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Authors: Subhash Ghosh and Chiranjit Sen

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Transition-Metal-Free Regioselective Alkylation of Quinoline N-Oxides via Oxidative Alkyl Migration and C-C Bond Cleavage of tert-/sec-Alcohols

Chiranjit Sen and Subhash C. Ghosh*

Natural Products and Green Chemistry Division and AcSIR, Central Salt and Marine Chemicals Research Institute (CSIR), G.B. Marg, Bhavnagar-364002, Gujarat, India. E-mail: scghosh@csmcri.res.in

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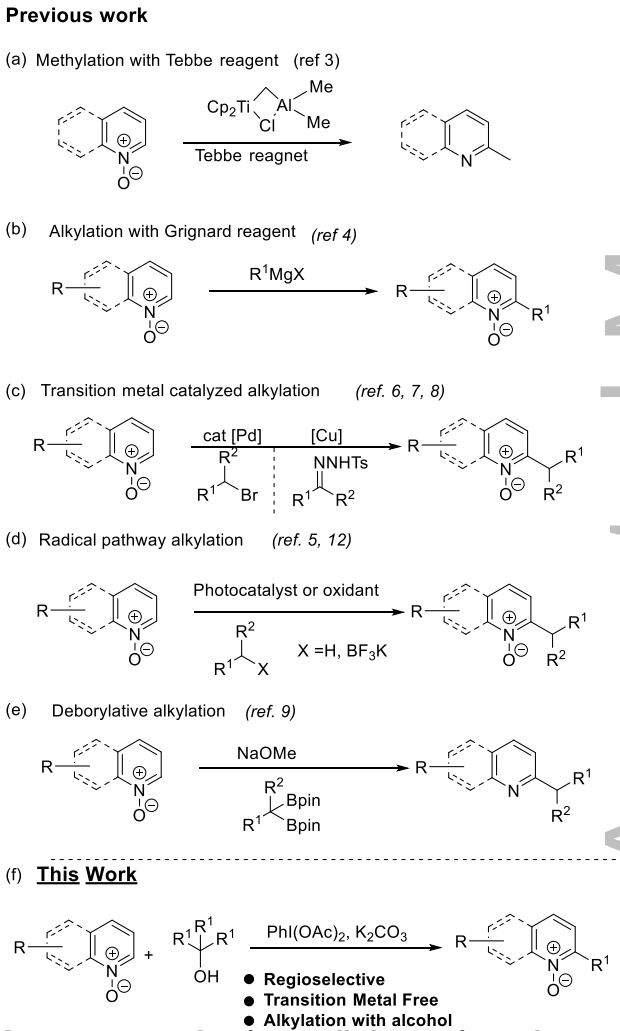
Abstract. An unprecedented C2-alkylation of quinoline N-oxide derivatives *via* C-C bond activation of *tert*- and *sec*-alkyl alcohol is described using hypervalent iodine (III) reagent $PhI(OAc)_2$ (PIDA). This regioselective alkylation using mild hypervalent iodine reagents is more practical, operationally simple and transition metal free. The reaction proceeds efficiently with a broad range of substrates including quinoline, isoquinoline, and pyridine N-oxides using a variety of *tert*-/*sec*- alcohols. From experimental outcome, we also propose a rationalized mechanism, mediated by PIDA.

Keywords: alkylation; C-C bond cleavage; transition-metal-free; regioselective; N-oxides; PIDA

Alkylated quinoline and pyridine motifs represent a significant class of molecules, as they possess the fundamental structural unit for many biologically active molecules, pharmaceuticals, and agro-chemicals.[1] Thus, the development of new methodology for the C-C bond construction of quinoline and pyridine N-oxides have received considerable efforts in recent years.[2] However, only a limited number of the direct regioselective alkylation of quinoline and pyridine N-oxides are reported (Scheme 1) till date. In 2000, K. C. Nicolaou *et al*. reported methylation of pyridine derived N-oxides using Tebbes reagent via a carbene pathway.[3] Grignard reagents are frequently used as a nucleophile for C2- alkylation/arylation of pyridine and other heterocyclic N-oxides.[4] The oxidative cross-coupling of pyridine N-oxides with cycloalkane under the influence of di-tert-butyl peroxide has been reported by Itami and Li *et al*., where reaction proceeds via a radical pathway with poor regioselectivity.[5] Fu and Wu *etal*. reported Pd catalyzed cross-coupling reaction of pyridine or quinoline N-oxides with alkyl bromides[6] and ethers[7] and copper-catalyzed regioselective cross-coupling with N-tosylhydrazones using excess base was reported by Jain *et al*.[8] for the synthesis of



Scheme 1: Approaches for C2-alkylation of quinoline N-oxide

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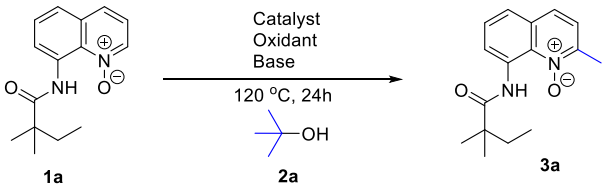
alkyl pyridine derivatives. In 2016, Cho *et al.* reported base promoted alkylation of pyridine N-oxide using 1,1 diborylalkanes as an alkylating agent.[9]

Table 1: Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant (equiv)	Base	Time (h)	Yield of **3a** (%)[b]
1[c]	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	K_2CO_3	24	41
2[c]	$Pd(OTf)_2$	$PhI(OAc)_2$ (2)	K_2CO_3	24	44
3	$Cu(OTf)_2$	$PhI(OAc)_2$ (2)	K_2CO_3	24	12
4	-	$PhI(OAc)_2$ (2)	K_2CO_3	24	44
5	-	$PhI(OAc)_2$ (3)	K_2CO_3	24	55
6	-	$PhI(OAc)_2$ (4)	K_2CO_3	24	60
7		$PhI(OAc)_2$ (4)	K_2CO_3	4	66[d]
8	-	$PhI(OAc)_2$ (4)	Na_2CO_3	4	57[d]
9	-	$PhI(OAc)_2$ (4)	Cs_2CO_3	4	50[d]
10	-	$PhI(OAc)_2$ (4)	CsOPiv	4	49[d]
11	-	$PhI(OAc)_2$ (4)	NaOH	4	45[d]
12	-	$PhI(OAc)_2$ (4)	NaOAc	4	16[d]
13	-	IBX (4)	K_2CO_3	24	Nr
14	-	$PhI(OTf)_2$ (4)	K_2CO_3	4	48[d]
15	-	Oxone (4)	K_2CO_3	24	Nr
16	-	-	K_2CO_3	24	Nr
17	-	$PhI(OAc)_2$ (4)	-	4	11[d]

[a]reaction conditions: **1a** 0.25 mmol, **2a** (1 mL), $PhI(OAc)_2$ (2-4 equiv.) as mentioned, base (2 equiv.) at 120 °C in a sealed tube; [b]isolated yields; [c]2 equiv. PhI was used; [d] oxidant was added in 3 batches (beginning, 2h, 3h).

A metal-free approach for the methylation of pyridine N-oxides using dicumylperoxide (DCP) reagents was reported by Li and Wu *et al*.[10] DCP also used as the oxidant for benzylation of quinoline N-oxides with toluene.[11] Very recently, Dai and Xu *et al*. reported alkylation of pyridine N-oxides using potassium alkyltrifluoroborate as an alkylating agent with a photo-redox Ru catalyst via the radical pathway.[12] Clearly, the development of a regioselective and efficient method for the alkylation of quinoline and other heterocyclic N-oxide moieties under transition-metal-free conditions highly anticipated. Meanwhile, cleavage of the C-C sigma bond and its simultaneous conversion into more complex products are highly challenging and desirable reactions for the synthetic chemists over the years.[13]

Till date, the most commonly recognized C-C sigma bond activations are (i) release of ring strain and (ii) directing group assisted C-C bond activation. In most of the cases, expensive transition metal catalysts are essential for the C-C bond activation and functionalization. Thus, development of a methodology for C-C bond activation that overcomes the limitations of using transition metal catalyst remains a challenge for the synthetic chemist.

In the light of annotations as mentioned above and challenges, we report herein, a $PhI(OAc)_2$ mediated alkylative C-C σ bond activation of secondary and tertiary- alcohols followed by alkylation of quinoline N-oxide. Recently, photochemical methylation of quinoline and pyridine derivatives with methanol through C-O bond cleavage was reported.[14] To the best of our knowledge; this is an unprecedented metal free approach for the synthesis of 2- alkyl quinoline N-oxide derivatives featuring an alkylation through C−C bond activation of sec-/tert- alcohols. It should be mentioned that present study instigated with an unexpected observation during our efforts towards sp^3 C-H functionalization of 8-amido quinoline N-oxides. During the reaction optimization with different solvents, we were amazed to isolate the C2-methylated product.

When 8-(2,2-dimethylbutanamido)quinoline 1-oxide (1a) was treated with iodobenzene in the presence of $Pd(OAc)_2$ as a catalyst and $PhI(OAc)_2$ as an oxidant in *tert*-butanol (2a) solvent, a modest yield (41%) of methylated product (3a) was obtained. The desired methylated product is obtained in 44% yield when $Pd(OTf)_2$ used as catalyst (entry 2). However, $Cu(OTf)_2$ produced comparatively much inferior results (12%, entry 3). Interestingly, in the absence of any transition metal catalyst, only $PhI(OAc)_2$ gave similar yield (44%, entry 4) with K_2CO_3 as a base. To our delight, yield increases significantly to 60% (entries 5-6), when loading of $PhI(OAc)_2$as increased. We have observed that starting material was not entirely consumed even after 24h. To our anticipation, PIDA might have decomposed in the reaction mixture. Therefore, we planned to add the oxidant in batches: 2 equivalent at the beginning and one equivalent each after 2h and 3h, which resulted in the reaction to complete in 4h, and the yield increased significantly to 66 % (entry 7). It should be noted here that replacing K_2CO_3 with other bases including Na_2CO_3, Cs_2CO_3, cesium pivalate, NaOH, and NaOAC was not successful, and leads to lower yield (entries 8-12).

Next, we examined other hypervalent iodine reagents towards the same reaction. Surprisingly, no reaction takes place with IBX (entry 13). However, when we used $PhI(OTf)_2$ little lower yield of desired alkylated product was obtained (48%, entry 14). Even when strong oxidant oxone used, no reaction was observed (entry 15). Control experiments revealed that both $PhI(OAc)_2$ and K_2CO_3 are essential to carry out the reaction (entries 16-17).

With the optimized reaction condition in hand, we next explored the scope and limitation of N-heteroaromatic N-oxides by employing tert-butanol (2a) as a methylating reagent and the results summarized in Table 2. The reaction proceeds well with a series of 8-alkylamido quinoline N-oxides, furnishing corresponding methylated product in moderate to good yields (3a-3d, Table 2). Aromatic amides, 8-benzamido quinoline N-oxides also provided good yields (3e**,** 53%) to corresponding 2-

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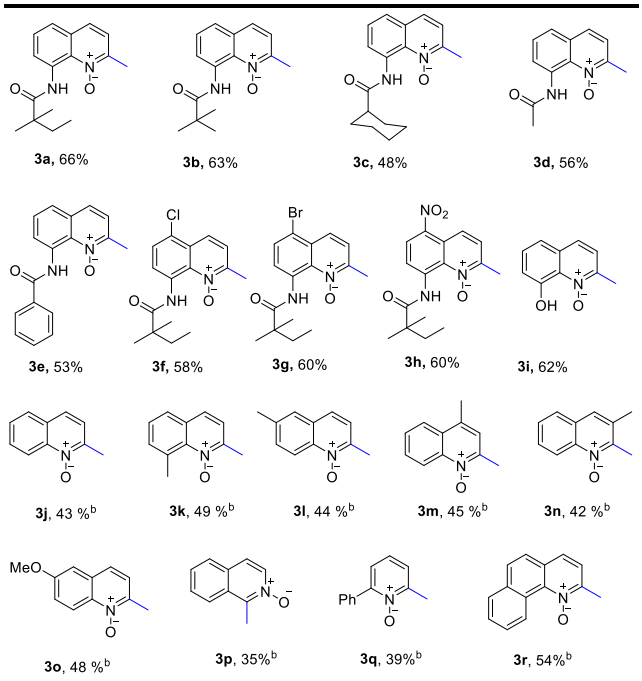
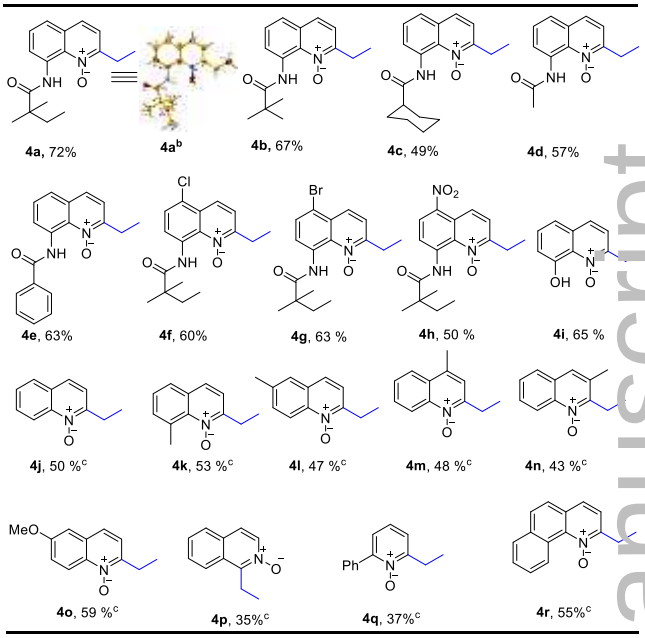
methylated products. In general, the reaction is well tolerated with a variety of synthetically useful functional groups; including amido (3a-3g), chloro and bromo substituents (3f-3g), electron donating methyl (3k-3n), and methoxy (3o) groups in different positions of the quinoline moiety. Also, electron withdrawing nitro group at the C-5 position provided the products in good yield (3h). Moreover, the reaction occurred very smoothly and afforded very good yield (62%, 3i) with the free hydroxy group at 8-position. We observed that simple quinoline N-oxide and methyl substituents in a different position of quinoline moiety required longer reaction time (12h) to complete and afforded lower yields compared to the 8-amido quinoline N-oxides (42-49%, **3j-3n**). On the other hand, 6-methoxy quinoline N-oxides provided very good yield on methylation reaction (48%, **3o**). Importantly, the alkylation reaction also goes smoothly with other types of heterocyclic N-oxides derived from pyridine, isoquinoline, and benzo[h]quinoline (**3p-3r**) from moderate to good yields. Encouraged by the facile synthesis of 2-methyl quinoline and other heteroaromatic N-oxide derivatives, the scope of the reaction was further extended by using unsymmetrical tertiary alcohol, i.e., *tert*-amyl alcohol (**2b**) to check whether there is any priority in the migration of alkyl group. To our delight, when 8-(2, 2-dimethylbutanamido)-quinoline N-oxides (**1a**) reacted with *the tert*-amyl alcohol (**2b**), the reaction proceeds smoothly, and the ethylated product was isolated (72%, entries **4a**) almost exclusively with a little-methylated product (7%, **3a).** We were fortunate to obtain single crystals of compound **4a**, and the structure was confirmed by the single crystal X-ray diffraction analysis (**Table 3, 4a**) and (**Figure S1,** supporting information). The reaction proceeds smoothly with other 8- amido quinoline N- oxides and afforded good yields (**Table 3,** entries **4b-4h**). The reaction has excellent compatibility with various functional groups (**4f-i**, and **4o**). Similar to the case of methylation reaction, methyl substituted quinoline N-oxides required longer reaction time (12h) and

Table 2: Substrate scope in direct methylation of N-heteroaromatic N-oxides using *tert*-butanol[a]



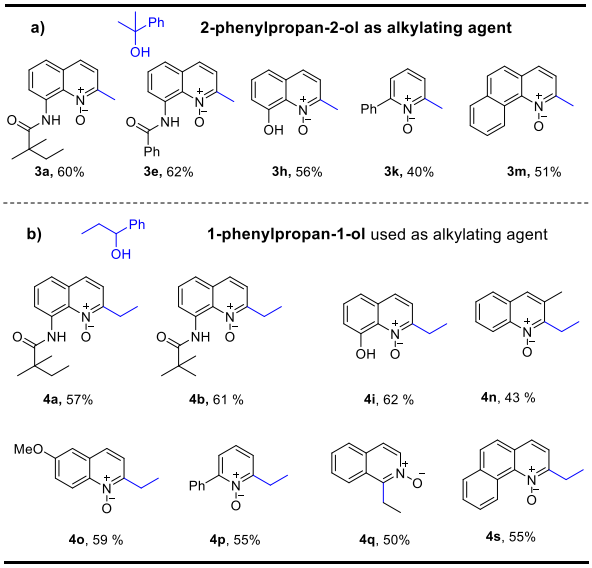
[a] reaction conditions: substrate 0.25 mmol, *t*-BuOH (1 mL), $PhI(OAc)_2$ (4 equiv.), K_2CO_3 (2 equiv.) at 120 °C in a sealed tube for 4h; [b] reaction was carried out for 12h, oxidant was added in 3 batches (beginning, 2h, 3h).

Table 3: Substrate scope in direct ethylation of heteroaromatic N-oxides with *tert*-amyl alcohol[a]



[a]Reaction conditions: substrate 0.25 mmol, TAA (1 mL), $PhI(OAc)_2$ (4 equiv.), K_2CO_3 (2 equiv.) at 120 °C in a sealed tube for 4h; [b]CCDC 1568886; [c] reaction was carried out for 12h, oxidant was added in 3 batches (beginning, 2h, 3h).

Table 4: substrate scope with other tertiary and secondary alcohols[a]



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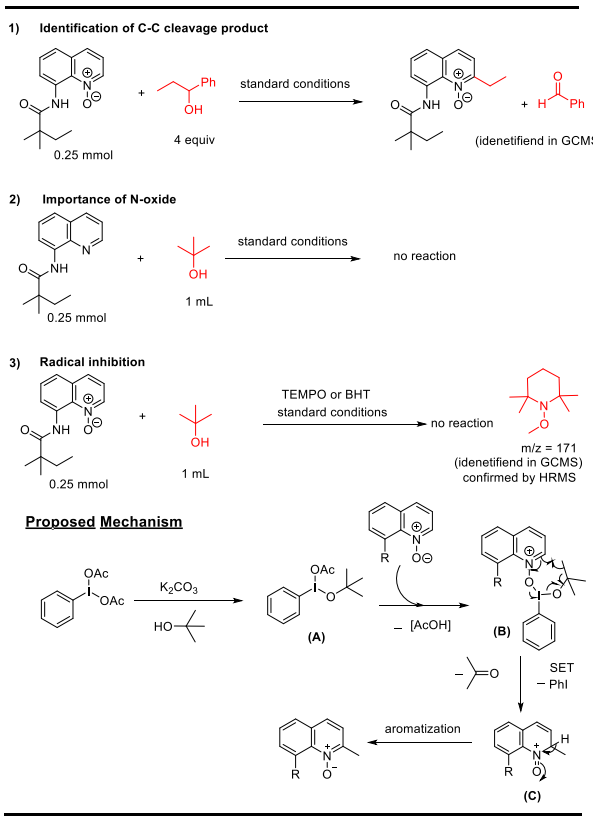
[a]Reaction conditions: substrate 0.25 mmol, 2-phenylpropan-2-ol (4 equiv), or 1-phenyl-propan-1-ol (4 equiv), toluene (1 mL), $PhI(OAc)_2$ (4 equiv.), K_2CO_3 (2 equiv.) at 120 °C in a sealed tube for 4h.



Scheme 2: Control experiment for mechanism studies and proposed mechanism

moderate yields were obtained (**4k-4n**). Pyridine, isoquinoline, and benzo[h]quinoline N-oxides are also capable and moderate to good yields were achieved (**4p-4r**) almost in all the cases.

To further demonstrate the synthetic utility of our reaction, we turned our attention to another tertiary alcohol, 2-phenylpropan-2-ol as an alkylating agent. In this case, we reoptimized the reaction conditions (see supporting information for details), where the reaction was carried out in a sealed tube with four equiv. alcohol, K_2CO_3 (2 equiv.), and $PhI(OAc)_2$ (4 equiv.) in toluene (1 mL) at 120 °C, for 4h. Under this condition, we have chosen few substrates, and the solely methylated product was obtained in moderate to good yield (40-62%, **Table 4a**). However, we could not observe aryl migration for any substrate.

Encouraged by the facile methylation and ethylation of quinoline N-oxides with tertiary alcohols the scope of the reaction. To our pleasure, the reaction with 1-phenyl-propan-1-ol goes smoothly, and the ethylated product was exclusively observed for a range of substrates (**Table 4b**). Interestingly, most of the reaction was completed in shorter time (within 2-4h). Unfortunately, the use of isopropanol as a methylating agent was unsuccessful,[15] under the present optimized reaction conditions

To elucidate the reaction mechanism, we have carried out some controlled experiment as shown in **Scheme 2**. When 1-phenyl propan-1-ol is used as an alkylating agent in standard reaction condition, we could identify the formation of benzaldehyde by GCMS (**eq. 1**) along with the desired ethylated product. The result indicates that the C-C bond cleavage of the alcohol is one of the key steps. Again, when 8-(2, 2-dimethylbutanamido) quinoline or 8-hydroxy quinoline or quinoline (N-oxide free) is treated with *tert*-butanol under standard reaction conditions, no reaction takes place, suggesting that N-oxide group is crucial for C2 alkylation and cleavage of *tert*- alcohol. Next, upon addition of the radical scavenger, 2, 6-Di-tert- butyl-4-methylphenol (BHT) or (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), the reaction is completely inhibited and we have identified the TEMPO trapped methyl radical in GC-MS and HRMS, indicating that reaction may proceed through a single electron transfer (SET) pathway. Based on the above experiments and previous literature report a tentative reaction mechanism route is proposed as shown in **Scheme 2**. At the onset, PIDA reacts with the alcohol to form intermediate **A**,[16] which reacts with the quinoline N-oxide to form the compound **B**. Then, it might proceed through a way homolytic C-C bond cleavage of alcohols[17] *via* a SET pathway, followed by alkylation and aromatization to generate the 2 alkylated product.

In summary, we have developed a highly efficient and convenient system for the regioselective ethylation/methylation of the quinoline and other N oxide system using tert-amyl alcohol or tert-butanol, respectively. This alkylation method is transition metal free, mediated by the mild hypervalent iodine reagents, and proceeds through a C-C bond cleavage of tertiary as well as secondary alcohols. Our method has broad substrate scope and vast functional group tolerances, including amide, alcohol, ether, nitro, and halides. Further exploration of the regioselective alkylation with other heteroaromatic substrates and study on the detailed mechanism is currently in progress.

Experimental Section

General conditions

All reactions were carried out in oven-dried glassware under standard reaction conditions. Tert amyl alcohol and tert-butanol, 1-phenyl-propan-1-ol, 2-phenyl propan-2-ol and other all chemicals were purchased from TCI and Sigma-Aldrich and used without further purification. Solvents were purchased from S. D. Fine chemicals Ltd India and dried by standard procedure, kept over molecular sieves and then used. Flash column chromatography purification of compounds was carried out by gradient elution using ethyl acetate (EA) and hexane and some cases with methanol. 1H/ 13C NMR was recorded on 600/151 MHz NMR spectrometer, in $CDCl_3$, unless otherwise mentioned, using

either TMS or the undeuterated solvent residual signal as the reference.

General procedure for synthesis of N-Heteroaromatic N-oxides

Representing procure: To a solution of 8-(2,2-dimethylbutanamido)quinoline (727 mg, 3 mmol) in CH_2Cl_2 (20ml) was added m-chloroperbenzoic acid (1035 mg, 70% mCPBA, 2 equiv.) at 0 °C and the reaction mixture was stirred at room temperature up to 24h, reaction progress was monitored by TLC. After completion of the reaction, saturated aqueous $NaHCO_3$ solution (60 mL) was added to the reaction mixture and extracted with dichloromethane (50 mL x 2). The organic part was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel with 30% ethyl acetate in hexane, 98% of the desired 8-(2,2-dimethylbutanamido)quinoline-1-oxide (1a) was isolated.

General procedure for Alkylation of Quinoline N-Oxides

Representing procure: A mixture of 8-(2,2-dimethylbutanamido)quinoline 1-oxide (**1a**) (64.5 mg, 0.25 mmol), phenyl iodonium diacetate [$PhI(OAc)_2$, 161 mg, 0.5 mmol, 2 eq] and K_2CO_3 (69 mg, 0.5 mmol) were taken in a carousel screw cap reaction tube equipped with a cross shape stirring bar. 1 mL *tert*-butanol was added over it, and the tube was sealed with the Teflon screw cap and stirred at 120 °C for 2h. Additional, each time 1 equiv.(80 mg) $PhI(OAc)_2$ was added after 2h and 3h. The reaction is monitored by TLC, and after completion (4h) the reaction mixture is cooled to room temperature and filtered through a plug of Celite, and then washed with EtOAc (30 mL). The filtrate was concentrated and evaporated to dryness in a rotary evaporator. The crude residue was purified by column chromatography (Ethyl acetate: Hexane 30: 70) to isolate 8-(2,2-dimethylbutanamido)-2-ethylquinoline 1-oxide (45 mg, 3a) in 66% yield.

CCDC-1568886 contains the supplementary crystallographic data for this paper (**4a**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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[15] 10-12% of C2- methylated product was observed.

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COMMUNICATION

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