-nor product from the tertiary *N*-methylamine.

Method B: The crude reaction mixture was concentrated to dryness and the remaining residue was purified via column chromatography on silica gel, eluting with a $CHCl_3$–MeOH gradient, which separated the *N*-nor product from the tertiary *N*-methylamine, both obtained as the corresponding hydrochloride salt.

The above procedure was also performed with other ferrocenes: Me_2Fc, $Me_{10}Fc$, $FcCO_2H$, $FcCH_2CO_2H$. Some reactions were also conducted in air.

One-Pot N-Demethylation Using Ferroceneacetic Acid; General Procedure

To a stirred solution of the *N*-methylamine **5a**, **6a**, or **7a** (0.67 mmol) in either $CHCl_3$ or 3:1 $CHCl_3$–*i*-PrOH (20 mL) at –5 °C under a N_2 atmosphere was added *m*-CPBA (1 equiv) portionwise over 5 min. The reaction mixture was left to stir for a further 15 min. Concd HCl (60 μL) and ferrocene or ferroceneacetic acid (6 or 12 mol%) were added. The reaction mixture was allowed to warm to r.t. and heated at 50 °C until complete consumption of the intermediate *N*-oxide [as monitored by TLC, eluent: CH_3Cl–MeOH (4:1) for **5b** and $CHCl_3$–MeOH–NH_4OH (85:15:1) for **6b** and **7b**].

The reactions for codeine (**5a**) and thebaine (**6a**) were diluted with further amounts of $CHCl_3$ (50 mL) and the resulting solution was washed successively with 5% aq NaOH (2 × 2 mL) and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. Subsequent column chromatography on SiO_2 using a $CHCl_3$–MeOH–NH_4OH gradient separated the desired *N*-nor product from some starting tertiary *N*-methylamine.

Reactions for oripavine (**7a**) in 3:1 $CHCl_3$–*i*-PrOH were concentrated to dryness and H_2O (30 mL) was added to the remaining residue. The mixture was then successively extracted with $CHCl_3$ (4 × 20 mL) and $CHCl_3$–*i*-PrOH (3:1; 4 × 20 mL). The $CHCl_3$–*i*-PrOH extracts were dried (Na_2SO_4), filtered, and concentrated. The resulting solid was column purified according to method B above.

***N*-Nordextromethorphan (4c) (Table 1, entry 6)**

Purified via method A using a gradient of $CHCl_3$–MeOH–NH_4OH (90:10:1–85:15:1); yield: 68 mg (85%); colorless oil; $[\alpha]_D^{24}$ +33 (*c* 0.82, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 7.03 (d, *J* = 8.4 Hz, 1 H), 6.81 (d, *J* = 2.6 Hz, 1 H), 6.72 (dd, *J* = 2.6, 8.4 Hz, 1 H), 3.22 (s, 3 H), 3.17–3.09 (m, 2 H), 2.82–2.61 (m, 5 H), 2.32 (m, 1 H), 1.83–1.77 (m, 1 H), 1.68–1.57 (m, 2 H), 1.55–1.48 (m, 1 H), 1.44–1.25 (m, 5 H), 1.12–0.99 (m, 1 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 158.8, 138.9, 129.3, 126.0, 112.0, 111.1, 55.1, 51.1, 40.7, 38.3, 37.4, 36.6, 35.4, 27.8, 25.5, 25.4, 21.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}NO$: 258.1852; found: 258.1851.

***N*-Norcodeine (5c) (Table 1, entry 12)**

Purified via method A using a gradient of $CHCl_3$–MeOH–NH_4OH (90:10:1–85:15:1); yield: 70 mg (86%); off-white solid; mp 183–184 °C (MeOH–Et_2O) (Lit.[31] mp 182–183 °C); $[\alpha]_D^{23}$ –120 (*c* 1.0, $CHCl_3$) {Lit.[31] $[\alpha]_D^{28}$ –90.9 (*c* 0.224, $CHCl_3$)}.

^{1}H NMR ($CDCl_3$): δ = 6.69 (d, *J* = 8.0 Hz, 1 H), 6.59 (d, *J* = 8.0 Hz, 1 H), 6.73 (dddd, *J* = 1.6, 1.6, 2.8, 9.6 Hz, 1 H), 5.28 (ddd, *J* = 2.8, 2.8, 9.6 Hz, 1 H), 4.88 (dd, *J* = 1.2, 6.4 Hz, 1 H), 4.22–4.17 (m, 1 H), 3.86 (s, 3 H), 3.67–3.63 (m, 1 H), 3.05–2.77 (m, 4 H), 2.62–2.57 (m, 1 H), 1.98–1.87 (m, 2 H), 1.80–1.50 (br, 2 H).

^{13}C NMR ($CDCl_3$): δ = 146.5, 142.0, 133.7, 131.1, 128.1, 127.4, 119.4, 112.9, 92.2, 66.4, 56.3, 51.7, 43.8, 41.2, 38.3, 36.5, 31.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$: 286.1438; found: 286.1449.

***N*-Northebaine (6c) (Table 1, entry 18)**
Purified via method A using a gradient of $CHCl_3$–MeOH–NH_4OH (90:10:1–85:15:1); yield: 66 mg (81%); off-white solid; mp 146–150 °C (Lit.[32] mp 157–158 °C); $[\alpha]_D^{24}$ –225 (*c* 0.82, 5% MeOH in $CHCl_3$) {Lit.[33] $[\alpha]_D^{23}$ –200 (*c* 0.1, 5% MeOH in $CHCl_3$)}.

^{1}H NMR ($CDCl_3$): δ = 6.68 (d, *J* = 8.4 Hz, 1 H), 6.62 (d, *J* = 8.4 Hz, 1 H), 5.51 (d, *J* = 6.4 Hz, 1 H), 5.27 (s, 1 H), 5.03 (d, *J* = 6.4 Hz, 1 H), 3.92 (dd, *J* = 1.6, 6.0 Hz, 1 H), 3.86 (s, 3 H), 3.61 (s, 3 H), 3.25–3.07 (m, 3 H), 2.94 (dd, *J* = 4.0, 13.6 Hz, 1 H), 2.40–2.20 (br, 1 H), 2.08 (ddd, *J* = 5.2, 12.8, 12.8 Hz, 1 H), 1.85–1.80 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 152.4, 144.7, 142.7, 133.9, 133.3, 127.7, 119.1, 112.8, 110.0, 95.7, 89.1, 56.3, 54.8, 53.8, 46.6, 40.6, 38.4, 37.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{20}NO_3$: 298.1438; found: 298.1432.

***N*-Nororipavine Hydrochloride (7c) (Table 1, entry 24)**
Purified via method B using a gradient of $CHCl_3$–MeOH (24:1–17:3); yield: 74 mg (81%); off-white solid; mp >200 °C (dec.); $[\alpha]_D^{24}$ –188 (*c* 1.0, 10% AcOH in H_2O).

^{1}H NMR (D_2O): δ = 6.78 (d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 5.90 (d, *J* = 6.4 Hz, 1 H), 5.50 (s, 1 H), 5.25 (d, *J* = 6.4 Hz, 1 H), 4.61 (d, *J* = 6.0 Hz, 1 H), 3.64 (s, 3 H), 3.46–3.22 (m, 4 H), 2.31 (ddd, *J* = 6.0, 13.3, 13.3 Hz, 1 H), 2.08–2.01 (m, 1 H).

^{13}C NMR (D_2O–CF_3CO_2D): δ = 153.0, 142.8, 138.6, 132.0, 124.4, 124.2, 120.8, 117.3, 117.0, 96.1, 87.7, 55.1, 53.2, 44.6, 37.0, 33.5, 33.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{18}NO_3$: 284.1281; found: 284.1287.

***N*-Northevinone (8c) (Table 1, entry 30)**
Purified via method A using a gradient of $CHCl_3$–MeOH–NH_4OH (98:2:1 to 95:5:1); yield: 46 mg (56%); off-white solid; mp 67–69 °C; $[\alpha]_D^{24}$ –234 (*c* 1.25, $CHCl_3$) {Lit.[34] $[\alpha]_D^{23}$ –240 (*c* 0.1, $CHCl_3$)}.

^{1}H NMR ($CDCl_3$): δ = 6.65 (d, *J* = 7.8 Hz, 1 H), 6.55 (d, *J* = 7.8 Hz, 1 H), 5.93 (d, *J* = 8.8 Hz, 1 H), 5.56 (d, *J* = 8.8 Hz, 1 H), 4.56 (s, 1 H), 3.82 (s, 3 H), 3.61 (s, 3 H), 3.54–3.47 (m, 1 H), 3.18–2.70 (m, 6 H), 2.16 (s, 3 H), 1.90–1.70 (m, 3 H), 1.42 (dd, *J* = 6.4, 12.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 208.7, 147.9, 141.7, 135.7, 133.8, 128.0, 126.1, 119.2, 113.4, 95.6, 80.9, 56.4, 53.4, 52.7, 50.5, 40.1, 42.2, 37.2, 34.3, 33.0, 30.5, 29.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{26}NO_4$: 368.1856; found: 368.1872.

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