REACTION OF QUINOLINE *N*-OXIDES WITH ALKYL- AND ARYLLITHIUMS IN THE PRESENCE OF OXIDANT[1]

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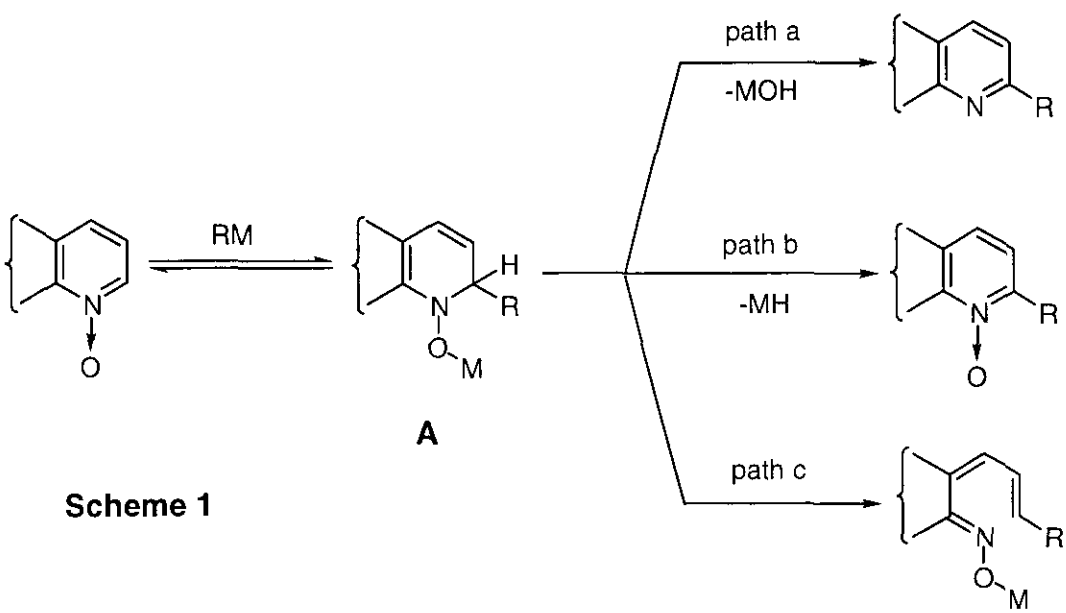
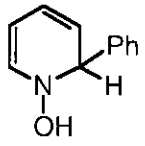
Abstract —Quinoline and some 4-substituted quinoline 1-oxides react with alkyl- and aryllithiums in the presence of an oxidant to afford 2-alkyl- and 2-arylquinoline 1-oxides in generally good yields. Among oxidants used, 9-fluorenone is most effective. On the other hand, quinaldine 1-oxide undergoes a base-induced electrophilic reaction with *n*-BuLi and 9-fluorenone to give 2-[(9-hydroxyfluoren-9-yl)methyl]quinoline 1-oxide.

The reaction of π-deficient heteroaromatic *N*-oxide with Grignard reagents and organolithiun compounds (M-R) is initiated by the formation of the primary adduct, 1,2-dihydrointermediate (**A**), which promptly undergoes further transformations following three paths as illustrated in Scheme 1.[2]

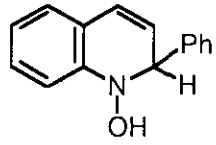


Scheme 1

Chemical proof of the intermediacy of **A** was provided by the isolation of 1-hydroxy-2-phenyl-1,2-dihydro derivatives (**B,C**) from reactions of pyridine and quinoline 1-oxides with phenylmagnesium bromide in THF.[3]



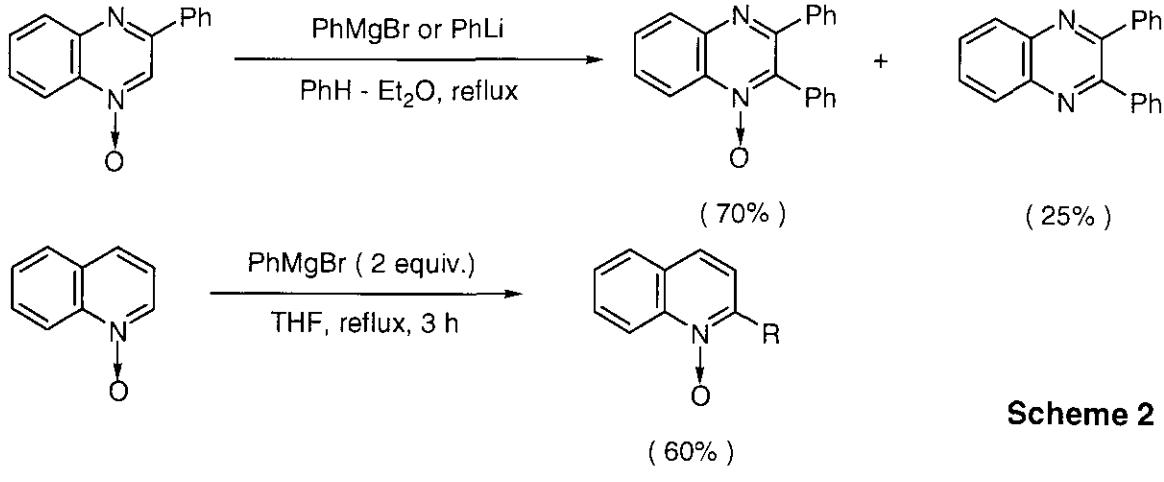
B



C

Path **a** reaction is the formation of the deoxygenated α-substitution product by the elimination of metal hydroxide(M-OH) from **A.** In path **b** reaction, metal hydride (M-H) instead of metal hydroxide (M-OH) is eliminated from **A** to yield α-substituted *N*-oxide. Path **c** is the ring-opening reaction of **A**;[2C,3,4] this path will be not dealt with in this paper.

Path **a** reaction is one of the typical nucleophilic substitution reactions of aromatic *N*-oxide by addition-elimination mechanism,[2] and a large numbers of reports on this type of reactions are available.[2] Path **b** reaction involves an oxidation process and the number of report is not so many but an appreciable amount of work has been described as exemplified in Scheme 2.[5,3a]



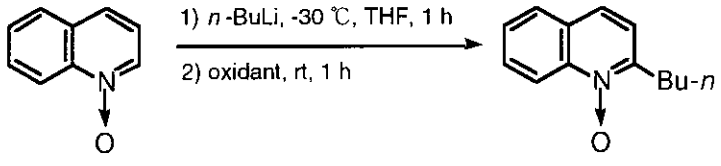
Scheme 2

Further, it was shown that the formation of 2-phenylquinoline 1-oxide from quinoline 1-oxide and phenylmagnesium bromide was observed even in the reaction under nitrogen.[6] From these results it seems possible that the choice of path **a** or **b** is governed principally by the nature of O-M bond in **A** rather than the presence or absence of an oxidant.[2a,7] Nevertheless, path **b** reaction should be accelerated by means of oxidizing agent. In fact, Hayashi and Iijima found that the yield of 2,3-diphenylquinoxaline 1-oxide substantially increased upon treatment of the reaction mixture with *p*-benzoquinone in the above depicted reaction[5] between 2-phenylquinoxaline 4-oxide and phenylmagnesium bromide (Scheme 2).[8] A similar observation was also obtained in phthalazine series.[9]

In order to test the general utility of the path **b** reaction in the presence of an oxidant for the preparative route to α–alkyl- and α-aryl-substituted *N*-oxides, we examined reactions of quinoline 1-oxide with organolithium compounds in the presence of oxidizing agents.

As a preliminary study, we explored the reaction of quinoline 1-oxide (**1**) with *n*-BuLi in THF at -30 °C in the presence of some oxidants and obtained the results shown in Table 1.

Table 1 The reaction of quinoline 1-oxide with *n*-BuLi in the presence of an oxidant

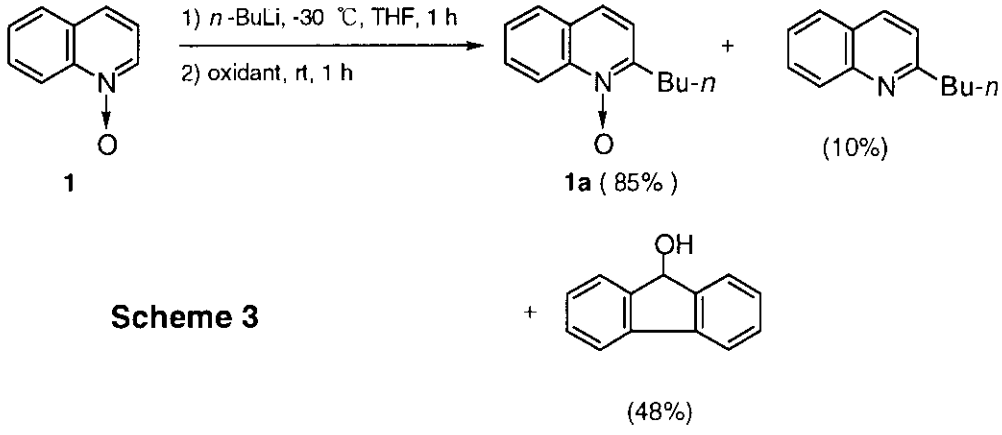


1 **1a**

Run	Oxidant	Yield(%) of **1a**
1	- [a]	42
2	air [b]	57
3	DDQ[c]+air [b]	66
4	$Pb(OAc)_4$	63
5	$K_3Fe(CN)_6$	62
6	DDQ	69
7	9-fluorenone	85

a) under nitrogen.
b) under air atmosphere without bubbling.
c) DDQ : 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Thus, it was disclosed that, while the oxidative alkylation giving 2-*n*-butylquinoline 1-oxide (**1a**) proceeded to some extent even in the absence of an oxidant (run 1), the presence of an oxidant evidently accelerated this process. Particularly significant is the high effectiveness of 9-fluorenone as an oxidant (run 7), **1a** being produced in a high yield of 85% accompanied with 2-*n*-butylquinoline(10%) and 9-fluorenol(48%) (Scheme 3).

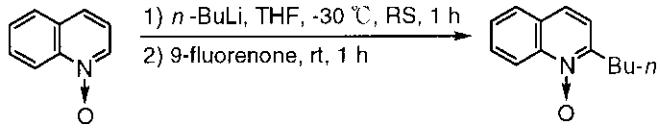


1 **1a** (85%) (10%) (48%)

Scheme 3

In exploring the participation of radical process,[10] the reaction was carried out in the presence of a radical scavenger(RS), *p*-dinitrobenzene or galvinoxyl[11](Table 2).

Table 2 Effect of radical scavenger on the yield of **1a**



1 **1a**

Run	RS	Molar Ratio of RS : **1**	Yield (%) of **1a**
1	-	0 : 100	73
2	*p*-dinitrobenzene	15 : 100	58
3	galvinoxyl	15 : 100	60

RS : Radical Scavenger

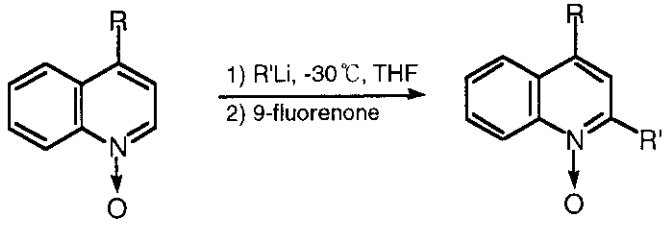
Table 2 indicates that the reaction is not substantially affected by radical scavengers, implying that the reaction is principally an ionic reaction.

Subsequently in order to ascertain the effectiveness of 9-fluorenone as an oxidant, we extended this procedure to reactions of **1** and some 4-substituted quinoline 1-oxides(**2-5**) with alkyl- and aryllithiums and found that this procedure is generally useful for preparation of 2-alkyl- and 2-arylquinoline 1-oxides (Table 3).

The observed poor reactivity for *t*-butylation may be well ascribed to the steric factor of *t*-BuLi. Although it seems that the electron-donating substituent on the 4-position is preferable to the electron-withdrawing one in these reactions, the general substituent effects on this type of reaction should be evaluated by examination of reactions under diverse conditions, because these reactions consist of two steps, nucleophilic addition and oxidation. Anyhow, it is noticeable that 4-nitroquinoline 1-oxide was able to undergo this type of reaction though to a small extent.

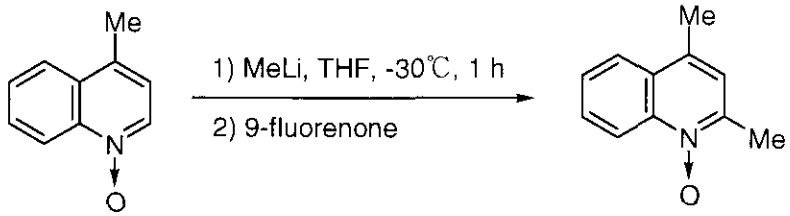
As an application of this procedure, we attempted the oxidative 2-methylation of lepidine 1-oxide (**2**). Whereas Cervinka and others obtained 2,4-dimethylquinoline (**7**) in *ca.* 70% yield by the reaction of 1-ethoxylepidinium iodide with methylmagnesium iodide,[15] the other preparative methods of **7** such as the reaction of 4-anilino-3-penten-2-one with $AlCl_3$,[16] and Wittig reaction of 4-chloroquinaldine,[17] suffer from difficulty in preparing the respective starting materials. Treatment of **2** with MeLi and 9-fluorenone afforded 2,4-dimethylquinoline 1-oxide (**6**) in 60% yield. Deoxygenation of **6** with Me_3SiCl-NaI-Zn[18] progressed quantitatively to give **7** (Scheme 4). This reaction sequence appears to be a more feasible and convenient method for preparation of **7** as compared with previous methods.

Table 3 Reaction of 4-substituted quinoline 1-oxide with alkyl- and aryllithiums in the presence of 9-fluorenone

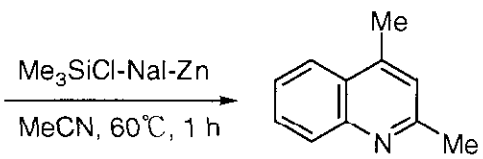


1 - 5 **1(a-d) - 5(a-d)**

Product No.	R	R'	Yield(%)
1a	H	*n* -Bu	85
1b		*t* -Bu	43
1c[12]		Ph	66
1d		2-thienyl	69
2a	Me	*n* -Bu	70
2b		*t* -Bu	28
2c[3a]		Ph	37
2d		2-thienyl	48
3a	OMe	*n* -Bu	55
3b		*t* -Bu	25
3c[13]		Ph	43
3d		2-thienyl	34
4a	Cl	*n* -Bu	37
4b		*t* -Bu	0
4c[3a]		Ph	34
4d		2-thienyl	44
5a	NO_2	*n* -Bu	5
5b		*t* -Bu	0
5c[14]		Ph	6
5d		2-thienyl	20



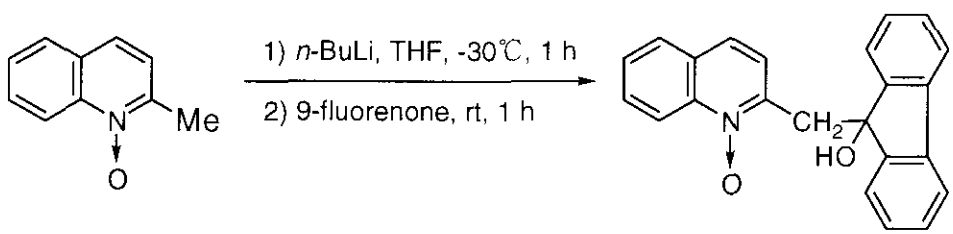
2 **6** (60%)



7

Scheme 4

Quinaldine 1-oxide (**8**), having the active methyl group at the 2-position, underwent an alternate reaction. Thus, treatment of **8** with *n*-BuLi and 9-fluorenone under the above-mentioned conditions resulted in the formation of 2-[(9-hydroxyfluoren-9-yl)methyl]quinoline 1-oxide (**9**) in 30% yield (Scheme 5). Apparently, this is one of the well-known base-induced electrophilic reactions of the active α-methyl group of aromatic *N*-oxides,[2] in which *n*-BuLi and 9-fluorenone behave, respectively, as a base and as an electrophile.



8 **9** (30%)

Scheme 5

In conclusion, quinoline 1-oxides bearing no substituent on the 2-position react with alkyl- and aryllithium compounds in the presence of an oxidant, especially 9-fluorenone, to afford 2-alkyl- and 2-arylquinoline 1-oxides, which are synthetically useful species because of the various reactions that the *N*-oxide function undergoes. Application of this process to other heteroaromatic *N*-oxides as well as to other nucleophilic reactions of aromatic *N*-oxides *via* 1,2-dihydrointermediates is currently under way.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometer and spectrometers : IR spectra, JASCO IR-810 ;^{1}H-NMR spectra, JEOL GX-400 (400 MHz) and JEOL A-500 (500 MHz) ;

^{13}C-NMR spectra, JEOL GX-400 (100 MHz) and JEOL A-500 (125 MHz) ; MS spectra, JEOL JMS-DX300 for EI-MS and JMS-HX100 for FAB-MS. The H-COSY, CH-COSY, DEPT and HMQC experiments were also used for the assignments of the structures. The chemical shifts are given in the δ scale. Elemental analyses were performed on a Yanaco CHN CORDER MT-6 instrument. Medium pressure liquid chromatography (MPLC) was carried out with Yamazen 540 FMI-C pump and Wakogel FC-40 (20-40 μm, Wako). Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck). High-performane thin layer chromatography (HPTLC) about the yields as shown in Table 1 was conducted on Shimadzu high speed thin layer chromatoscanner (CS-9300PC) with the detector set at uv 254nm.

General procedure for the reaction of quinoline 1-oxide (1) with *n*-BuLi in the presence of an oxidant

To a solution of **1** (0.5 g, 3.45 mmol) in anhydrous THF (20 mL) was added dropwise a 1.57 M *n*-BuLi (2.2 mL, 3.45 mmol) hexane solution at -30 ℃ under nitrogen with stirring and the solution was then stirred at -30 ℃ for 1 h. An oxidant (3.45 mmol) in anhydrous THF (10 mL) was added at -30 ℃ and the resulting mixture was allowed to reach rt and then further stirred at rt for 1 h followed by quenching with ice water (20 mL) and extraction with Et_2O (100 mL). The residue from Et_2O extract was purified by MPLC (hexane : ethyl acetate = 5 : 1) to give 2-*n*-butylquinoline 1-oxide (**1a**). Compound (**1a**) was recrystallized from hexane-ethyl acetate (5 : 1) to afford colorless prisms, mp 34-36 ℃. The exact yields were determined using chromatoscanner (CS-9300PC). HPTLC conditions : HPTLC plate, silica gel 60 F_{254} precoated (Merck) ; solvent system, ethyl acetate. *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.58 ; H, 7.51 ; N, 6.96. Found : C, 77.35 ; H, 7.68 ; N, 6.80.IR (neat) : 3396, 2958, 1561, 1515, 1358, 1343, 1290, 1239, 810 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 0.94 (3H, t, J=7.3 Hz, -CH_3), 1.39 (2H, dt, J=7.3 and 22.6 Hz, -$CH_2CH_2\underline{C}H_2CH_3$), 1.68-1.74 (2H, m, -$CH_2\underline{C}H_2CH_2CH_3$), 3.02 (2H, t, J=7.6 Hz, -$\underline{C}H_2CH_2CH_2CH_3$), 7.53 (1H, d, J=8.5 Hz, H-3), 7.68 (1H, dd, J=7.2 and 8.1 Hz, H-6), 7.80 (1H, dd, J=7.2 and 8.2 Hz, H-7), 7.86 (1H, d, J=8.5 Hz, H-4), 8.04 (1H, d, J=8.1 Hz, H-5), 8.58 (1H, d, J=8.2 Hz, H-8). ^{13}C-NMR (DMSO-d_6) :δ 13.6 (q, -CH_3), 22.1 (t, -$CH_2CH_2\underline{C}H_2CH_3$), 27.5 (t, -$CH_2\underline{C}H_2CH_2CH_3$), 30.3 (t, -$\underline{C}H_2CH_2CH_2CH_3$), 118.8 (d, C-8), 122.5 (d, C-3), 124.1 (d, C-4), 127.7 (d, C-6), 128.4 (d, C-5), 128.8 (s, C-10), 130.0 (d, C-7), 140.9 (s, C-9), 148.1 (s, C-2). MS (FAB$^+$) : 202 (M^++H).

Reaction of 1 with *n*-BuLi in the presence of 9-fluorenone

Reaction was carried out as described in General procedure for the reaction of **1** with *n*-BuLi in the presence of an oxidant but using 9-fluorenone (0.62 g, 3.45 mmol) as an oxidant. The residue from Et_2O extract was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give successively 2-*n*-butylquinoline [19] (60 mg, 10%), 9-fluorenol (0.3 g, 48%) and compound (**1a**) (0.6 g, 85%).

Reaction of 1 with *n*-BuLi and 9-fluorenone in the presence of radical scavenger

To a solution of **1** (0.5 g, 3.45 mmol) and a radical scavenger (0.6 mmol) in anhydrous THF (25 mL) was added dropwise at -30 ℃ under nitrogen with stirring a 1.57 M *n*-BuLi (2.2 mL, 3.45

mmol) hexane solution and the mixture was stirred at -30 ℃ for 1 h followed by the addition of 9-fluorenone (0.62 g, 3.45 mmol) in THF (10 mL). The resulting solution was further stirred at rt for 1 h and quenched with a little amount of water and extracted with Et_2O (100 mL). The yield of **1a** was determined by using chromatoscanner(CS-9300PC) as shown in Table 2. HPTLC conditions : HPTLC plate, silica gel 60 F_{254} precoated (Merck) ; solvent system, ethyl acetate.

General procedure for the reaction of 4-substituted quinoline 1-oxide with alkyl- and aryllithium in the presence of 9-fluorenone

Reaction was carried out as described in General procedure for the reaction of **1** with *n*-BuLi in the presence of an oxidant but using 4-substituted quinoline 1-oxide (3.45 mmol) instead of compound (**1**), 9-fluorenone (0.62 g, 3.45 mmol) as an oxidant and 1.7 M *t*-butyllithium pentane solution, 0.94 M phenyllithium cyclohexane-Et_2O solution, 1.0 M 2-thienyllithium THF solution(respectively, 3.45 mmol).

Reaction of 1 with *t*-BuLi

The residue was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 0.3 g (43%) of 2-*t*-butylquinoline 1-oxide (**1b**). Compound (**1b**) was recrystallized from hexane to afford pale yellow prisms, mp 91-92 ℃. *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.58 ; H, 7.51 ; N, 6.96. Found : C, 77.57 ; H, 7.65 ; N, 6.91. IR (KBr) : 2962, 1345, 1332, 1248, 1210, 1131, 1082, 904, 804, 748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) :δ 1.63 (9H, s, -C $(CH_3)_3$), 7, 45 (1H, d, J=8.7 Hz, H-3), 7.57 (1H, dd, J=7.0 and 8.1 Hz, H-6), 7.63 (1H, d, J=8.7 Hz, H-4), 7.72 (1H, dd, J=7.0 and 8.8 Hz, H-7), 7.80 (1H, d, J=8.1 Hz, H-5), 8.80 (1H, d, J=8.8 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 26.9 (q, -C $(\underline{C}H_3)_3 \times 3$), 36.6 (s, -$\underline{C}$ $(CH_3)_3$), 119.9 (d, C-8), 120.0 (d, C-3), 124.7 (d, C-4), 127.6 (d, C-5), 127.8 (d, C-6), 129.1 (s, C-10), 130.1 (d, C-7), 143.2 (s, C-9), 154.1 (s, C-2). MS (FAB^+) ; 202 (M^++H).

Reaction of 1 with PhLi

The residue was purified by MPLC to give 67 mg (9%) of 2-phenylquinoline (hexane : ethyl acetate = 10 : 1 as an eluent) and 0.5 g (66%) of 2-phenylquinoline 1-oxide (**1c**)[12] (hexane : ethyl acetate = 5 : 1 as an eluent).

Reaction of 1 with 2-thienyllithium

The residue was purified by MPLC to give 2- (2-thienyl)quinoline[20] (hexane as an eluent) and 0.54 g (69%) of 2- (2-thienyl)quinoline 1-oxide (**1d**) (hexane : ethyl acetate = 10 : 1 as an eluent). Compound (**1d**) was triturated with Et_2O to afford yellow prisms, mp 126-128 ℃. *Anal.* Calcd for $C_{13}H_9NOS$: C, 68.70 ; H, 3.99 ; N, 6.16. Found : C, 68.80 ; H, 4.04 ; N, 6.03. IR (KBr) : 3126, 3080, 1562, 1417, 1351, 1210, 1075, 812, 767, 720, 561 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 7.24 (1H, dd, J=4.0 and 5.2 Hz, H-4'), 7.57 (1H, dd, J=7.3 and 7.9 Hz, H-6), 7.61 (1H, d, J=5.2 Hz, H-5'), 7.70 (1H, d, J=9.0 Hz, H-3), 7.75 (1H, dd, J=7.3 and 8.5 Hz, H-7), 7.78 (1H, d, J=7.9 Hz, H-5), 7.94 (1H, d, J=9.0 Hz, H-4), 7.95 (1H, d, J=4.0 Hz, H-3'), 8.80 (1H, d, J=8.5 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 118.7 (d, C-4), 119.7 (d, C-8), 126.0 (d, C-3), 126.3 (d, C-4'), 127.8 (d, C 5), 127.8 (s, C-10), 128.0

(d, C-6), 128.3 (d, C-3'), 130.7 (d, C-7), 131.3 (d, C-5'), 132.5 (s, C-2'), 139.4 (s, C-9), 141.2 (s, C-2). MS (FAB$^+$) ; 228 (M$^+$+H).

Reaction of lepidine 1-oxide (2) with *n*-BuLi

The residue was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 62 mg (9%) of 2-*n*-butyllepidine[21] and 0.52 g (70%) of 2-*n*-butyllepidine 1-oxide (**2a**). Compound (**2a**) was orange oil, bp 200 ℃/4 mmHg. *Anal.* Calcd for $C_{14}H_{17}NO \cdot 0.2H_2O$: C, 76.82 ; H, 8.01 ; N, 6.40. Found : C, 76.82 ; H, 8.02 ; N, 6.27. IR (neat) : 2958, 2872, 1655, 1565, 1453, 1389, 1341, 1231, 1147, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 0.99 (3H, t, J=7.3 Hz, -$CH_2CH_2CH_2C\underline{H}_3$), 1.49 (2H, dt, J=7.3 and 22.3 Hz, -$CH_2CH_2C\underline{H}_2CH_3$), 1.80 (2H, m, -$CH_2C\underline{H}_2CH_2CH_3$), 2.63 (3H, s, -$CH_3$), 3.09 (2H, t, J=7.8 Hz, -$C\underline{H}_2CH_2CH_2CH_3$), 7. 11 (1H, s, H-3), 7.60 (1H, dd, J=6.8 and 8.7 Hz, H-6), 7.73 (1H, dd, J=6.8 and 8.7 Hz, H-7), 7.92 (1H, d, J=8.7 Hz, H-5), 8.81 (1H, d, J=8.7 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 13.8 (q, -$CH_2CH_2CH_2\underline{C}H_3$), 18.2 (q, -$CH_3$), 22.8 (t, -$CH_2CH_2\underline{C}H_2CH_3$), 28.3 (t, -$CH_2\underline{C}H_2CH_2CH_3$), 31.1 (t, -$\underline{C}H_2CH_2CH_2CH_3$), 120.2 (d, C-8), 122.5 (d, C-3), 124.4 (d, C-5), 127.4 (d, C-6), 128.5 (s, C-10), 129.9 (d, C-7), 133.5 (s, C-4), 141.1 (s, C-9), 148.7 (s, C-2). MS (FAB$^+$); 216 (M$^+$+H).

Reaction of 2 with *t*-BuLi

The residue was purified by MPLC (hexane : ethyl acetate = 10: 1) to give 0.21 g (28%) of 2-*t*-butyllepidine 1-oxide (**2b**). Compound (**2b**) was recrystallized from hexane to afford pale yellow powder, mp 82 ℃. *Anal.* Calcd for $C_{14}H_{17}NO$: C, 78.10 ; H, 7.96 ; N, 6.51. Found : C, 78.04 ; H, 8.07 ; N, 6.46. IR (KBr) : 2952, 1395, 1352, 1325, 1249, 1225, 1208, 1141, 767, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 1.64 (9H, s, -C (CH_3)$_3$), 2.65 (3H, s, -CH_3), 7, 29 (1H, s, H-3), 7.61 (1H, dd, J=7.1 and 8.3 Hz, H-6), 7.74 (1H, dd, J=7.1 and 8.6 Hz, H-7), 7.91 (1H, d, J=8.3 Hz, H-5), 8.86 (1H, d, J=8.6 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 18.5 (q, -CH_3), 27.1 (q, -C ($\underline{C}H_3$)$_3$ × 3), 36.6 (s, -$\underline{C}$ (CH_3)$_3$), 120.5 (d, C-8), 120.6 (d, C-3), 124.3 (d, C-5), 127.6 (d, C-6), 128.6 (s, C-10), 130.0 (d, C-7), 142.6 (s, C-9), 153.7 (s, C-2). MS (FAB$^+$) ; 216 (M$^+$+H).

Reaction of 2 with PhLi

The residue was purified by MPLC to give 0.14 g (18%) of 2-phenyllepidine[22] (hexane as an eluent) and 0.3 g (37%) of 2-phenyllepidine 1-oxide (**2c**)[3a] (hexane : ethyl acetate = 5 : 1 as an eluent).

Reaction of 2 with 2-thienyllithium

The residue was purified by MPLC (hexane : ethyl acetate = 5 : 1) to give 0.4 g (48%) of 2- (2-thienyl)lepidine 1-oxide (**2d**). Compound (**2d**) was triturated with Et_2O to afford yellow prisms, mp 148-150 ℃. *Anal.* Calcd for $C_{14}H_{11}NOS$: C, 69.68 ; H, 4.59 ; N, 5.80. Found : C, 69.68 ; H, 4.68 ; N, 5.73. IR (KBr) : 3040, 1564, 1419, 1384, 1370, 1216, 1149, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 2.66 (3H, s, -CH_3), 7.22-7.24 (1H, m, H-4'), 7.58-7.61 (2H, m, H-6 and H-5'), 7.73-7.75 (2H, m, H-3 and H-7), 7.87(1H, d, J=8.2 Hz, H-5), 7.95(1H, s, H-3'), 8.84 (1H, d, J=8.6 Hz, H-8).^{13}C-NMR ($CDCl_3$): δ 18.5 (q, -CH_3), 118.8 (d, C-3), 120.2 (d, C-8), 124.4 (d, C-5), 126.2 (d, C 4'), 127.6 (s, C-10),

127.7 (d, C-6), 128.2 (d, C-3'), 130.4 (d, C-7), 131.4 (d, C-5'), 132.5 (s, C-2'), 134.4 (s, C-4), 138.8 (s, C-9), 140.6 (s, C-2). MS (FAB$^+$) ; 242 (M$^+$+H).

Reaction of 4-methoxyquinoline 1-oxide (3) with *n*-BuLi

The residue was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 0.44 g (55%) of 2-*n*-butyl-4-methoxyquinoline 1-oxide (**3a**). Compound (**3a**) was recrystallized from Et_2O to afford brown prisms, mp 52 ℃. *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot 0.25H_2O$: C, 71.31 ; H, 7.48 ; N, 5.94. Found : C, 71.35 ; H, 7.36 ; N, 5.87.IR(KBr): 3274, 2958, 1609, 1453, 1388, 1220, 1125, 1090, 973, 760cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 1.00 (3H, t, J=7.6 Hz, -CH_3), 1.51 (2H, dt, J=7.6 and 22.6 Hz, -$CH_2CH_2C\underline{H}_2CH_3$), 1.79-1.86 (2H, m, -$CH_2C\underline{H}_2CH_2CH_3$), 3.16 (2H, t, J=7.8 Hz, -$C\underline{H}_2CH_2CH_2CH_3$), 4.06 (3H, s, -$OCH_3$), 6.64 (1H, s, H-3), 7.58 (1H, dd, J=7.4 and 8.0 Hz, H-6), 7.78 (1H, dd, J=7.4 and 8.7 Hz, H-7), 8.17 (1H, d, J=8.0 Hz, H-5), 8.76 (1H, d, J=8.7 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 13.8 (q, -CH_3), 22.7 (t, -$CH_2CH_2\underline{C}H_2CH_3$), 28.6 (t, -$CH_2\underline{C}H_2CH_2CH_3$), 32.0 (t, -$\underline{C}H_2CH_2CH_2CH_3$), 56.1 (q, -$OCH_3$), 100.4 (d, C-3), 119.7 (d, C-8), 121.5 (s, C-10), 122.3 (d, C-5), 127.0 (d, C-6), 131.1 (d, C-7), 141.3 (s, C-4), 150.8 (s, C-9), 154.4 (s, C-2). MS (FAB$^+$) ; 232 (M$^+$+H).

Reaction of 3 with *t*-BuLi

The residue was purified by MPLC (hexane : ethyl acetate = 1 : 1) to give 0.2 g (25%) of 2-*t*-butyl-4-methoxyquinoline 1-oxide (**3b**). Compound (**3b**) was recrystallized from Et_2O to afford pale yellow prisms, mp 51-55 ℃.*Anal.*Calcd for$C_{14}H_{17}NO_2 \cdot 0.3H_2O$: C, 71.04 ; H, 7.49 ; N, 5.92. Found : C, 71.06 ; H, 7.34 ; N, 5.96.IR (KBr) : 3372, 2958, 1605, 1367, 1245, 1113, 903, 774 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 1.69 (9H, s, -C (CH_3)$_3$), 4.11 (3H, s, -OCH_3), 6.85 (1H, s, H-3), 7.62 (1H, m, H-6), 7.83 (1H, m, H-7), 8.18 (1H, d, J=7.9 Hz, H-5), 8.80 (1H, d, J=8.5 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 27.7 (q, -C ($\underline{C}H_3$)$_3$), 37.6 (s, -$\underline{C}$ (CH_3)$_3$), 56.2 (q, -OCH_3), 98.5 (d, C-3), 120.0 (d, C-8), 121.4 (s, C-10), 122.2 (d, C-5), 127.6 (d, C-6), 131.9 (d, C-7), 142.5 (s, C-9), 157.5 (s, C-2). MS (FAB$^+$) ; 232 (M$^+$+H).

Reaction of 3 with PhLi

The residue was purified by MPLC to give 0.12 g (15%) of 4-methoxy-2-phenylquinoline[3a] (hexane : ethyl acetate = 10 : 1 as an eluent) and 0.37 g (43%) of 4-methoxy-2-phenylquinoline 1-oxide (**3c**)[13] (hexane : ethyl acetate = 1 : 1 as an eluent).

Reaction of 3 with 2-thienyllithium

The residue was purified by MPLC to give 32 mg (4%) of 4-methoxy-2- (2-thienyl)quinoline (hexane : ethyl acetate = 10 : 1 as an eluent) and 0.3 g (34%) of 4-methoxy-2- (2-thienyl)quinoline 1-oxide (**3d**) (hexane : ethyl acetate = 1 : 1 as an eluent). Compound (**3d**) was recrystallized from Et_2O to afford pale yellow prisms, mp 136-138 ℃. *Anal.* Calcd for $C_{14}H_{11}NO_2S \cdot 0.35H_2O$: C, 63.79 ; H, 4.47 ; N, 5.31. Found : C, 63.81 ; H, 4.60 ; N, 5.16. IR (KBr) : 3332, 1612, 1571, 1450, 1384, 1255, 1104, 979, 794, 709 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 4.14 (3H, s, -OCH_3), 7.18 (1H, s, H-4'), 7.21 (1H, s, H-3), 7.56-7.59 (2H, m, H-6 and H-5'), 7.80 (1H, dd, J=8.0 and 7.5 Hz, H-7), 7.99 (1H,

s, H-3'), 8.12 (1H, d, J=7.9 Hz, H-5), 8.76 (1H, d, J=8.0 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 56.4 (q, $-OCH_3$), 96.5 (d, C-3), 119.7 (d, C-8), 121.1 (s, C-10), 122.4 (d, C-5), 126.3 (s, C-4'), 127.4 (d, C-6), 129.0 (d, C-3'), 131.4 (d, C-7), 132.2 (d, C-5'), 132.4 (s, C-2'), 140.4 (s, C-4), 140.9 (s, C-9), 154.5 (s, C-2). MS (FAB^+) ; 258 (M^++H).

Reaction of 4-chloroquinoline 1-oxide (4) with *n*-BuLi

The residue was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 48 mg (6%) of 2-*n*-butyl-4-chloroquinoline[23] and 0.3 g (37%) of 2-*n*-butyl-4-chloroquinoline 1-oxide (**4a**). Compound (**4a**) was orange oil, bp 162 ℃/2.6×10^{-2} mmHg. *Anal.* Calcd for $C_{13}H_{14}NOCl$: C, 66.24 ; H, 5.99 ; N, 5.94. Found : C, 66.34 ; H, 6.06 ; N, 6.10. IR (KBr) : 2958, 2872, 1556, 1339, 1300, 1268, 1230, 763, 637, 587 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 1.00 (3H, t, J=7.5 Hz, $-CH_3$), 1.51 (2H, dt, J=7.5 and 22.6 Hz, $-CH_2CH_2\underline{C}H_2CH_3$), 1.78-1.84 (2H, m, $-CH_2\underline{C}H_2CH_2CH_3$), 3.18 (2H, s, $-\underline{C}H_2CH_2CH_2CH_3$), 7.45 (1H, s, H-3), 7.72 (1H, dd, J=7.1 and 7.9 Hz, H-6), 7.81 (1H, dd, J=7.1 and 6.6 Hz, H-7), 8.17 (1H, d, J=7.9 Hz, H-5), 8.82 (1H, d, J=6.6 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 13.8 (q, $-CH_3$), 22.7 (t, $-CH_2CH_2\underline{C}H_2CH_3$), 28.3 (t, $-CH_2\underline{C}H_2CH_2CH_3$), 31.0 (t, $-\underline{C}H_2CH_2CH_2CH_3$), 120.1 (d, C-8), 121.5 (d, C-3), 125.1 (d, C-5), 128.6 (d, C-6), 131.5 (d, C-7). MS (FAB^+) ; 236 (M^++H).

Reaction of 4 with PhLi

The residue was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 0.3 g (34%) of 4-chloro-2-phenylquinoline 1-oxide (**4c**).[3a]

Reaction of 4 with 2-thienyllithium

The residue was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 0.4 g (44%) of 4-chloro-2-(2-thienyl)quinoline 1-oxide (**4d**). Compound (**4d**) was recrystallized from Et_2O to afford pale yellow prisms, mp 148-152 ℃. *Anal.* Calcd for $C_{13}H_8NOClS$: C, 59.66 ; H, 3.08 ; N, 5.35. Found : C, 59.58 ; H, 3.14 ; N, 5.29. IR (KBr) : 3376, 1562, 1353, 1223, 750, 715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 7.26 (1H, dd, J=3.9 and 5.1 Hz, H-4'), 7.65 (1H, d, J=5.1 Hz, H-5'), 7.69 (1H, dd, J=8.2 and 7.1 Hz, H-6), 7.83 (1H, dd, J=8.4 and 7.1 Hz, H-7), 7.96 (1H, d, J=3.9 Hz, H-3'), 8.05 (1H, s, H-3), 8.16 (1H, d, J=8.2 Hz, H-5), 8.83 (1H, d, J=8.4 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 118.5 (d, C-3), 120.3 (d, C-8), 125.0 (d, C-5), 125.6 (s, C-10), 126.6 (d, C-4'), 128.7 (d, C-6), 128.7 (d, C-3'), 130.7 (s, C-4), 131.6 (s, C-2'), 131.7 (d, C-7), 132.1 (d, C-5'), 139.5 (s, C-9), 141.8 (s, C-2). MS (FAB^+) : 262 (M^++H).

Reaction of 4-nitroquinoline 1-oxide (5) with 2-thienyllithium

The residue was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 0.14 g (20%) of 2- (2-thienyl)-4-nitroquinoline 1-oxide (**5d**). Compound (**5d**) was recrystallized from hexane-Et_2O to afford yellow needles, mp 180-181 ℃ (decomp). *Anal.* Calcd for $C_{13}H_8N_2O_3S$: C, 57.35 ; H, 2.96 ; N, 10.29. Found : C, 57.40 ; H, 3.07 ; N, 10.03. IR (KBr) : 1527, 1305, 1273, 767 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 7.34 (1H, dd, J=4.1 and 5.0 Hz, H-4'), 7.71 (1H, d, J=5.0 Hz, H-5'), 7.82 (1H, dd, J=7.1 and 8.5 Hz, H-6), 7.90 (1H, dd, J=7.1 and 8.6 Hz, H-7), 8.08 (1H, d, J=4.1 Hz, H-3'), 8.75 (1H, d,

J=8.5 Hz, H-5), 8.86 (1H, s, H-3), 8.88 (1H, d, J=8.6 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 117.0 (d, C-3), 119.6 (s, C-10), 120.5 (d, C-8), 124.5 (d, C-5), 127.0 (d, C-4'), 129.1 (d, C-3'), 130.5 (d, C-6), 131.9 (d, C-7), 132.0 (d, C-5'), 138.4 (s, C-4), 140.8 (s, C-9), 142.7 (s, C-2). MS (FAB$^+$) ; 273 (M^++H).

Reaction of 2 with methyllitium in the presence of 9-fluorenone

1.14 M Methyllitium (11.2 mL, 12.6 mmol) Et_2O solution was added dropwise at -30 ℃ under nitrogen with stirring to a solution of **2** (2.0 g, 12.6 mmol) in anhydrous THF (50 mL) and then the resulting solution was further stirred at -30 ℃ for 1 h. The solution of 9-fluorenone (2.27 g, 12.6 mmol) in anhydrous THF (20 mL) was added dropwise to the reaction mixture at -30 ℃ and the resulting solution was allowed to reach rt and furthermore stirred at rt for 1 h. After the mixture was quenched with a little amount of ice, the residue from the solvents was purified by MPLC (chloroform : methanol = 30 : 1) to give 1.3 g (60%) of 2, 4-dimethylquinoline 1-oxide (**6**).[24] This compound was recrystallized from hexane to give colorless prisms, mp 122-123 ℃.

Reaction of 2, 4-dimethylquinoline 1-oxide (6) with chlorotrimethylsilane in the presence of sodium iodide and zinc

To a solution of sodium iodide (3.38 g, 22.5 mmol) and zinc dust (0.98 g, 15.0 mmol) in anhydrous MeCN (30 mL) was added dropwise a mixture of **6** (1.3 g, 7.51 mmol) and chlorotrimethylsilane (2.86 mL, 22.5 mmol) in anhydrous MeCN (30 mL) over 0.5 h during which the reaction temperature was kept at 20-30 ℃ by the exothermic reaction. The reaction mixture was then heated at 55-60 ℃ for 1 h and filtered to exclude insoluble substances. The filtrate was washed with 5% NaOH aqueous solution (100 mL) and extracted with Et_2O. The residue from Et_2O fraction was purified by MPLC (hexane : ethyl acetate = 10 : 1) to give 1.0 g (85%) of 2, 4-dimethylquinoline (**7**)[15-17] as pale yellow oil.

Reaction of quinaldine 1-oxide (8) with *n*-BuLi in the presence of 9-fluorenone

Reaction was carried out as described in General procedure for the reaction of **1** with *n*-BuLi in the presence of an oxidant but using **8** (0.5 g, 3.14 mmol) instead of **1**. The residue was purified by MPLC (hexane : ethyl acetate = 1: 1) to give 0.32 g (30%) of 2-[(9-hydroxyfluoren-9-yl)methyl]quinoline 1-oxide (**9**). This compound was recrystallized from ethyl acetate to give pale yellow prisms, mp 164-165 ℃. *Anal.* Calcd for $C_{23}H_{17}NO_2$: C, 81.40 ; H, 5.05 ; N, 4.13. Found : C, 81.31 ; H, 5.23 ; N, 3.93. IR (KBr) : 3056, 2862, 1568, 1448, 1230, 1138, 816, 771, 741 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 3.83 (2H, s, CH_2), 5.40-6.80(1H, br s, OH), 7.05 (1H, d, J=8.5 Hz, H-3), 7.19 (2H, dd, J=7.5 and J=7.8 Hz, H-2' and H-7'), 7.27 (2H, d, J=7.8 Hz, H-1' and H-8'), 7.33 (2H, dd, J=7.3 and J=7.5 Hz, H-3' and H-6'), 7.63 (2H, d, J=7.3 Hz, H-4' and H-5'), 7.73 (1H, dd, J=7.7 and J=7.9 Hz, H-6), 7.83 (1H, d, J=8.5 Hz, H-4), 7.89 (1H, dd, J=7.7 and 8.2 Hz, H-7), 7.92 (1H, d, J=7.9 Hz, H-5), 8.86 (1H, d, J=8.2 Hz, H-8). ^{13}C-NMR ($CDCl_3$) : δ 43.7 (t, CH_2), 119.9 (d, C-8), 120.0 (d, C-4' and C-5'), 123.8 (d, C-1' and C-8'), 124.8 (d, C-3), 127.7 (d, C-2' and C-7'), 128.1 (d, C-5), 128.9 (d, C-3' and C-6'), 129.0 (d, C-4 and C-6), 129.5 (s, C-10), 131.7 (d, C-7), 138.9 (s, C-8'a and C-9'a), 140.9 (s, C-9), 147.8 (s, C-2), 149.1 (s, C-4'a and C-4'b). MS (FAB$^+$) ; 340 (M^++H).

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