

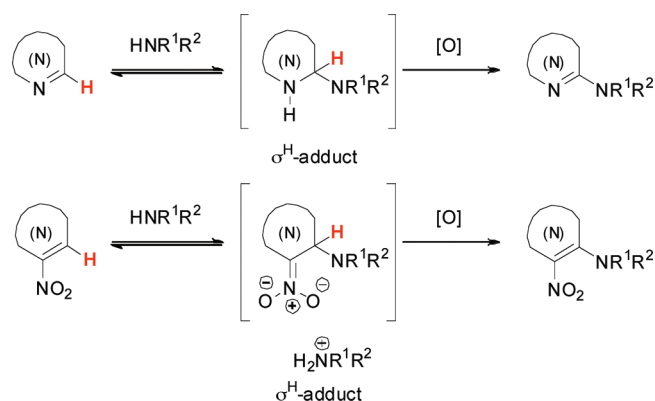
ONSH: Optimization of Oxidative Alkylamination Reactions through Study of the Reaction Mechanism

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Oxidative alkylamination of electron-deficient (hetero)aromatic compounds, *via* the nucleophilic substitution of hydrogen, is a methodology that has made significant progress since the introduction of $\text{AgPy}_2\text{MnO}_4$ as oxidant. This oxidant generally gives good conversions and yields, whereas the use of KMnO_4 only sometimes works equally well. In order to rationalize this, the reaction mechanism of oxidative alkylamination has been studied. 3-Nitropyridine (**1**), 1,3-dinitrobenzene (**2**), and quinazoline (**3**) were chosen as model substrates and *n*-butylamine and pyrrolidine as model alkylamines. The rate-limiting step of the mechanism for these substrate/alkylamine combinations was determined. With the use of ^1H NMR spectroscopy thermodynamic properties of σ^{H} -adduct formation were deduced and the effect of additives on the adduct formation was investigated. The fundamental insights resulting from these studies led to the identification of a cheap additive (tetrabutylammonium chloride), which in combination with the standard and cheap oxidant KMnO_4 generally gave excellent yields, similar to the ones previously obtained with more expensive $\text{AgPy}_2\text{MnO}_4$.

Introduction

Alkylamino-substituted arenes and heteroarenes are important entities because they appear in a large number of drugs, agrochemicals, and polymers.¹ Mild, simple, and

efficient protocols to introduce an alkylamino group onto (hetero)arenes are thus of great importance.² The classical procedure involves the direct nucleophilic substitution of a leaving group, the so-called *ipso*-substitution.^{2,3} This process is limited to electron-deficient substrates. For pyridine and benzo analogues specific synthetic routes for the alkylamination have recently also been developed starting from the

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(2) For a recent microreview on modern amination reactions, see: Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 25, 4166.

(3) (a) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968. (b) Terrier, F. *Nucleophilic Aromatic Displacement*; Verlag Chemie: Weinheim, 1991.

corresponding *N*-oxides.⁴ This preactivation allows the direct substitution of hydrogen in the substrate *via* a *cine*-substitution mechanism. Transition-metal-catalyzed amination of halo(hetero)arenes with alkylamines is a much more broadly applicable method since there is no limitation to activated (electron-deficient) substrates. Among these the Buchwald–Hartwig reaction⁵ is certainly the best developed. A common drawback of all these existing methods is the requirement of a halogen or pseudohalogen in the substrate, which can act as a leaving group. In addition these protocols can generally not be performed at room temperature. Procedures that do not require such preactivation of substrate and can be carried out at ambient temperature are therefore highly attractive. The oxidative alkylation, *via* oxidative nucleophilic aromatic substitution of hydrogen (ONSH),⁶ pioneered by H. van der Plas, offers such an alternative since no leaving group is required.⁷ The oxidative alkylation is considered to involve a two-step mechanism: σ^H -adduct formation followed by oxidative rearomatization. The required reaction conditions are mild. The balance between the electrophilicity of the substrate and the nucleophilicity of the attacking alkylamine has to be favorable, which currently limits the substrate scope. KMnO_4 was standardly used in the role of oxidant, and its bad solubility in alkylamines was considered to be responsible for the often poor results obtained when trying to extend oxidative amination toward oxidative alkylation. Therefore the alkylation has hitherto mainly been limited to methylation. Researchers have attempted to tackle this solubility problem by using electrochemical oxidation instead of chemical oxidation, thereby expanding the scope to other alkylamines than methylamine.⁸ We have previously found that $\text{AgPy}_2\text{MnO}_4$ is a general oxidant for the oxidative alkylation and successfully reported on the alkylation of a variety of substrates both with primary and secondary alkylamines.⁹ The observation that in some cases KMnO_4 as well as $\text{AgPy}_2\text{MnO}_4$ gave a good result for a specific alkylamine–substrate combination and that for another substrate in the same alkylamine $\text{AgPy}_2\text{MnO}_4$ was superior to KMnO_4 indicated that solubility of the oxidant in the alkylamine cannot be the only factor governing

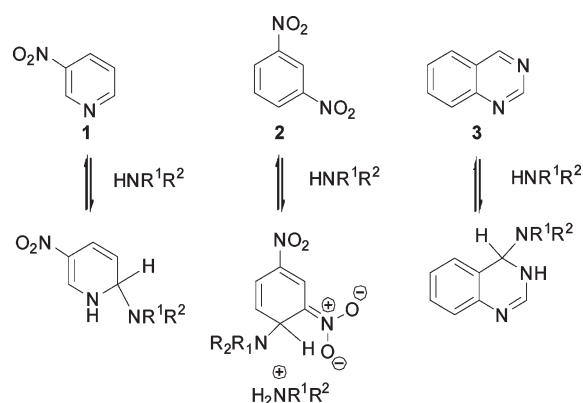


FIGURE 1. Equilibrium of the three substrates with their respective σ^H -adduct in alkylamine.

the success of these reactions. Insight into the reaction mechanism and, in particular, in the rate-determining step of the oxidative alkylation reaction is therefore required and is the subject of this study. As model substrates 3-nitropyridine (**1**), 1,3-dinitrobenzene (**2**), and quinazoline (**3**) (Figure 1) were selected because comparative experimental data on oxidative alkylation on these substrates with KMnO_4 and $\text{AgPy}_2\text{MnO}_4$ were already available in our lab.^{9a,d} As nucleophiles *n*-butylamine and pyrrolidine were chosen as representatives for a primary and secondary alkylamine, respectively.

Results and Discussion

Determination of the Rate-Determining Step of the Oxidative Alkylations *via* Measurement of Primary Kinetic Isotope Effects (KIEs). 3-Nitropyridine-*d*₄ (**1'**) was prepared by nitration of pyridine-*d*₅ according to a literature procedure published for pyridine.¹⁰ 1,3-Dinitrobenzene-*d*₄ (**2'**) was obtained from commercial source. Quinazoline-*d*₆ (**3'**) was synthesized starting from commercially available phthalic acid-*d*₄ (**4'**) (Scheme 1); **4'** could be transformed into quinazolinone (**8'**) following literature procedures reported to synthesize the undeuterated analogue.^{11a–d} Quinazolinone **8'** was then converted into 2,4-dichloroquinazolinone (**9'**) with POCl_3 following a slightly modified literature procedure;^{11c,f} **9'** was subsequently hydrodehalogenated to **3'**, and a Pd-catalyzed H/D exchange in the 2 and 4 positions, following an exchange procedure described for quinoline, finalized the synthesis of **3'**.^{11g} At first we tried the obvious deuterodehalogenation with D_2 , immediately introducing additional deuterium into the molecule. The maximum deuteration grade achieved was however only 85%, which we felt to be insufficient to use the molecule for competitive KIE experiments. We therefore altered the

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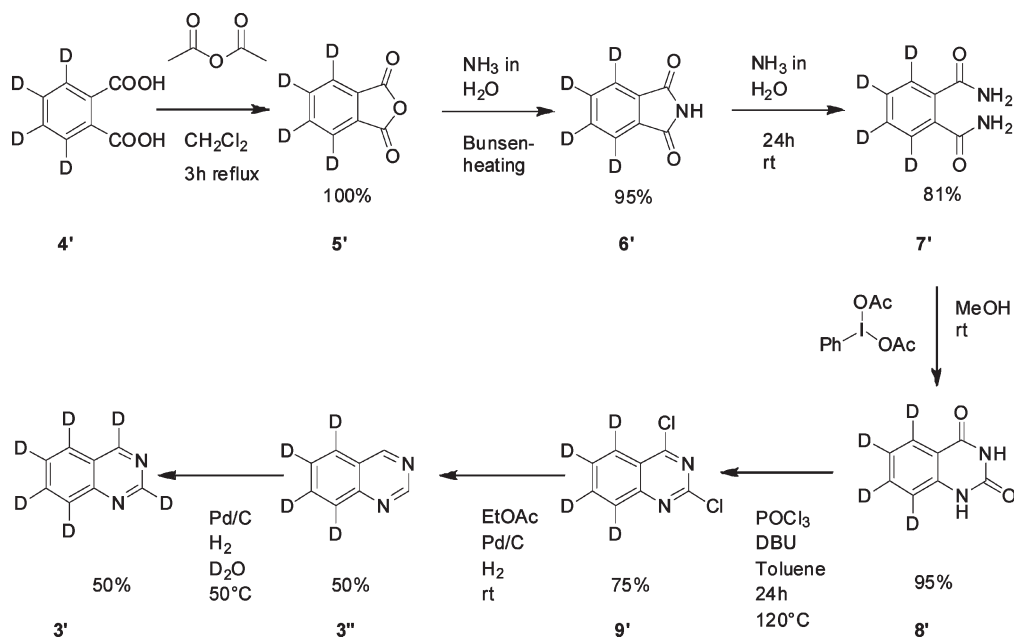
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SCHEME 1. Synthesis of Quinazoline-*d*₆ (3') from Phthalic Acid-*d*₄ (4')

approach and first introduced a hydrogen and then exchanged it for a deuterium. This resulted in a deuteration grade of over 98% in the 2 and 4 positions (determined by ¹H NMR with dioxane as an internal standard).

To the best of our knowledge there is only one report dealing with the determination of a primary kinetic isotope effect (KIE) for an oxidative amination reaction.¹² For the three model substrates the KIE was estimated *via* competitive experiments involving a 1:1 mixture of polydeuterated and undeuterated substrate as this immediately indicates whether σ^H -adduct formation or its subsequent oxidation is rate-limiting in the oxidative alkylamination reaction. The ratio of undeuterated and polydeuterated reaction products P_H/P_D was determined *via* ¹H NMR or high resolution mass spectrometry. When oxidation is rate-limiting, the P_H/P_D measured does not exactly reflect the k_H/k_D because the concentration of deuterated substrate and its hydrogen analogue do not vary in the same way during the oxidative alkylamination reaction. The P_H/P_D ratio value therefore does not allow one to draw any other conclusion than the presence ($P_H/P_D > 1$; rate-limiting oxidation of σ^H -adduct) or absence ($P_H/P_D = 1$; rate-limiting formation of σ^H -adduct) of a KIE. In case of a rate-limiting oxidation the P_H/P_D ratio will be an underestimation of the true k_H/k_D ratio. The determination of the k_H and k_D in separate oxidative alkylamination reactions involving, respectively, the undeuterated and deuterated substrate was unfortunately not possible as the addition of solid oxidant (in small portions) cannot be performed in a reproducible way, as would be required for such kinetic analysis. The measured P_H/P_D values (Table 1) show that the oxidation step is generally rate-limiting, both for KMnO_4 and $\text{AgPy}_2\text{MnO}_4$ as oxidant. An exception is the combination of 3-nitropyridine/*n*-butylamine/ KMnO_4 , where adduct formation was surprisingly

TABLE 1. Estimated KIE Values Following Competitive Experiments

entry	substrate	amine	oxidant	P_H/P_D	KIE
1	1/1'	<i>n</i> -butylamine	KMnO_4	1.10 ^{a,b}	no
2	1/1'	<i>n</i> -butylamine	$\text{AgPy}_2\text{MnO}_4$	3.83 ^a	yes
3	1/1'	pyrrolidine	KMnO_4	3.62 ^a	yes
4	1/1'	pyrrolidine	$\text{AgPy}_2\text{MnO}_4$	2.81 ^a	yes
5	2/2'	<i>n</i> -butylamine	KMnO_4	6.42 ^c	yes
6	2/2'	<i>n</i> -butylamine	$\text{AgPy}_2\text{MnO}_4$	8.09 ^c	yes
7	3/3'	<i>n</i> -butylamine	KMnO_4	6.14 ^c	yes
8	3/3'	<i>n</i> -butylamine	$\text{AgPy}_2\text{MnO}_4$	4.55 ^c	yes
9	3/3'	pyrrolidine	KMnO_4	<i>d</i>	<i>d</i>
10	3/3'	pyrrolidine	$\text{AgPy}_2\text{MnO}_4$	5.25 ^c	yes

^aDetermined by MS. ^bStandard deviation: 0.1. ^cDetermined by ¹H NMR. ^dThe KIE cannot be determined as the reaction does not proceed.^{9a}

found to be rate-limiting (Table 1, entry 1). A change in rate-limiting step was observed upon changing the oxidant. The most significant difference between the two experiments is the cation of the oxidant, Ag^+ versus K^+ . This observation led us to the hypothesis that Ag^+ might play an active role and possibly promotes the σ^H -adduct formation. The well-known coordination properties of Ag^+ for a sp^2 nitrogen atom of (di)azines support this.¹³ Similarly, in the case of the 1,3-dinitrobenzene (2) substrate an oxygen atom of a nitro group can be involved in such a coordination. The KIEs determined indicate that the oxidation of the σ^H -adducts is generally rate-limiting in the ONSH reactions with alkylamine nucleophiles. The [σ^H -adduct] therefore influences the overall rate of the oxidative alkylamination reactions, and we therefore decided to look more closely to the adduct formation and the effect of Ag^+ addition on this process.

Study of σ^H -Adduct Formation *via* ¹H NMR, Raman, and IR: Effect of Additives and Thermodynamics of the Process. The first step of the mechanism of the oxidative alkylamination is σ^H -adduct formation, which is reversible. The involvement

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TABLE 2. ΔH_r° (kJ/mol), ΔS_r° (J/K·mol), and ΔG_r° (kJ/mol) Values of σ^H -Adduct Formation (0.4 M Solution of Substrate in Alkylamine)

entry	substrate	alkylamine	no additive			AgNO ₃			TBACl		
			ΔH_r°	ΔS_r°	ΔG_r° ^a	ΔH_r°	ΔS_r°	ΔG_r° ^a	ΔH_r°	ΔS_r°	ΔG_r° ^a
1	1	<i>n</i> -butylamine	<i>b</i>	<i>b</i>	<i>b</i>	−30	−155	13.9	−24	−118	9.4
2	1	pyrrolidine	−33	−172	15.7	−27	−128	9.2	−17	−79	5.4
3	2	<i>n</i> -butylamine	−86	−374	23.6	−43	−173	7.7	−36	−129	1.8
4	2	pyrrolidine	−65	−277	16.2	−41	−164	7.1	<i>c</i>	<i>c</i>	
5	3	<i>n</i> -butylamine	−36	−150	6.4	−35	−137	3.8	−31	−119	2.7
6	3	pyrrolidine	−50	−167	−2.7	−58	−189	−4.5	−43	−137	−4.2

^a1: 10 °C; 2: 20 °C; 3: 10 °C. ^bFor **1**/*n*-butylamine, no σ^H -adduct can be observed. ^c ΔH_r° and ΔS_r° values could not be determined because of overlapping peaks in the ¹H NMR spectrum.

of σ^H -adducts in the oxidative alkylation reaction has previously been qualitatively proven using ¹H NMR at low temperature.^{14,15} If experimental conditions are well controlled, thermodynamic properties of this step are deducible via ¹H NMR measurements.¹⁵ To perform such analysis, we dissolved substrate in alkylamine, serving as nucleophile and solvent. The concentration of substrate in alkylamine (0.4 M solution) was increased in comparison with the original ONSH experiments (0.1 M), since a low [σ^H -adduct] makes it more difficult to integrate the peak area within a reasonable error.

Measurement of the amount of σ^H -adduct at different temperatures enabled the construction of van't Hoff plots (see Figure 3 as an example). ΔH_r° and ΔS_r° for σ^H -adduct formation were derived of these plots for all reactions under study and are summarized in Table 2. The required K_{eq} was calculated from the ¹H NMR spectrum via the determination of the [σ^H -adduct]/[substrate] ratio. The alkylamine, being the nucleophile and solvent present in a very large excess, was left out of the equation. Pyrrolidine, being the more nucleophilic secondary amine, gives as expected more σ^H -adduct at a given temperature than *n*-butylamine does (for all three substrates). We previously reported that adducts of **1** with primary and secondary alkylamines could not be observed at −30 °C.^{9a,16} Interestingly, lowering the analysis temperature to the −50 °C range enabled detection of the σ^H -adduct with more nucleophilic pyrrolidine, thus providing evidence that the reaction of **1** indeed proceeds via a σ^H -adduct intermediate. The adduct of **1** with less nucleophilic *n*-butylamine could not even be observed with ¹H NMR around the melting temperature of pure *n*-butylamine. Therefore we replaced *n*-butylamine with *n*-propylamine, further lowering the temperature to −70 °C. At this lower temperatures σ^H -adduct of **1** with a primary alkylamine was observed, although still only in a very low quantity (7%). Since the σ^H -adduct is visible only at temperatures close to the melting point of *n*-propylamine, thermodynamic properties for this alkylamine/substrate combination could not be derived, as no series of relevant data points to construct a van't Hoff plot can be obtained. The difficulty of adduct formation of **1** with primary alkylamine is in accordance with the absence of a KIE for the 3-nitropyridine/*n*-butylamine/KMnO₄ combination

(14) For examples of the identification of σ^H -adduct intermediates in oxidative alkylation reactions with ¹H NMR, see: (a) Rykowski, A.; Chupakhin, O. N.; Kozhevnikov, D. N.; Kozhevnikov, V. N.; Rusinov, V. L.; van der Plas, H. C. *Heterocycles* **2001**, 55 (1), 127. (b) Szpakiewicz, B.; Wozniak, M. *Mol. Phys. Rep.* **2001**, 33, 66.

(15) For a general review dealing with σ -adduct formation and its thermodynamic properties, see: Terrier, F. *Chem. Rev.* **1982**, 82, 78.

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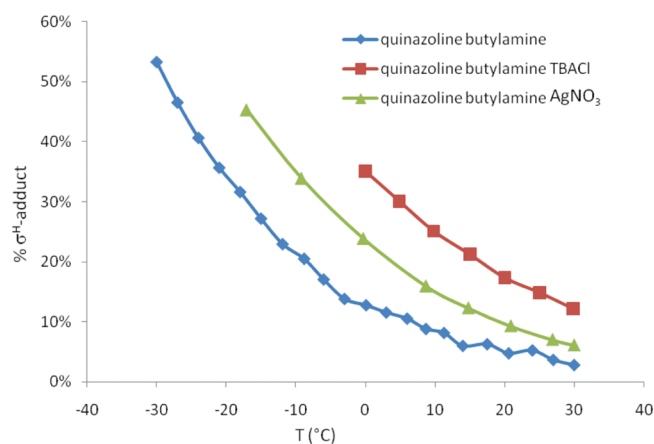


FIGURE 2. Fraction of σ^H -adduct formed at different temperatures upon dissolving quinazoline (**3**) in *n*-butylamine (0.4 M solution) in the absence and presence of 2 equiv of additive.

(Table 1, entry 1). Further spectroscopic evidence illustrating the formation of σ^H -adducts was obtained by studying the infrared and Raman spectra of solutions of quinazoline in liquid *n*-butylamine, as model case, at temperatures between 320 and 232 K (Figures S28 and S29 in Supporting Information).

To study the influence of Ag⁺ on σ^H -adduct formation, 2 equiv of AgNO₃ were added as an additive. ¹H NMR measurements were carried out in the same way as described in the previous paragraph. AgNO₃ was chosen as Ag⁺ source to mimic AgPy₂MnO₄, as it proved not to be capable of acting as an oxidant in the oxidative alkylation reactions under study.^{9a} In almost all cases a massive increase in σ^H -adduct concentration was observed upon addition of AgNO₃ (Table 2). As an illustration, a comparative graph of quinazoline in *n*-butylamine in the presence and absence of AgNO₃ is depicted in Figure 2.

As proposed above the active role of Ag⁺ might be coordination with the substrate. This coordination allows an easier attack of nucleophile and subsequent stabilization of the σ^H -adduct formed. However, the ¹H NMR spectra showed no proof of such a direct interaction. Shifts in ppm values of substrate and adduct protons were only moderate upon additive addition. Also no major shifts in the IR spectrum were observed. These observations did not support a direct interaction of Ag⁺ with the σ^H -adduct. Furthermore, addition of tetrabutylammonium chloride (TBACl) resulted in the same spectacular increase in [σ^H -adduct] for all substrate/alkylamine combinations. A tetrabutylammonium cation cannot increase σ^H -adduct formation via complexation, further supporting that there is no direct interaction

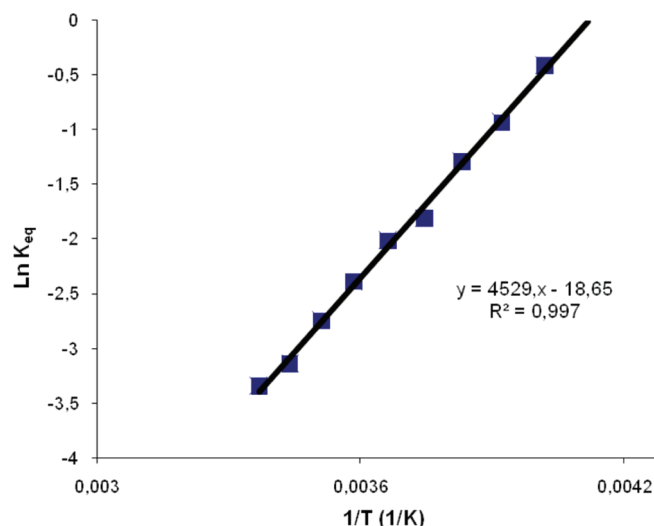


FIGURE 3. van't Hoff plot of a quinazoline/*n*-butylamine solution (0.4 M).

with Ag^+ . Moreover, 1H NMR spectra in the presence of TBACl showed the same modest ppm shifts as with $AgNO_3$. The thermodynamic parameters of σ^H -adduct formation changed in a similar direction upon addition of $AgNO_3$ and TBACl (Table 2). The exergonic effect of salt addition ($AgNO_3$ and TBACl) on the ΔG_r° values is caused by a change in the $T\Delta S_r^\circ$ term since the ΔH_r° contributes in an endergonic fashion to the ΔG_r° value.¹⁷ The positive effect of salts on the $[\sigma^H\text{-adduct}]$ therefore has to be interpreted as due to an interference in the ordering of the solution. An effect of salts on the concentration of a neutral σ^H -adduct has hitherto not been reported.¹⁸ The increased $[\sigma^H\text{-adduct}]$ has a direct influence on the efficiency of the ONSH reactions due to the rate-limiting oxidation (Table 1). As TBACl has a beneficial effect similar to that of $AgNO_3$ on the $[\sigma^H\text{-adduct}]$, we decided to test whether excellent synthetic yields can also be obtained when using a combination of cheap TBACl and $KMnO_4$ oxidant instead of the expensive $AgPy_2MnO_4$ previously used by us.^{9a,d}

Oxidative Alkylaminations of Substrates 1–3 in the Absence and Presence of Additives. The oxidative alkylamination experiments with the substrates 3-nitropyridine (**1**), 1,3-dinitrobenzene (**2**), and quinazoline (**3**) and our two model alkylamines, previously performed with $KMnO_4$ and $AgPy_2MnO_4$ as oxidant,^{9a,d} were repeated with simple and cheap $KMnO_4$ in the presence of TBACl as additive. The yields obtained were compared. Only when the use of $KMnO_4$ and $AgPy_2MnO_4$ as oxidants gave a substantial difference in conversion, as evaluated by comparison of their yield, an effect of the use of $KMnO_4$ /additive is expected in comparison with $KMnO_4$. Although $AgNO_3$ is certainly less attractive than TBACl as additive from a cost and environmental point of view, we also included it in our set of reactions on the

(17) The combination of 3/pyrrolidine/ $AgNO_3$ is an exception since the exergonic effect of salt addition on ΔG_r° is caused by the ΔH_r° term.

(18) The effect of salts on anionic $[\sigma^H\text{-adduct}]$ has been attributed to tight ion pairing. However, because substrates **1** and **3** give neutral σ^H -adducts, tight ion pairing cannot explain the increased $[\sigma^H\text{-adduct}]$ upon addition of salts. For references dealing with tight ion pairing, see: (a) Snyder, S. E.; Carey, J. R.; Shvets, A. B.; Pirkle, W. H. *J. Org. Chem.* **2005**, *70*, 4073. (b) Crampton, M. R.; Kahn, H. A. *J. Chem. Soc., Perkin Trans. 2* **1972**, *15*, 2286.

TABLE 3. Oxidative Alkylamination of 3-Nitropyridine (**1**)

entry	HNR^1R^2	oxidant	yield (%)	product	additive
1	<i>n</i> -butylamine	$KMnO_4$	93 ^{9a}	1a	
2	<i>n</i> -butylamine	$AgPy_2MnO_4$	91 ^{9a}	1a	
3	<i>n</i> -butylamine	$KMnO_4$	88	1a	$AgNO_3$
4	<i>n</i> -butylamine	$KMnO_4$	87	1a	TBACl
5	<i>n</i> -butylamine	TBAP	87	1a	
6	pyrrolidine	$KMnO_4$	50 ^{9a}	1a	
7	pyrrolidine	$AgPy_2MnO_4$	99 ^{9a}	1a	
8	pyrrolidine	$KMnO_4$	81	1b	$AgNO_3$
9	pyrrolidine	$KMnO_4$	93	1b	TBACl
10	pyrrolidine	TBAP	98	1b	$AgNO_3$
11	pyrrolidine	TBAP	25	1b	

TABLE 4. Oxidative *n*-Butylamination of 1,3-Dinitrobenzene (**2**)

entry	oxidant	product	yield (%)	additive
1	$KMnO_4$	2a	74 ^{9d}	
2	$AgPy_2MnO_4$	2a	63 ^{9d}	
3	$KMnO_4$	2a	81	$AgNO_3$
4	$KMnO_4$	2a	55	TBACl
5	TBAP	2a	60	

TABLE 5. Oxidative Alkylamination of Quinazoline (**3**)

entry	HNR^1R^2	oxidant	product	yield (%)	additive
1	<i>n</i> -butylamine	$KMnO_4$	3a	39 ^{9a}	
2	<i>n</i> -butylamine	$AgPy_2MnO_4$	3a	93 ^{9a}	
3	<i>n</i> -butylamine	$KMnO_4$	3a	96	$AgNO_3$
4	<i>n</i> -butylamine	$KMnO_4$	3a	92	TBACl
5	<i>n</i> -butylamine	TBAP	3a	95	$AgNO_3$
6	<i>n</i> -butylamine	TBAP	3a	61	
7	pyrrolidine	$KMnO_4$	3b	tr ^{9a}	
8	pyrrolidine	$AgPy_2MnO_4$	3b	31 ^{9a}	
9	pyrrolidine	$KMnO_4$	3b	tr	$AgNO_3$
10	pyrrolidine	$KMnO_4$	3b	tr	TBACl
11	pyrrolidine	TBAP	3b	27	

basis of theoretical considerations. The results are summarized in Tables 3, 4, and 5.

For the reaction of **1** with *n*-butylamine the previously reported yield with $AgPy_2MnO_4$ was over 90% (Table 3, entry 2). Even with $KMnO_4$ the yield was 93% (Table 3, entry 1) due to an exceptional rate-limiting adduct formation (Table 1). As full conversion was already obtained with

KMnO₄ for this specific case, no difference between the KMnO₄/AgNO₃ (Table 3, entry 3) or KMnO₄/TBACl (Table 3, entry 4) combination was expected nor observed. Switching to **1** and pyrrolidine as the nucleophile, the yield with KMnO₄ (Table 3, entry 6) and AgPy₂MnO₄ (Table 3, entry 7) differed substantially. Therefore, as here no full conversion was achieved with KMnO₄, the use of KMnO₄/AgNO₃ (Table 3, entry 8) or KMnO₄/TBACl (Table 3, entry 9) gave, as expected, a significantly higher conversion and yield compared with that obtained with KMnO₄ alone. The yields approached that obtained with AgPy₂MnO₄ (Table 3, entry 7). Similar experiments were carried out with 1,3-dinitrobenzene (**2**) as a substrate. The difference between the reference experiments involving KMnO₄ and AgPy₂MnO₄ (Table 4, entries 1, 2) is small, and therefore KMnO₄/AgNO₃ (Table 4, entry 3) and KMnO₄/TBACl (Table 4, entry 4) would not be expected to show significantly different yields. Interestingly and unexpectedly, the combination of KMnO₄/AgNO₃ gave a substantially higher yield than the reference reaction with AgPy₂MnO₄ (Table 4, compare entries 3 and 2). We currently have no explanation for this observation. For quinazoline (**3**) *n*-butylation with both KMnO₄/additive combinations gave similar yields as with AgPy₂MnO₄ (Table 5, compare entries 2, 3, and 4). The KMnO₄/additive combinations gave a significantly higher yield than with KMnO₄ alone (Table 5, compare entries 1, 3, and 4). When the oxidative alkylation of quinazoline (**3**) was performed with pyrrolidine, the KMnO₄/AgNO₃ and KMnO₄/TBACl combinations (Table 5, entries 9 and 10) did not differ in comparison with the use of KMnO₄ oxidant alone (Table 5, entry 7). In the three cases only traces of end product were observed, and this can be rationalized looking back at the ¹H NMR measurements. At the temperature of the reaction, even in the absence of additives, the equilibrium between **3** and its pyrrolidine adduct is already in favor of the adduct supporting its high stability (negative ΔG°_r value at the temperature of the reaction) (Table 2, entry 6). A difficult oxidation is therefore predicted. Addition of additives therefore only increases the adduct concentration to some extent, offering no real advantage, and consequently no improved yields are obtained. The stable and difficult to oxidize σ^H -adduct is in this case in competition with the alkylamine solvent for oxidation. Low yields can therefore only be accessed when an oxidant concentration is used that is high enough to enable oxidation of at least a fraction of the σ^H -adduct. This justifies why upon using AgPy₂MnO₄ at least a low yield of reaction product was observed (Table 5, entry 8).

Oxidative Alkylaminations of Substrates 1–3 in the Presence of TBAP (Tetrabutylammonium Permanganate). The overall rate of oxidative alkylation with rate-limiting oxidation is influenced by both the [σ^H -adduct] and the [oxidant]. Of course the solubility of manganate in the cases where KMnO₄ was used in combination with AgNO₃ and TBACl additive was also influenced, as respectively more soluble AgMnO₄ and TBAP can be formed *in situ*. So besides influencing the [σ^H -adduct], AgNO₃ and TBACl probably also play a role as phase transfer agents indirectly also changing the overall rate by increasing the [MnO₄[−]]. Therefore we also tested the use of cheap TBAP as oxidant in the oxidative

alkylation reactions and compared it with the yields of expensive AgPy₂MnO₄, as both are completely soluble in the alkylamines used at the reaction temperature applied.¹⁹ For the reactions of **1** and **2** with *n*-butylamine and **3** with pyrrolidine (Tables 3, 4, and 5, entries 5, 5, and 11) the same yield as obtained with AgPy₂MnO₄ (Tables 3, 4, and 5, entries 2, 2, and 8) was achieved. For the reaction of **1** with pyrrolidine and **3** with *n*-butylamine, however, this was not the case (Tables 3 and 5, entries 11 and 6). The same performance could only be achieved by using AgNO₃ as additive, probably influencing the [σ^H -adduct] (Tables 3 and 5, entries 10 and 5). TBAP on itself might also influence the [σ^H -adduct], but unfortunately this cannot be measured *via* ¹H NMR because of the immediate oxidation of the σ^H -adduct formed. To support the concept that both anion and cation of the salt are important for the [σ^H -adduct], the effect of tetrabutylammonium tetrafluoroborate (TBATFB) versus TBACl was tested for the **3**/*n*-butylamine combination. Gratifyingly, 10% and 35% σ^H -adduct fractions were measured at 0 °C for the former and for the latter, respectively. All of these results do indicate that a high concentration of oxidant in solution is certainly no guarantee for a good conversion in an ONSH with a rate-limiting oxidation.

Conclusion

In this study we showed, on the basis of competitive KIE experiments, that the rate-limiting step of oxidative alkylation is usually the oxidation step of the intermediate σ^H -adduct. In such a case both the [σ^H -adduct] and [oxidant] influence the overall rate of the reaction. The addition of salt additives (AgNO₃, TBACl) was shown to have a major impact on the ΔS°_r value and consequently on the [σ^H -adduct]. These insights fundamentally explain the previously reported success of AgPy₂MnO₄ as a general oxidant for oxidative alkylation; AgPy₂MnO₄ increases both the [MnO₄[−]] and the [σ^H -adduct], which favor the overall rate of the reaction. In those cases where the reaction with KMnO₄ gave a low conversion and yield, a combination of AgNO₃/KMnO₄ or TBACl/KMnO₄ results in similar yields as obtained with AgPy₂MnO₄. Especially, the latter combination is interesting as it involves cheaper and more environmentally friendly reagents. TBAP, a more soluble variant of KMnO₄, was also tested and is often a suitable alternative for TBACl/KMnO₄. We believe that our fundamental insights into the oxidative alkylation process will enable extension of the scope of the reaction to substrates that hitherto were not or very modestly susceptible to oxidative alkylation.

Experimental Section

3-Nitropyridine-*d*₄ (1'**).** The title compound was synthesized following a literature procedure and obtained as a pale white solid in 37% yield.²⁰ ¹³C NMR (DMSO-*d*₆): δ 154.7 (t, *J* = 28.03 Hz), 144.2 (t and s, 2C, *J* = 28.57 Hz), 131.1 (t, *J* = 26.44 Hz), 124.0 (t, *J* = 26.20 Hz). HRMS (ESI) for C₅D₄HN₂O₂⁺ [M + H]⁺, calcd 129.0597, found 129.0605.

Synthesis of Quinazoline-*d*₆ (3'**).** The multistep route for the synthesis of quinazoline-*d*₆ (**3'**) was first explored and optimized for the undeuterated analogue **3**.

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2-Benzofuran-1,3-dione (5). The title compound was obtained following a literature procedure as a white solid in quantitative yield.²¹ ¹H NMR (CDCl₃/DMSO-*d*₆ 1:1): δ 12.77 (m, 2H), 12.71 (m, 2H). ¹³C NMR (CDCl₃/DMSO-*d*₆ 1:1): δ 167.9, 141.2, 136.1, 130.50. HRMS (ESI) for C₈H₅O₃⁺ [M + H]⁺, calcd 149.0233, found 149.0235.

Phthalimide (6). The title compound was obtained as a white solid following a literature procedure in 95% yield.^{11b} ¹H NMR, ¹³C NMR, and MS data are in agreement with literature.²² ¹H NMR (CDCl₃): δ 7.87 (m, 2H), 7.76 (m, 2H), 7.52 (br s, 1H, NH). ¹³C NMR (CDCl₃): δ 167.7, 134.4, 132.7, 123.7. HRMS (ESI) for C₈H₆NO₂⁺ [M + H]⁺, calcd 148.0399, found 148.0385.

Phthalamide (7). The title compound was obtained as a white solid following a literature procedure in 81% yield.^{11c} ¹H NMR (DMSO-*d*₆): δ 7.69 (s, 2H), 7.43–7.49 (m, 4H), 7.31 (s, 2H). ¹³C NMR (DMSO-*d*₆): δ 170.7, 136.7, 129.7, 128.1. HRMS (ESI) for C₈H₉N₂O₂⁺ [M + H]⁺, calcd 165.0659, found 165.0645.

Quinazoline-2,4(1*H*,3*H*)-dione (8). The title compound was obtained as a white solid following a literature procedure in 95% yield.^{11d} ¹H NMR and ¹³C NMR data are in agreement with literature.²³ ¹H NMR (DMSO-*d*₆): δ 11.20 (s, 1H), 11.10 (s, 1H), 7.87 (dd, 1H, *J* = 8.11 Hz, 1.46 Hz), 7.61 (ddd, 1H, *J* = 8.21 Hz, 7.61 Hz, 1.52 Hz), 7.13–7.17 (m, 2H). ¹³C NMR (DMSO-*d*₆): δ 163.3, 150.8, 141.3, 135.4, 127.4, 122.8, 115.8, 114.8. HRMS (ESI) for C₈H₇N₂O₂⁺ [M + H]⁺, calcd 163.0508, found 163.0515.

2,4-Dichloroquinazoline (9). In a 50-mL three-necked round-bottomed flask equipped with a reflux condenser and septum was placed quinazoline-2,4(1*H*,3*H*)-dione (**8**) (1.420 g, 8.76 mmol) in toluene (10 mL). The solution was flushed with Ar, stirred, and then heated up to 50 °C. Phosphoryl trichloride (9 mL, 8.76 mmol) was added, and the temperature was increased to 105 °C. DBU (2.6 mL, 17.25 mmol) was added in small portions with a syringe through the septum. The mixture was refluxed for 24 h (oil bath temperature 120 °C) under magnetic stirring, then allow to cool to room temperature, and poured on ice. The water layer was extracted with EtOAc (2 × 100 mL). The organic layer was dried on MgSO₄, and the solvent was evaporated. Purification by flash column chromatography with DCM as the eluent provided the title compound as a white solid in 75% yield (1.334 g). ¹H NMR data are in agreement with literature.²⁴ ¹H NMR (CDCl₃): δ 8.27 (d, 1H, *J* = 8.38 Hz), 8.01 (d, 1H, *J* = 3.64 Hz), 7.74–7.78 (m, 2H). ¹³C NMR (CDCl₃): δ 163.0, 154.1, 151.4, 135.1, 128.2, 127.0, 125.0, 121.3. HRMS (ESI) for C₈H₅N₂Cl₂⁺ [M + H]⁺, calcd 198.9824, found 198.9822.

Quinazoline (3). In a 50-mL round-bottomed flask equipped with a septum were added 2,4-dichloroquinazoline (**9**) (1.393 g, 7 mmol), Pd/C (0.112 g, 0.105 mmol), and flame-dried Cs₂CO₃ (6.84 g, 21.00 mmol) in 15 mL of EtOAc. Air was replaced by Ar atmosphere. A hydrogen balloon was put on the flask *via* a needle through the septum under magnetic stirring. The mixture was flushed with hydrogen *via* a second needle through the septum, then the extra needle was removed. When all starting material had reacted, the mixture was poured over Celite and rinsed with EtOAc. The solvent was evaporated to dryness, and the crude product was purified by flash column chromatography over silica gel with DCM/EtOAc (6:4) as the eluent. The title compound was obtained as a pale white solid in 50% yield (0.455 g). ¹H NMR (CDCl₃): δ 9.39 (s, 1H), 9.35 (s, 1H), 8.04 (d, 1H, *J* = 8.86 Hz), 7.89–7.93 (m, 2H), 7.65 (ddd, 1H, *J* = 8.43 Hz, 6.91 Hz, 1.05 Hz). ¹³C NMR (CDCl₃): δ 160.1, 155.2, 149.9, 134.0, 128.3, 127.8, 127.1, 125.00. HRMS (ESI) for C₈H₇N₂⁺ [M + H]⁺, calcd 131.0609, found 131.0605.

Quinazoline-*d*₆ (3'). In a 20-mL pressure tube equipped with a septum and cap were placed brought quinazoline-*d*₄ (3'') (0.175 g, 1.305 mmol) and Pd/C (0.075 g, 0.0705 mmol) in 10 mL of D₂O under Ar atmosphere. A H₂ balloon was put on the tube *via* a needle through the septum. The mixture was flushed with H₂ *via* a second needle through the septum. After flushing for 30 min the balloon and the extra needle were removed, and the mixture was heated at 55 °C for 48 h and then to 90 °C for 6 h. The mixture was filtered through a paper filter and extracted with 3 × 100 mL of EtOAc, and the organic phase was dried over MgSO₄. The solvent was evaporated to near dryness. The residue was brought onto a silica gel column and separated using DCM/EtOAc (6:4) as the eluent. The title compound was obtained as a cream colored solid in 50% yield (0.088 g). ¹³C NMR (CDCl₃): δ 159.8 (t, *J* = 26.97 Hz), 154.9 (t, *J* = 30.29 Hz), 150.0, 133.7 (t, *J* = 24.55 Hz), 128.0 (t, *J* = 24.85 Hz), 127.4 (t, *J* = 24.66 Hz), 126.7 (t, *J* = 25.65 Hz), 124.9. HRMS (ESI) for C₈D₆HN₂⁺ [M + H]⁺, calcd 137.0986, found 137.1001.

Procedures Followed for the Determination of KIEs for Different Substrate/Alkylamine Combinations Using KMnO₄ or AgPy₂MnO₄ as Oxidant. 3-Nitropyridine (**1**): To a stirred solution of equimolar amounts of 3-nitropyridine (1 mmol, 124 mg) and 3-nitropyridine-*d*₄ (1 mmol, 128 mg) in alkylamine (10 mL) at 8–10 °C was added 0.8 mmol of oxidant (KMnO₄ or AgPy₂MnO₄) in small portions over 30 min. After a stirring time of 1.5 h, the alkylamine was removed under reduced pressure. The residue was dissolved in DCM and filtered over Celite. The *P_H/P_D* ratio was measured *via* high resolution mass spectrometry.

1,3-Dinitrobenzene (**2**): 1,3-Dinitrobenzene (0.5 mmol, 0.084 g) and 1,3-dinitrobenzene-*d*₄ (0.5 mmol, 0.086 g) were dissolved in *n*-butylamine (10 mL) at room temperature. The oxidant (KMnO₄ or AgPy₂MnO₄) (0.4 mmol) was added in small portions over 30 min under magnetic stirring. After overnight stirring, the alkylamine was removed under reduced pressure. The residue was dissolved in DCM and silica gel was added. The DCM was evaporated, and the residue was brought onto a silica gel column and subsequently eluted using DCM and DCM/heptane (7:3). The *P_H/P_D* ratio was measured *via* ¹H NMR on the isolated mixture of deuterated and undeuterated reaction product.

Quinazoline (**3**): Quinazoline (0.5 mmol, 65 mg) and quinazoline-*d*₆ (0.5 mmol, 68 mg) were dissolved in alkylamine (10 mL) at 8–10 °C. The oxidant (KMnO₄ or AgPy₂MnO₄) (0.4 mmol) was added in small portions over 30 min under magnetic stirring. After overnight stirring, the alkylamine was removed under reduced pressure. The residue was dissolved in DCM, and silica gel was added. The DCM was evaporated, and the residue was brought onto a silica gel column and subsequently eluted with DCM/MeOH (98: 2). The *P_H/P_D* ratio was measured *via* ¹H NMR on the isolated mixture of deuterated and undeuterated reaction product.

General Procedure for the Preparation of Samples for the ¹H NMR Studies. A 0.4 M solution of substrate in alkylamine was added to a small NMR tube. This small tube was placed in a broader NMR tube, filled with CDCl₃. In the case where AgNO₃ or TBACl were added as an additive, the sample preparation procedure was identical, with 2 equiv of additive relative to the substrate. The mixtures obtained were allowed to achieve equilibrium for 15 min at the set temperature before each measurement.

van't Hoff equation

$$\ln(K_{\text{eq}}, T) = \frac{-\Delta H_{\text{r}}^{\circ}}{RT} + \frac{\Delta S_{\text{r}}^{\circ}}{R}$$

with

$$K_{\text{eq}, T} = \frac{[\sigma^{\text{H-adduct}}]}{[\text{substrate}]}$$

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allows the determination of ΔH_r° and ΔS_r° :

$$\Delta H_r^\circ = \frac{\text{slope}(-R)}{1000} \text{ (kJ/mol)} \quad \text{and}$$

$$\Delta S_r^\circ = \text{intercept} \cdot R \text{ (J/K} \cdot \text{mol)}$$

See Figure 3 for an example and the Supporting Information for all plots.

Oxidative Alkylamination of 3-Nitropyridine (1). To a stirred solution of substrate (1 mmol, 0.124 g) in alkylamine (10 mL) at 8–10 °C was added 2 equiv of oxidant (KMnO₄, TBAP) in small portions over a period of 30 min. After overnight stirring, the alkylamine was removed under reduced pressure. The residue was ground with silica, brought onto a silica gel column, and subsequently eluted with DCM. When the procedure was carried out in the presence of an additive, 2 equiv of additive (AgNO₃ or TBACl) was added before starting the gradual addition of the oxidant.

N-Butyl-5-nitropyridin-2-amine (1a)^{9a}. Yellow solid, yield (KMnO₄/AgNO₃: 170 mg, 88%; KMnO₄/TBACl: 169 mg, 87%; TBAP: 169 mg, 87%). ¹H NMR (CDCl₃): δ 9.00 (s, 1H), 8.18 (d, 1H, *J* = 8.72), 6.34 (d, 1H, 9.30 Hz), 5.35 (br s, 1H), 3.39 (m, 2H), 1.63 (m, 2H), 1.44 (m, 2H), 0.98 (t, 3H, *J* = 7.32). ¹³C NMR (CDCl₃): δ 161.4, 147.1, 135.7, 133.00, 105.3, 42.1, 31.3, 20.1, 13.7. HRMS (ESI) for C₉H₁₄N₃O₂⁺ [M + H]⁺, calcd 196.1081, found 196.1090.

5-Nitro-2-(pyrrolidin-1-yl)pyridine (1b)^{9a}. Yellow solid, yield (KMnO₄/AgNO₃: 157 mg, 81%; KMnO₄/TBACl: 179 mg, 93%; TBAP/AgNO₃: 189 mg, 98%; TBAP: 48 mg, 25%). ¹H NMR (CDCl₃): δ 9.09 (d, 1H, *J* = 2.71 Hz), 8.20 (dd, 1H, *J* = 9.51 Hz, 2.73 Hz), 6.33 (d, 1H, *J* = 9.50 Hz), 3.53 (br s, 4H), 2.09 (s, 4H). ¹³C NMR (CDCl₃): δ 158.8, 147.1, 134.6, 132.4, 105.1, 47.5, 25.4. HRMS (ESI) for C₉H₁₂N₃O₂⁺ [M + H]⁺, calcd 194.0924, found 194.0933.

Oxidative Alkylamination of 1,3-Dinitrobenzene (2). To a stirred solution of substrate (1 mmol, 0.168 g) in alkylamine (10 mL) at room temperature was added 2 equiv of oxidant (KMnO₄, TBAP) in small portions over a period of 30 min. After overnight stirring, the alkylamine was removed under reduced pressure. The residue was ground with silica, brought onto a silica gel column, and subsequently eluted with DCM/heptane (7:3). When the procedure is carried out in the presence of an additive, 2 equiv of additive (AgNO₃ or TBACl) was added before starting the gradual addition of the oxidant.

N-Butyl-2,4-dinitroaniline (2a)^{9d}. Yellow solid, yield (KMnO₄/AgNO₃: 194 mg, 81%; KMnO₄/TBACl: 131 mg, 55%; TBAP: 143 mg, 60%). ¹H NMR (CDCl₃): δ 9.12 (d, 1H, *J* = 2.62 Hz), 8.55 (br s, 1H, NH), 8.26 (dd, 1H, *J* = 9.52 Hz, 2.64 Hz), 6.93 (d, 1H, *J* = 9.53 Hz), 3.43 (m, 2H), 1.78 (m, 2H), 1.51 (m, 2H), 1.04 (t, 3H, *J* = 7.33, 3H). ¹³C NMR (CDCl₃): δ 148.4, 135.9, 130.3, 124.3,

113.9, 43.3, 30.7, 20.1, 13.6. HRMS (ESI) for C₁₀H₁₄N₃O₄⁺ [M + H]⁺, calcd 240.0984, found 240.0981.

Oxidative Alkylamination of Quinazoline (3). To a stirred solution of substrate (1 mmol, 0.130 g) in alkylamine (10 mL) at 8–10 °C was added 2 equiv of oxidant (KMnO₄, TBAP) in small portions over a period of 30 min. After overnight stirring, the alkylamine was removed under reduced pressure. The residue was ground with silica, brought onto a silica gel column, and eluted with DCM/MeOH (98:2). When the procedure is carried out in the presence of an additive, 2 equiv of additive (AgNO₃ or TBACl) was added before starting the gradual addition of the oxidant.

N-Butylquinazolin-4-amine (3a)^{9a}. White solid, yield (KMnO₄/AgNO₃: 194 mg, 96%; KMnO₄/TBACl: 186 mg, 92%; TBAP/AgNO₃: 193 mg, 95%; TBAP: 123 mg, 61%). ¹H NMR (CDCl₃): δ = 8.67 (s, 1H), 7.83 (d, 1H, *J* = 8.10 Hz), 7.75 (d, 1H, *J* = 8.29 Hz), 7.71 (ddd, 1H, *J* = 8.35 Hz, 7.03 Hz, 1.26 Hz), 7.43 (ddd, 1H, *J* = 8.12 Hz, 7.12 Hz, 1.17 Hz), 5.99 (br s, 1H, NH), 3.66 (m, 2H), 1.71 (m, 2H), 1.46 (m, 2H), 0.98 (t, 3H, *J* = 7.32 Hz). ¹³C NMR (CDCl₃): δ 159.6, 155.5, 149.4, 132.4, 128.5, 125.9, 120.5, 115.0, 41.1, 31.4, 20.2, 13.8. HRMS (ESI) for C₁₂H₁₆N₃⁺ [M + H]⁺, calcd 202.1339, found 202.1335.

4-(Pyrrolidin-1-yl)quinazoline (3b)^{9a}. Yellow-brown solid, yield (KMnO₄/AgNO₃: trace; KMnO₄/TBACl: trace; TBAP: 54 mg, 27%). ¹H NMR (CDCl₃): δ 8.57 (s, 1H), 8.17 (d, 1H, *J* = 8.28 Hz), 7.84 (d, 1H, *J* = 8.38 Hz), 7.69 (dd, 1H, *J* = 7.24 Hz), 7.39 (dd, 1H, *J* = 7.39 Hz), 3.95 (t, 4H, *J* = 6.60), 2.07 (m, 4H). ¹³C NMR (CDCl₃): δ 159.6, 154.4, 131.9, 127.9, 125.3, 124.3, 116.5, 50.92, 25.6. HRMS (ESI) for C₁₂H₁₄N₃⁺ [M+H]⁺, calcd 200.1182, found 200.1196.

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Supporting Information Available: Procedures for the preparation of starting materials, van't Hoff plots, IR and Raman spectra, theoretical calculations, and ¹H NMR spectra of σ^{H} -adducts, NMR spectra of reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.