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

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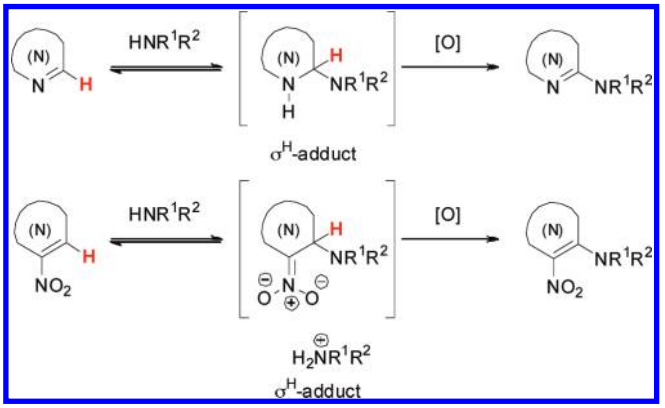

Oxidative alkylamination of electron-deficient (hetero)aromatic compounds, *via* the nucleophilic substitution of hydrogen, is a methodology that has made significant progress since the introduction of $AgPy_2MnO_4$ as oxidant. This oxidant generally gives good conversions and yields, whereas the use 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 ^{1}H 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 $AgPy_2MnO_4$.

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.

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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 reaction[5] 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 alkylamination, *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 alkylamination 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 alkylamination. Therefore the alkylamination has hitherto mainly been limited to methylamination. 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 $AgPy_2MnO_4$ is a general oxidant for the oxidative alkylamination and successfully reported on the alkylamination of a variety of substrates both with primary and secondary alkylamines.[9] The observation that in some cases $KMnO_4$ as well as $AgPy_2MnO_4$ gave a good result for a specific alkylamine−substrate combination and that for another substrate in the same alkylamine $AgPy_2MnO_4$ was superior to $KMnO_4$ indicated that solubility of the oxidant in the alkylamine cannot be the only factor governing the success of these reactions. Insight into the reaction mechanism and, in particular, in the rate-determining step of the oxidative alkylamination 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 alkylamination on these substrates with $KMnO_4$ and $AgPy_2MnO_4$ 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.

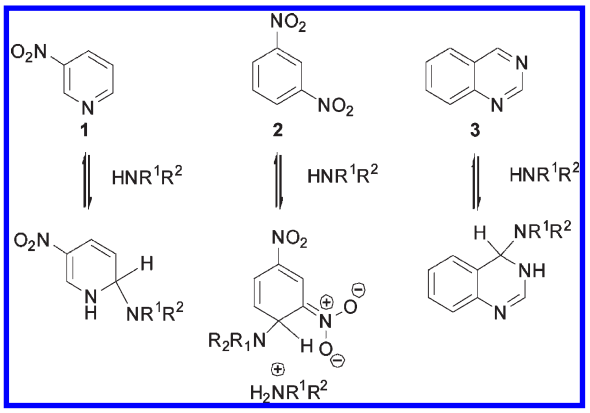

FIGURE 1. Equilibrium of the three substrates with their respective σ^H-adduct in alkylamine.

Results and Discussion

Determination of the Rate-Determining Step of the Oxidative Alkylaminations *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 quinazolinedione (**8′**) following literature procedures reported to synthesize the undeuterated analogue.[11a−d] Quinazolinedione **8′** was then converted into 2,4-dichloroquinazoline-d_4 (**9′**) with $POCl_3$ following a slightly modified literature procedure;[11e,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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(5) (a) Liang, J.; Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 699. (b) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002.

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(8) (a) Huertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett.* **2000**, *41*, 279. (b) Huertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett.* **2001**, *42*, 3439. (c) Moutiers, G.; Pinson, J.; Terrier, F.; Goumont, R *Chem.—Eur. J.* **2001**, *7*, 1712. (d) Gallardo, I.; Guirado, G.; Marquet, J. *Eur. J. Org. Chem.* **2002**, 251.

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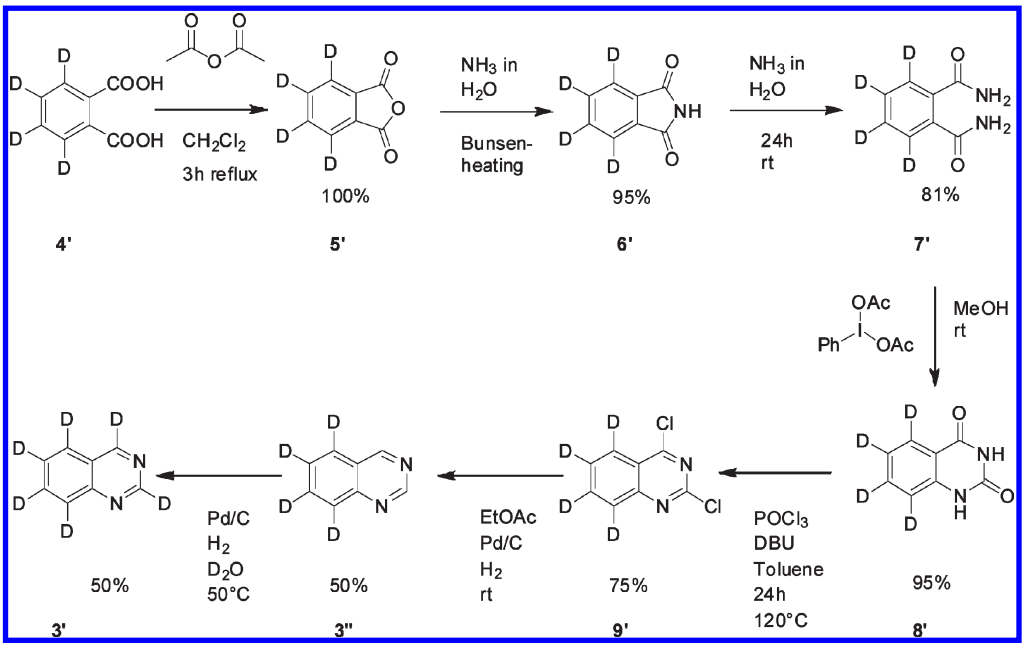
SCHEME 1. Synthesis of Quinazoline-d_6 (3′) from Phthalic Acid-d_4 (4′)



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 ^{1}H 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* ^{1}H 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 $AgPy_2MnO_4$ as oxidant. An exception is the combination of 3-nitropyridine/*n*-butylamine/$KMnO_4$, where adduct formation was surprisingly 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.

TABLE 1. Estimated KIE Values Following Competitive Experiments

entry	substrate	amine	oxidant	P_H/P_D	KIE
1	**1/1′**	*n*-butylamine	$KMnO_4$	1.10[a,b]	no
2	**1/1′**	*n*-butylamine	$AgPy_2MnO_4$	3.83[a]	yes
3	**1/1′**	pyrrolidine	$KMnO_4$	3.62[a]	yes
4	**1/1′**	pyrrolidine	$AgPy_2MnO_4$	2.81[a]	yes
5	**2/2′**	*n*-butylamine	$KMnO_4$	6.42[c]	yes
6	**2/2′**	*n*-butylamine	$AgPy_2MnO_4$	8.09[c]	yes
7	**3/3′**	*n*-butylamine	$KMnO_4$	6.14[c]	yes
8	**3/3′**	*n*-butylamine	$AgPy_2MnO_4$	4.55[c]	yes
9	**3/3′**	pyrrolidine	$KMnO_4$	*d*	*d*
10	**3/3′**	pyrrolidine	$AgPy_2MnO_4$	5.25[c]	yes

[a]Determined by MS. [b]Standard deviation: 0.1. [c]Determined by ^{1}H NMR. [d]The KIE cannot be determined as the reaction does not proceed.[9a]

Study of σ^H-Adduct Formation *via* ^{1}H 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

(12) For the determination of the KIE for the reaction of aniline with azobenzene, see: Stern, M. K.; Cheng, B. K.; Hileman, F. D.; Allman, J. M. *J. Org. Chem.* **1994**, *59*, 5627.

(13) See for instance: (a) Bosch, E.; Barnes, C. L.; Brennan, N. L.; Eakins, G. L.; Breyfogle, B. E. *J. Org. Chem.* **2008**, *73*, 3931. (b) Inokuma, S.; Yatsuzuka, T.; Ohtsuki, S.; Hino, S.; Nishimura, J. *Tetrahedron* **2007**, *63*, 5088.

TABLE 2. $\Delta H°_r$ (kJ/mol), $\Delta S°_r$ (J/K·mol), and $\Delta G°_r$ (kJ/mol) Values of σ^H-Adduct Formation (0.4 M Solution of Substrate in Alkylamine)

			no additive			$AgNO_3$			TBACl		
entry	substrate	alkylamine	$\Delta H°_r$	$\Delta S°_r$	$\Delta G°_r$[a]	$\Delta H°_r$	$\Delta S°_r$	$\Delta G°_r$[a]	$\Delta H°_r$	$\Delta S°_r$	$\Delta G°_r$[a]
1	**1**	*n*-butylamine	*b*	*b*	*b*	−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**	*n*-butylamine	−86	−374	23.6	−43	−173	7.7	−36	−129	1.8
4	**2**	pyrrolidine	−65	−277	16.2	−41	−164	7.1	*c*	*c*	
5	**3**	*n*-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

[a] **1**: 10 °C; **2**: 20 °C; **3**: 10 °C. [b] For **1**/*n*-butylamine, no σ^H-adduct can be observed. [c] $\Delta H°_r$ and $\Delta S°_r$ values could not be determined because of overlapping peaks in the ^1H NMR spectrum.

of σ^H-adducts in the oxidative alkylamination 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). $\Delta H_r°$ and $\Delta S_r°$ 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/$KMnO_4$ combination

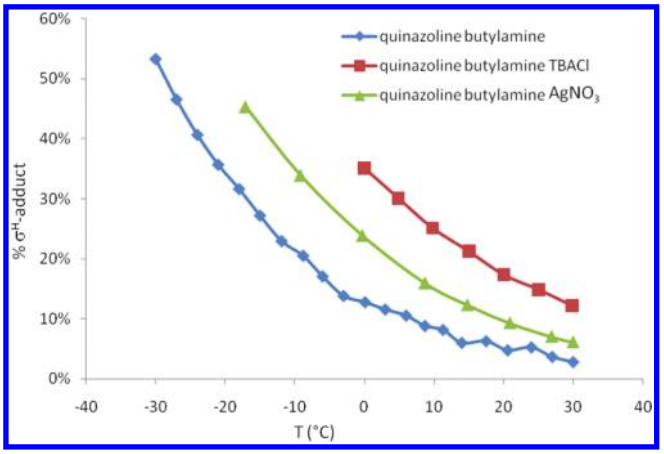


FIGURE 2. Fraction of σ^H-adduct formed at different temperatures upon dissolving quinazoline (**3**) in *n*-butylamine (0.4 M solution) in the absence and presence of 2 equiv of additive.

(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 $AgNO_3$ were added as an additive. ^1H NMR measurements were carried out in the same way as described in the previous paragraph. $AgNO_3$ was chosen as Ag^+ source to mimic $AgPy_2MnO_4$, as it proved not to be capable of acting as an oxidant in the oxidative alkylamination reactions under study.[9a] In almost all cases a massive increase in σ^H-adduct concentration was observed upon addition of $AgNO_3$ (Table 2). As an illustration, a comparative graph of quinazoline in *n*-butylamine in the presence and absence of $AgNO_3$ 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 obervations 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

(14) For examples of the identification of σ^H-adduct intermediates in oxidative alkylamination 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.

(16) For another example, see: Szpakiewicz, B.; Wozniak, M. *J. Prakt. Chem.* **1999**, *341*, 75.

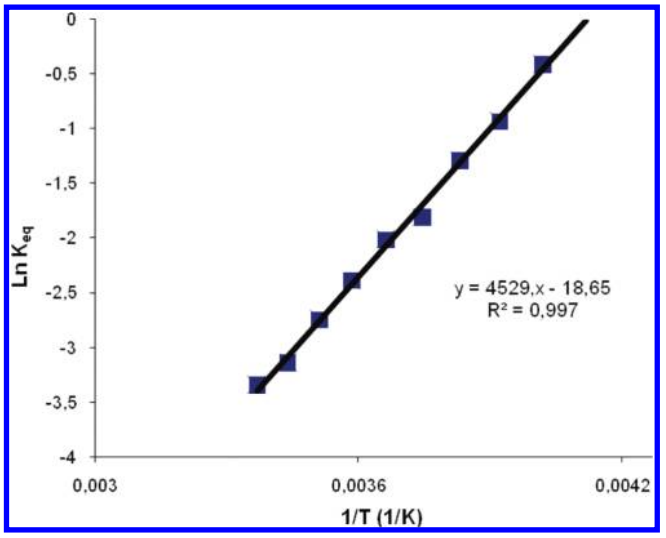


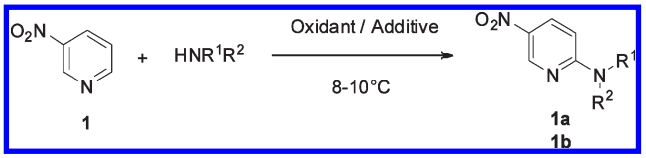
FIGURE 3. van't Hoff plot of a quinazoline/*n*-butylamine solution (0.4 M).

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 exergonical effect of salt addition ($AgNO_3$ and TBACl) on the $\Delta G_r°$ values is caused by a change in the $T\Delta S_r°$ term since the $\Delta H_r°$ contributes in an endergonical fashion to the $\Delta G_r°$ value.[17] The positive effect of salts on the [σ^H-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 [σ^H-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 [σ^H-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 TABCl as additive from a cost and environmental point of view, we also included it in our set of reactions on the basis of theoretical considerations. The results are summarized in Tables 3, 4, and 5.

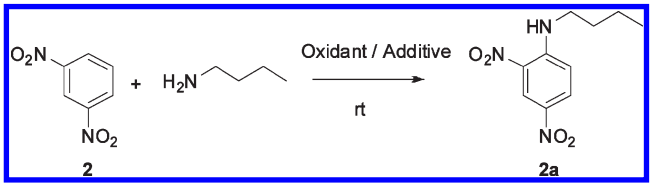
For the reaction of **1** with *n*-butylamine the previously reported yield with $AgPy_2MnO_4$ was over 90% (Table 3, entry 2). Even with $KMnO_4$ the yield was 93% (Table 3, entry 1) due to an exceptional rate-limiting adduct formation (Table 1). As full conversion was already obtained with

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



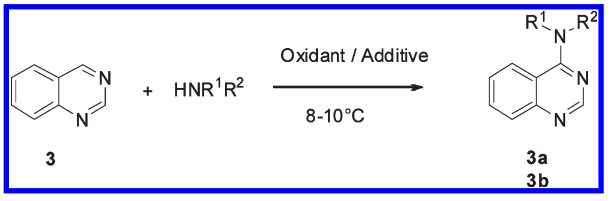
entry	HNR^1R^2	oxidant	yield (%)	product	additive
1	*n*-butylamine	$KMnO_4$	93[9a]	**1a**	
2	*n*-butylamine	$AgPy_2MnO_4$	91[9a]	**1a**	
3	*n*-butylamine	$KMnO_4$	88	**1a**	$AgNO_3$
4	*n*-butylamine	$KMnO_4$	87	**1a**	TBACl
5	*n*-butylamine	TBAP	87	**1a**	
6	pyrrolidine	$KMnO_4$	50[9a]	**1a**	
7	pyrrolidine	$AgPy_2MnO_4$	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	*n*-butylamine	$KMnO_4$	**3a**	39[9a]	
2	*n*-butylamine	$AgPy_2MnO_4$	**3a**	93[9a]	
3	*n*-butylamine	$KMnO_4$	**3a**	96	$AgNO_3$
4	*n*-butylamine	$KMnO_4$	**3a**	92	TBACl
5	*n*-butylamine	TBAP	**3a**	95	$AgNO_3$
6	*n*-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	

(17) The combination of **3**/pyrrolidine/$AgNO_3$ is an exception since the exergonical effect of salt addition on $\Delta G_r°$ is caused by the $\Delta H_r°$ term.

(18) The effect of salts on anionic [σ^H-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 [σ^H-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.

$KMnO_4$ for this specific case, no difference between the $KMnO_4/AgNO_3$ (Table 3, entry 3) or $KMnO_4$/TBACl (Table 3, entry 4) combination was expected nor observed. Switching to **1** and pyrrolidine as the nucleophile, the yield with $KMnO_4$ (Table 3, entry 6) and $AgPy_2MnO_4$ (Table 3, entry 7) differed substantially. Therefore, as here no full conversion was achieved with $KMnO_4$, the use of $KMnO_4/AgNO_3$ (Table 3, entry 8) or $KMnO_4$/TBACl (Table 3, entry 9) gave, as expected, a significantly higher conversion and yield compared with that obtained with $KMnO_4$ alone. The yields approached that obtained with $AgPy_2MnO_4$ (Table 3, entry 7). Similar experiments were carried out with 1,3-dinitrobenzene (**2**) as a substrate. The difference between the reference experiments involving $KMnO_4$ and $AgPy_2MnO_4$ (Table 4, entries 1, 2) is small, and therefore $KMnO_4/AgNO_3$ (Table 4, entry 3) and $KMnO_4$/TBACl (Table 4, entry 4) would not be expected to show significantly different yields. Interestingly and unexpectedly, the combination of $KMnO_4/AgNO_3$ gave a substantially higher yield than the reference reaction with $AgPy_2MnO_4$ (Table 4, compare entries 3 and 2). We currently have no explanation for this observation. For quinazoline (**3**) *n*-butylamination with both $KMnO_4$/additive combinations gave similar yields as with $AgPy_2MnO_4$ (Table 5, compare entries 2, 3, and 4). The $KMnO_4$/additive combinations gave a significantly higher yield than with $KMnO_4$ alone (Table 5, compare entries 1, 3, and 4). When the oxidative alkylamination of quinazoline (**3**) was performed with pyrrolidine, the $KMnO_4/AgNO_3$ and $KMnO_4$/TBACl combinations (Table 5, entries 9 and 10) did not differ in comparison with the use of $KMnO_4$ 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 ^{1}H 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 $\Delta G°_r$ 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 $AgPy_2MnO_4$ 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 alkylamination 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 $KMnO_4$ was used in combination with $AgNO_3$ and TBACl additive was also influenced, as respectively more soluble $AgMnO_4$ and TBAP can be formed *in situ*. So besides influencing the [σ^H-adduct], $AgNO_3$ and TBACl probably also play a role as phase transfer agents indirectly also changing the overall rate by increasing the [MnO_4^-]. Therefore we also tested the use of cheap TBAP as oxidant in the oxidative alkylamination reactions and compared it with the yields of expensive $AgPy_2MnO_4$, 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 $AgPy_2MnO_4$ (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 $AgNO_3$ 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* ^{1}H 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 alkylaminations 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 ($AgNO_3$, TBACl) was shown to have a major impact on the $\Delta S_r°$ value and consequently on the [σ^H-adduct]. These insights fundamentally explain the previously reported success of $AgPy_2MnO_4$ as a general oxidant for oxidative alkylaminations; $AgPy_2MnO_4$ increases both the [MnO_4^-] and the [σ^H-adduct], which favor the overall rate of the reaction. In those cases where the reaction with $KMnO_4$ gave a low conversion and yield, a combination of $AgNO_3/KMnO_4$ or TBACl/$KMnO_4$ results in similar yields as obtained with $AgPy_2MnO_4$. Especially, the latter combination is interesting as it involves cheaper and more environmentally friendly reagents. TBAP, a more soluble variant of $KMnO_4$, was also tested and is often a suitable alternative for TBACl/$KMnO_4$. We believe that our fundamental insights into the oxidative alkylamination process will enable extension of the scope of the reaction to substrates that hitherto were not or very modestly susceptible to oxidative alkylamination.

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] ^{13}C 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 $C_5D_4HN_2O_2^+$ $[M + H]^+$, 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**.

(19) Makosza used TBAP as an oxidant for C-C bond formation *via* ONSH reactions; see: Makosza, M.; Kamienska-Trela, K.; Paszewski, M.; Bechcicka, M *Tetrahedron* **2005**, *61*, 11952.

(20) Katritzky, A. R.; Scriven, E. F. V.; Majmunder, S.; Akhmedova, R. G.; Vakulenko, A. V.; Akhmedov, N. G.; Murugan, R.; Abboud, K. A. *Org. Biomol. Chem.* **2005**, *3*, 538.

2-Benzofuran-1,3-dione (5). The title compound was obtained following a literature procedure as a white solid in quantitative yield.[21] ^{1}H NMR ($CDCl_3$/DMSO-d_6 1:1): δ 12.77 (m, 2H), 12.71 (m, 2H). ^{13}C NMR ($CDCl_3$/DMSO-d_6 1:1): δ 167.9, 141.2, 136.1, 130.50. HRMS (ESI) for $C_8H_5O_3^+$ $[M + H]^+$, 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] ^{1}H NMR, ^{13}C NMR, and MS data are in agreement with literature.[22] ^{1}H NMR ($CDCl_3$): δ 7.87 (m, 2H), 7.76 (m, 2H), 7.52 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 167.7, 134.4, 132.7, 123.7. HRMS (ESI) for $C_8H_6NO_2^+$ $[M + H]^+$, 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] ^{1}H NMR (DMSO-d_6): δ 7.69 (s, 2H), 7.43−7.49 (m, 4H), 7.31 (s, 2H). ^{13}C NMR (DMSO-d_6) δ: 170.7, 136.7, 129.7, 128.1. HRMS (ESI) for $C_8H_9N_2O_2^+$ $[M + H]^+$, 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] ^{1}H NMR and ^{13}C NMR data are in agreement with literature.[23] ^{1}H 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). ^{13}C NMR (DMSO-d_6): δ 163.3, 150.8, 141.3, 135.4, 127.4, 122.8, 115.8, 114.8. HRMS (ESI) for $C_8H_7N_2O_2^+$ $[M + H]^+$, 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 $MgSO_4$, 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). ^{1}H NMR data are in agreement with literature.[24] ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H, J = 8.38 Hz), 8.01 (d, 1H, J = 3.64 Hz), 7.74−7.78 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 163.0, 154.1, 151.4, 135.1, 128.2, 127.0, 125.0, 121.3. HRMS (ESI) for $C_8H_5N_2Cl_2^+$ $[M + H]^+$, 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 Cs_2CO_3 (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). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): δ 160.1, 155.2, 149.9, 134.0, 128.3, 127.8, 127.1, 125.00. HRMS (ESI) for $C_8H_7N_2^+$ $[M + H]^+$, 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 D_2O under Ar atmosphere. A H_2 balloon was put on the tube *via* a needle through the septum. The mixture was flushed with H_2 *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 $MgSO_4$. 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). ^{13}C NMR ($CDCl_3$): 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 $C_8D_6HN_2^+$ $[M + H]^+$, calcd 137.0986, found 137.1001.

Procedures Followed for the Determination of KIEs for Different Substrate/Alkylamine Combinations Using $KMnO_4$ or $AgPy_2MnO_4$ 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 ($KMnO_4$ or $AgPy_2MnO_4$) 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 ($KMnO_4$ or $AgPy_2MnO_4$) (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* ^{1}H 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 ($KMnO_4$ or $AgPy_2MnO_4$) (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* ^{1}H NMR on the isolated mixture of deuterated and undeuterated reaction product.

General Procedure for the Preparation of Samples for the ^{1}H 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 $CDCl_3$. In the case where $AgNO_3$ 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

$$\ln(K_{eq,T}) = \frac{-\Delta H_r^\circ}{RT} + \frac{\Delta S_r^\circ}{R}$$

with

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

(21) Brown, R. F. C.; Coulston, K. J.; Eastwood, F. W.; Vogel, C. *Aust. J. Chem.* **1988**, *41*, 1687.
(22) Lasri, J.; Kopylovich, M. N.; Guedes da Silva, M. F. C.; Charmier, M. A. J.; Pombeiro, A. J. L. *Chem.—Eur. J.* **2008**, *14*, 9312.
(23) Mizuno, T.; Mihara, M.; Nakai, T.; Iwai, T.; Ito, T. *Synthesis* **2007**, *16*, 2524.
(24) Kanuma, K.; et al. *Bioorg. Med. Chem.* **2006**, *14*, 3307.

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 ($KMnO_4$, 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 ($AgNO_3$ or TBACl) was added before starting the gradual addition of the oxidant.

***N*-Butyl-5-nitropyridin-2-amine (1a)[9a].** Yellow solid, yield ($KMnO_4$/$AgNO_3$: 170 mg, 88%; $KMnO_4$/TBACl: 169 mg, 87%; TBAP: 169 mg, 87%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): δ 161.4, 147.1, 135.7, 133.00, 105.3, 42.1, 31.3, 20.1, 13.7. HRMS (ESI) for $C_9H_{14}N_3O_2^+$ $[M + H]^+$, calcd 196.1081, found 196.1090.

5-Nitro-2-(pyrrolidin-1-yl)pyridine (1b)[9a]. Yellow solid, yield ($KMnO_4$/$AgNO_3$: 157 mg, 81%; $KMnO_4$/TBACl: 179 mg, 93%; TBAP/$AgNO_3$: 189 mg, 98%; TBAP: 48 mg, 25%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): δ 158.8, 147.1, 134.6, 132.4, 105.1, 47.5, 25.4. HRMS (ESI) for $C_9H_{12}N_3O_2^+$ $[M + H]^+$, 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 ($KMnO_4$, 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 ($AgNO_3$ or TBACl) was added before starting the gradual addition of the oxidant.

***N*-Butyl-2,4-dinitroaniline (2a)[9d].** Yellow solid, yield ($KMnO_4$/$AgNO_3$: 194 mg, 81%; $KMnO_4$/TBACl: 131 mg, 55%; TBAP: 143 mg, 60%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): δ 148.4, 135.9, 130.3, 124.3, 113.9, 43.3, 30.7, 20.1, 13.6. HRMS (ESI) for $C_{10}H_{14}N_3O_4^+$ $[M + H]^+$, 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 ($KMnO_4$, 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 ($AgNO_3$ or TBACl) was added before starting the gradual addition of the oxidant.

***N*-Butylquinazolin-4-amine (3a)[9a].** White solid, yield ($KMnO_4$/$AgNO_3$: 194 mg, 96%; $KMnO_4$/TBACl: 186 mg, 92%; TBAP/$AgNO_3$ 193 mg, 95%; TBAP: 123 mg, 61%). ^{1}H NMR ($CDCl_3$): 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,). ^{13}C NMR ($CDCl_3$): 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 $C_{12}H_{16}N_3^+$ $[M + H]^+$, calcd 202.1339, found 202.1335.

4-(Pyrrolidin-1-yl)quinazoline (3b)[9a]. Yellow-brown solid, yield ($KMnO_4$/$AgNO_3$: trace; $KMnO_4$/TBACl: trace; TBAP: 54 mg, 27%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): δ 159.6, 154.4, 131.9, 127.9, 125.3, 124.3, 116.5, 50.92, 25.6. HRMS (ESI) for $C_{12}H_{14}N_3^+$[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 ^{1}H 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.