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t-BuOK-Mediated Oxidative C(sp^3)-H Arylation of 2-Alkylazaarenes with Nitroarenes

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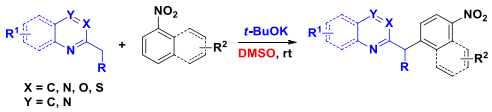
Graphic Abstract



Abstract: The first transition-metal free and regioselective C(sp^3)-H arylation of 2-alkylazaarenes with nitroarenes has been achieved *via t*-BuOK-mediated dehydrogenative C(sp^3)-C(sp^2) coupling. This reaction provides an efficient access to the biologically important and synthetically useful 2-benzyl-substituted azaarenes under mild conditions without the need of prefunctionalization of 2-alkylazaarenes or using the specialized arylating agents.

The azaarene unit is a privileged pharmacophore existing in numerous pharmacologically and biologically active compounds.[1] Among the family of these compounds, the 2-benzyl-substituted azaarenes have drawn much attention from the organic and medicinal communities owing to their biological and medicinal importance.[2] For example, compound (**A**)[2a] and compound (**B**)[2b] are used in the treatment of arrhythmia disease and inhibition of phosphodiesterase-4, respectively. In addition, some representative pharmacologically important agents incorporating this skeleton are also listed, such as P2×3 and P2×2/3 receptor antagonist (**C**),[2c] antihistamine drug (**D**),[2d] psychoactive drug (**E**)[2e] and amino acid transporter B^0AT2 inhibitor (**F**)[2f] (Figure 1).

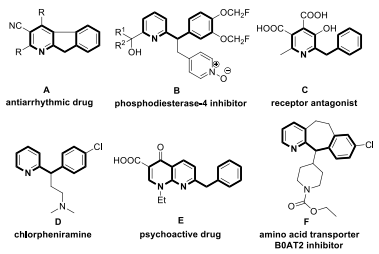


Figure 1. Representative Examples of Biologically Active Pharmaceuticals

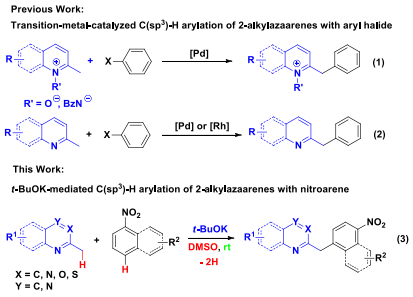
Due to the high significance of 2-benzyl-substituted azaarenes, several efficient and facile methodologies for the benzylic arylation of 2-alkylazaarenes have been developed in the last few years.[3-5] In 2008, Fagnou and Charette realized the palladium-catalyzed direct benzylic C−H arylation of 2-alkylpyridine *N*-oxides and *N*-iminopyridinium ylides with aryl halides, respectively (Scheme 1, eq 1).[4] Later, the continuous exploration of arylation of benzylic C(sp^3)−H bond of unactivated 2-alkylazaarenes was reported by Knochel, Liu, Li, Walsh and Glorius groups, etc (Scheme 1, eq 2).[5] Despite the significant progress, all these arylation reactions necessitate the use of noble transition-metals (Pd or Rh), which are not only expensive but also detrimental to the environment. Morevoer, these transition-metal-involved process are quite troublesome in final product purification, especially in the pharmaceutical industry. Lastly, the pre-functionalization of starting materials, the employment of costly ligands as well as the harsh reaction conditions also abate their practicality. Therefore, the development of transition-metal-free, environmentally benign and practical methods for the synthesis of arylated 2-alkylazaarenes has become urgent and increasingly important in organic synthesis.

Recently, *t*-BuOK-mediated C-C coupling reactions emerged as efficient and environmentally friendly alternatives to transition-metal catalyzed reactions.[6-13] The breakthrough was achieved by Itami,[8] Shi,[9] Lei and Kwong,[10] Shirakawa and Hayashi[11] groups, who independently reported the *t*-BuOK promoted biaryl coupling of aromatic compounds and haloarenes without any exogenous transition-metals. Very recently, the *t*-BuOK catalyzed direct silylation of aromatic heterocycles with hydrosilanes was discovered by Grubbs and coworkers to furnish heteroarylsilanes in a single step.[12] However, to the best of our knowledge, the facile oxidative Cross-Dehydrogenative-Coupling (CDC) of two C-H bonds from readily accessible starting

materials via C(sp^3)-H arylation has rarely been reported despite their atom-economy and high efficiency.[13]

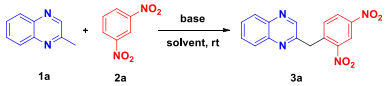
During our synthetic journey towards transition-metal free C(sp^3)−H bond functionalization of 2-alkylazaarenes, we reported the first organocatalytic reaction of 2-alkylazaarenes with carbonyl groups and double bonds.[14] As our continuous research in manipulation of 2-alkylazaarenes under transition-metal free conditions, herein we reported the *t*-BuOK-mediated CDC arylation of 2-alkylazaarenes with readily accessible and inexpensive nitroarenes[15] *via* regioselective benzylic C(sp^3)-H bond functionalization under mild conditions (Scheme 1, eq 3).

Scheme 1. C(sp^3)-H Arylation of 2-Alkylazaarenes



The model reaction was initiated between methylquinoxaline **1a** and 1,3-dinitrobenzene **2a** at room temperature. However, only trace amount of product was observed when the reaction was carried out in DMSO using LiOH as a base under air (Table 1, entry 1). To our delight, the desired cross-coupling product **3a** was obtained in moderate yield when NaOH, KOH and CsOH were used instead of LiOH (Table 1, entries 2-4). The stronger base NaH could promote this reaction to give the product in comparatively higher yield, but the best result was given with *t*-BuOK (Table 1, entries 5-6). However, the carbonates and organic bases were all invalid in this coupling reaction (Table 1, entries 7-12). Subsequently, the screening of the solvents revealed that DMSO was the irreplaceable solvent for this reaction and the other solvents failed to yield the product (entries 13-17). Thus, the optimized reaction condition was used DMSO as a solvent, employing 2.0 equiv. *t*-BuOK as a base at room temperature.

Table 1. Optimization of the Reaction Conditions[a]



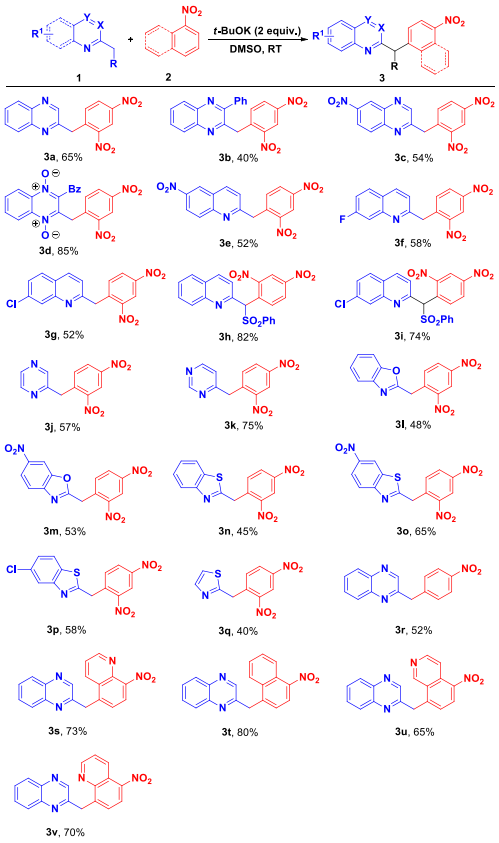
entry	base	solvent	yield (%)[b]

1	LiOH	DMSO	trace
2	NaOH	DMSO	37
3	KOH	DMSO	30
4	CsOH	DMSO	40
5	NaH	DMSO	57
6	*t*-BuOK	DMSO	65
7	K_2CO_3	DMSO	NR
8	Cs_2CO_3	DMSO	trace
9	Et_3N	DMSO	NR
10	DMAP	DMSO	NR
11	DBU	DMSO	trace
12	Morphine	DMSO	NR
13	*t*-BuOK	Toluene	NR
14	*t*-BuOK	CH_3CN	NR
15	*t*-BuOK	Dioxane	NR
16	*t*-BuOK	DCE	NR
17	*t*-BuOK	DMF	NR

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), base (2.0 equiv.) in 2 mL solvent at room temperature under air, 12 h. [b] Isolated yield after column chromatography.

Next, we continued to examine the efficiency of the different coupling partners under the optimized conditions (Table 2). Firstly, various 2-alkylazaarenes were examined to investigate the generality of this protocol. Notably, the electronically and sterically diverse substituents located at 2-alkylazaarenes manifested significant effect in terms of the efficiency of this reaction. As an example, when 2-methyl-3-phenylquinoxaline was employed as a coupling partner, only 40% yield of the expected product **3b** was obtained, which was possibly due to the steric hindrance of phenyl group. Quinoxalines with electron-withdrawing group such as nitro-group **3c** could give satisfactory yield, but electron-donating groups were not tolerated in this reaction, which might be ascribed to the decreased acidity of methyl group. Intriguingly, when steric hindered 2-methylquinoxaline *N*-oxide was subjected to this reaction, the desired product **3d** was isolated in 85% yield, which indicated that the electronic factor had stronger impact on this transformation than the steric hindrance. Subsequently, 2-methylquinoline derivatives were used instead of quinoxalines. Similarly, the substrates with electron-withdrawing groups installed on the phenyl ring of quinolines were well tolerated to furnish the desired products in good yields (**3e**-**3g**). These outcomes demonstrated the importance of electronic property of substituents on phenyl ring once more. Remarkably, comparatively higher yields (**3h**-**3i**) were observed when sulfonyl group was

Table 2. The Scope of 2-Alkylazaarenes[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), *t*-BuOK (2.0 equiv.) in 2 mL DMSO at room temperature under air, isolated yield after column chromatography.

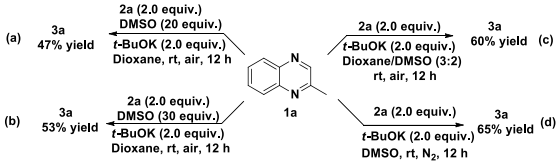
linked to methyl group which might be ascribed to the highly reactive C(sp^3)−H bond. Apart from 2-methylquinoline derivatives, 2-methylpyrazine and 4-methylpyrimidine also proceeded smoothly to give the corresponding products **3j** and **3k** in 57% and 75% yields, respectively. Interestingly, 2-methyloxazole and 2-methylthiazole proved to be amenable to the established strategy as well, and the corresponding products were obtained in good results (**3l-3q**). Especially, 2-methylbenzoxazole and 2-methylbenzothiazole with nitro-group on the phenyl ring displayed comparatively higher reactivity in this process (**3m** and **3o**). Additionally, 2-methylthiazole was also tolerated, giving rise to the desired product **3q** in 40% yield.

Subsequently, various nitroarenes were tested to further demonstrate the generality of this protocol. Satisfyingly, nitrobenzene, 1-nitronaphthalene and nitro-substituted azaarenes were all good coupling partners to deliver the arylated products in moderate to good yields (**3r-3v**). However, both electron-donating and -withdrawing substituents incorporated into nitrobenzene were not compatible with the present protocol even heating up the reaction system. It was worth

mentioning that the substitution occurred at the *para*-position of nitro group exclusively and the *ortho*-substituted products were not detected.

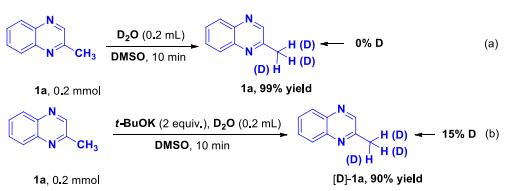
In order to illustrate the real role of DMSO in this oxidative reaction, several control experiments were performed. Although no reaction occurred in the pure dioxane solvent (Table 1, entry 15), the reaction did proceed with significant yield when 20 equiv. of DMSO was added to the dioxane (Scheme 2, eq a). Furthermore, higher yield of **3a** could be obtained along with the increase of DMSO (Scheme 2, eq b) and 60% yield of **3a** had been furnished when employing DMSO as a co-solvent (Scheme 2, eq c). These results highlighted the irreplaceable role of DMSO played in the yielding of **3a**. Moreover, when the reaction was carried out under N_2 atmosphere, good yield of **3a** still could be obtained (Scheme 2, eq d). The above control experiments implied that DMSO might act as an oxidant[16] rather than O_2 in this oxidative CDC process, which was different from the previous reports pertaining to *t*-BuOK-mediated process.[13]

Scheme 2. Control Experiments



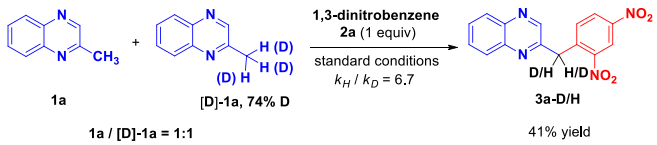
In addition, deuterium experiments were carried out to probe the effect of *t*-BuOK in the reaction (Scheme 3). As expected, no deuterium rate was observed from ^{1}H NMR when **1a** were stirred in D_2O and DMSO at room temperature (Scheme 3, eq a). However, 15% deuterium rate of methyl group was observed when the reaction mixture was performed in the presence of D_2O and *t*-BuOK (Scheme 3, eq b).[17] The deuterium experiments displayed that *t*-BuOK played an important role to deprotonate the methyl group.

Scheme 3. Deuterium Experiments



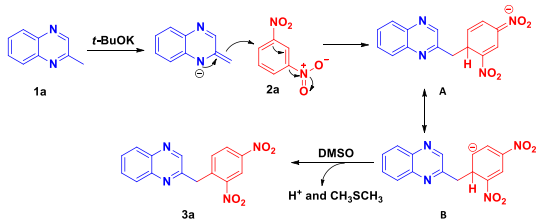
In order to further investigate the mechanism of the reaction, the KIE experiment between **1a** and [D]-**1a** in methyl group was performed (Scheme 4). The deuterium kinetic isotopic effects were determined to be 6.7, indicating that the cleavage of C(sp^3)−H bond might be involved in the rate-determining step.

Scheme 4. KIE Experiment



On the basis of the control experiments, deuterium experiments and regioselective outcome, a plausible mechanism was proposed (Scheme 5).[13b-c] Initially, an enamine anion intermediate is generated in the presence of *t*-BuOK and subsequent nucleophilic attack occurs at the *para* position of nitrobenzene. As a consequence, the anionic adduct **A** is formed, which undergoes resonance to generate intermediate **B**. Subsequently, both of them was oxidized by DMSO to yield the arylated the product **3a,** releasing Me_2S as a side product. The presence of Me_2S has been detected by crude ^{1}H NMR after the reaction ends up (See Supporting Information).

Scheme 5. A Plausible Mechanism



CONCLUSION

In summary, we have developed a *t*-BuOK-mediated oxidative cross-coupling reaction of 2-alkylazaarenes with nitroarenes under mild conditions. This is the first transition-metal-free and regioselective C(sp^3)-H arylation of 2-alkylazaarenes, providing an array of 2-benzyl-substituted azaarenes in good yields without the use of specialized arylating agents. In addition to the reaction solvent, DMSO also acts as an oxidant in this arylation process. This strategy provides an

alternative method to arylate 2-alkylazaarenes efficiently and will find applications in the future, in light of the importance of arylated 2-alkylazaarenes in natural products and pharmaceuticals.

Experimental Section

All the reactions were performed in sealed tube and monitored by TLC (0.2 mm silica gel-coated HSGF 254 plates). The products were purified by flash column chromatography (200-300 mesh silica gel) eluted with the gradient of petroleum ether and ethyl acetate. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker 500 MHz NMR spectrometer ($CDCl_3$ or DMSO-d_6 solvent). The chemical shifts were reported in parts per million (ppm), downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet) or dimethyl sulfoxide-d6 (δ 2.54, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet) or m (multiplets). The number of protons for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were reported in ppm using solvent $CDCl_3$ (δ (ppm) = 77.16 ppm) as an internal standard. HRMS analyses were performed on a Waters XEVO QTOF mass spectrometer. All the chemical reagents, unless otherwise noted, were purchased from commercial companies and used without further purification. All reactions were performed in flask and monitored by TLC (0.2 mm silica gel-coated HSGF 254 plate). The reaction mixtures were purified by flash column chromatography (200-300 mesh silica gel) eluted with the gradient of petroleum ether and ethyl acetate. The substrates **1c**, **1d**, **1h**, **1i** were prepared according to the literatures[18] and other substrates were commercially available.

General Procedure for Synthesis of 2-Benzyl Substituted Azaarenes

Potassium *tert*-butoxide (2.0 equiv., 0.4 mmol) was added to a solution of 2-methylquinoxaline **1a** (1.0 equiv., 0.2 mmol) and 1,3-dinitrobenzene **2a** (2.0 equiv., 0.4 mmol) in DMSO (2 mL) under air. The reaction mixture was stirred at room temperature for a night until **1a** was completely consumed up (TLC monitor). The reaction mixture was quenched by the addition of water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL). Dried by $MgSO_4$ and concentrated to afford the crude product. After

completion, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:15 to 1:10) to give the product **3**.

*2-(2,4-dinitrobenzyl)quinoxaline (**3a**).* 12 h, 40.4 mg, 65% yield, brown solid; mp: 66-69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.3 Hz, 1H), 8.88 (d, *J* = 5.3 Hz, 1H), 8.49 – 8.42 (m, 1H), 8.12 – 8.06 (m, 1H), 7.87 (ddd, *J* = 9.1, 5.4, 2.4 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.75 – 7.69 (m, 2H), 4.85 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 149.5, 147.3, 145.3, 142.0, 141.6, 139.6, 134.8, 130.5, 130.0, 129.4, 129.2, 127.3, 120.7, 39.7 ppm. HRMS (ESI): calcd for $C_{15}H_{10}N_4NaO_4$ $[M+Na]^+$: 333.0600, found 333.0605.

*2-(2,4-dinitrobenzyl)-3-phenylquinoxaline (**3b**).* 14 h, 30.9 mg, 40% yield, brown solid; mp: 50-52 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.4 Hz, 1H), 8.40 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.83 (dt, *J* = 4.4, 2.1 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.68 – 7.66 (m, 2H), 7.58 – 7.52 (m, 4H), 4.88 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 151.0, 149.8, 147.2, 141.1, 141.0, 140.5, 138.3, 134.7, 130.2, 129.6, 129.3, 129.1, 128.9, 128.9, 127.2, 120.6, 40.9 ppm. HRMS (ESI): calcd for $C_{21}H_{15}N_4O_4$ $[M+H]^+$: 387.1093, found 387.1099.

*2-(2,4-dinitrobenzyl)-6-nitroquinoxaline (**3c**).* 14 h, 38.3 mg, 54% yield, brown solid; mp: 148-151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.99 (t, *J* = 2.5 Hz, 2H), 8.52 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.48 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 4.92 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 147.9, 147.6, 144.3, 140.5, 138.5, 135.2, 130.8, 127.7, 125.9, 124.0, 120.9, 40.2 ppm. HRMS (ESI): calcd for $C_{15}H_{10}N_5O_6$ $[M+H]^+$: 356.0631, found 356.0629.

*2-benzoyl-3-(2,4-dinitrobenzyl)quinoxaline 1,4-dioxide (**3d**).* 14 h, 75.8 mg, 85% yield, brown solid; mp: 167-170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 4.69 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 152.1, 149.6, 147.5, 144.1, 138.3, 136.6, 135.7, 135.3, 135.1, 134.8, 132.7, 130.6, 129.9, 129.6, 129.2, 127.5, 120.7, 118.8, 39.3 ppm. HRMS (ESI): calcd for $C_{22}H_{15}N_4O_7$ $[M+H]^+$: 447.0941, found 447.0935.

*2-(2,4-dinitrobenzyl)-6-nitroquinoline (**3e**)*. 12 h, 36.8 mg, 52% yield, brown solid; mp: 178-180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.1 Hz, 1H), 8.75 (d, *J* = 2.2 Hz, 1H), 8.46 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.41 (dd, *J* = 9.3, 2.3 Hz, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 4.87 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 149.8, 147.3, 145.6, 139.7, 138.8, 134.8, 131.0, 127.3, 125.8, 124.4, 123.4, 123.3, 120.6, 42.4 ppm. HRMS (ESI): calcd for $C_{16}H_{11}N_4O_6$ $[M+H]^+$: 355.0679, found 355.0682.

*2-(2,4-dinitrobenzyl)-7-fluoroquinoline (**3f**)*. 14 h, 37.9 mg, 58% yield, brown solid; mp: 100-103 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.76 (s, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 8.34 (d, *J* = 8.2 Hz, 1H), 7.99 (dd, *J* = 16.9, 9.8 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.51 – 7.37 (m, 3H), 4.81 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO) δ 163.4, 161.5, 159.2, 149.4, 147.8, 147.7, 146.4, 140.0, 136.9, 134.8, 130.5, 130.4, 127.3, 123.7, 121.0, 119.8, 116.4, 116.2, 111.8, 111.6, 40.9 ppm. HRMS (ESI): calcd for $C_{16}H_{11}FN_3O_4$ $[M+H]^+$: 328.0734, found 328.0740.

*7-chloro-2-(2,4-dinitrobenzyl)quinoline (**3g**)*. 15 h, 35.7 mg, 52% yield, brown solid; mp: 130-133 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.77 (s, 1H), 8.52 (d, *J* = 8.1 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.55 (t, *J* = 10.0 Hz, 2H), 4.84 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO) δ 159.3, 149.4, 147.1, 146.5, 139.9, 136.9, 134.8, 134.2, 129.8, 127.4, 126.9, 126.8, 125.1, 122.0, 119.9, 40.9 ppm. HRMS (ESI): calcd for $C_{16}H_{11}ClN_3O_4$ $[M+H]^+$: 344.0438, found 344.0440.

*2-((2,4-dinitrophenyl)(phenylsulfonyl)methyl)quinoline (**3h**)*. 12 h, 73.6 mg, 82% yield, brown solid; mp: 171-173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 – 9.18 (m, 1H), 8.67 (d, *J* = 2.4 Hz, 1H), 8.53 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.83 (t, *J* = 6.7 Hz, 1H), 7.76 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.61 (qd, *J* = 8.3, 1.1 Hz, 4H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.41 (m, 2H), 6.80 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 149.9, 147.9, 147.7, 137.5, 137.3, 135.9, 134.7, 132.4, 130.4, 129.9, 129.4, 129.3, 127.9, 127.7, 127.6, 126.3, 123.5, 119.9, 69.7 ppm. HRMS (ESI): calcd for $C_{22}H_{16}N_3O_6S$ $[M+H]^+$: 450.0760, found 450.0764.

*7-chloro-2-((2,4-dinitrophenyl)(phenylsulfonyl)methyl)quinoline (**3i**)*. 12 h, 71.5 mg, 74% yield, brown solid; mp: 207-210 °C; ^{1}H NMR (500 MHz, DMSO) δ 9.02 – 8.97 (m, 1H), 8.67 (dd, *J* = 7.3, 2.3 Hz, 2H), 8.49 (d, *J* = 8.5 Hz, 1H), 8.07 (dd, *J* = 15.0, 5.3 Hz, 2H), 7.74 – 7.71 (m, 2H),

7.70 (d, *J* = 5.9 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 6.78 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO) δ 151.7, 150.0, 147.5, 147.1, 137.6, 136.7, 135.0, 135.0, 134.9, 130.6, 130.0, 129.4, 129.1, 128.4, 127.6, 126.6, 125.8, 124.3, 119.7, 68.8 ppm. HRMS (ESI): calcd for $C_{22}H_{15}ClN_3O_6S$ $[M+H]^+$: 484.0370, found 484.0375.

*2-(2,4-dinitrobenzyl)pyrazine (**3j**)*. 12 h, 29.8 mg, 57% yield, brown solid; mp: 56-58 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.4 Hz, 1H), 8.64 (d, *J* = 1.2 Hz, 1H), 8.46 – 8.42 (m, 2H), 8.41 – 8.39 (m, 1H), 7.72 (t, *J* = 6.7 Hz, 1H), 4.64 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 149.3, 147.25, 145.0, 144.3, 143.3, 139.8, 134.9, 127.4, 120.7, 38.8 ppm. HRMS (ESI): calcd for $C_{11}H_8N_4NaO_4$ $[M+Na]^+$: 283.0443, found 283.0443.

*4-(2,4-dinitrobenzyl)pyrimidine (**3k**)*. 13 h, 39 mg, 75% yield, brown solid; mp: 50-53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.90 (d, *J* = 2.3 Hz, 1H), 8.67 (d, *J* = 5.2 Hz, 1H), 8.50 – 8.38 (m, 1H), 7.73 (t, *J* = 6.7 Hz, 1H), 7.33 (d, *J* = 5.2 Hz, 1H), 4.58 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 158.9, 157.5, 149.3, 147.4, 139.0, 135.0, 127.4, 121.0, 120.7, 41.1 ppm. HRMS (ESI): calcd for $C_{11}H_9N_4O_4$ $[M+H]^+$: 261.0624, found 261.0629.

*2-(2,4-dinitrobenzyl)benzo[d]oxazole (**3l**)*. 16 h, 28.7 mg, 48% yield, brown solid; mp: 84-87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (d, *J* = 2.3 Hz, 1H), 8.46 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.61 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.49 (dd, *J* = 7.1, 1.7 Hz, 1H), 7.31 (pd, *J* = 7.4, 1.4 Hz, 2H), 4.77 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 151.0, 149.0, 147.7, 141.0, 136.7, 134.4, 127.8, 125.4, 124.7, 121.1, 120.1, 110.7, 33.2 ppm. HRMS (ESI): calcd for $C_{14}H_{10}N_3O_5$ $[M+H]^+$: 300.0620, found 300.0619.

*2-(2,4-dinitrobenzyl)-6-nitrobenzo[d]oxazole (**3m**)*. 15 h, 36.5 mg, 53% yield, brown solid; mp: 58-60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (d, *J* = 2.4 Hz, 1H), 8.54 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.42 (d, *J* = 2.1 Hz, 1H), 8.28 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 4.85 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 150.1, 148.9, 148.0, 146.1, 145.5, 135.6, 134.7, 128.1, 121.4, 120.9, 120.2, 107.4, 33.8 ppm. HRMS (ESI): calcd for $C_{14}H_9N_4O_7$ $[M+H]^+$: 345.0471, found 345.0468.

*2-(2,4-dinitrobenzyl)benzo[d]thiazole (**3n**)*. 14 h, 28.4 mg, 45% yield, brown solid; mp: 155-158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.4 Hz, 1H), 8.45 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.46 (ddd, *J* = 8.3,

7.3, 1.2 Hz, 1H), 7.38 (td, *J* = 7.7, 1.2 Hz, 1H), 4.91 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 153.0, 148.9, 147.5, 138.8, 135.5, 134.4, 127.7, 126.5, 125.6, 123.2, 121.8, 120.9, 37.6 ppm. HRMS (ESI): calcd for $C_{14}H_{10}N_3O_4S$ $[M+H]^+$: 316.0392, found 316.0383.

*2-(2,4-dinitrobenzyl)-6-nitrobenzo[d]thiazole (**3o**).* 14 h, 46.8 mg, 65% yield, brown solid; mp: 136-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* = 2.3 Hz, 1H), 8.78 (d, *J* = 2.2 Hz, 1H), 8.51 (dt, *J* = 14.0, 5.0 Hz, 1H), 8.32 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.99 (dd, *J* = 8.9, 3.3 Hz, 1H), 7.85 – 7.81 (m, 1H), 4.97 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 156.6, 148.8, 147.8, 145.3, 137.7, 135.9, 134.7, 128.0, 123.5, 122.0, 121.2, 118.3, 38.3 ppm. HRMS (ESI): calcd for $C_{14}H_9N_4O_6S$ $[M+H]^+$: 361.0243, found 361.0240.

*5-chloro-2-(2,4-dinitrobenzyl)benzo[d]thiazole (**3p**).* 14 h, 40.5 mg, 58% yield, brown solid; mp: 82-84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.73 (t, *J* = 10.2 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 4.89 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 153.7, 148.8, 147.5, 138.4, 134.5, 133.7, 132.5, 127.8, 126.1, 123.0, 122.4, 120.9, 37.7 ppm. HRMS (ESI): calcd for $C_{14}H_9ClN_3O_4S$ $[M+H]^+$: 350.0002, found 350.0006.

*2-(2,4-dinitrobenzyl)thiazole (**3q**).* 14 h, 21.2 mg, 40 yield, brown solid; mp: 45-47 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.41 (t, *J* = 9.7 Hz, 1H), 7.73 (t, *J* = 10.0 Hz, 1H), 7.68 (s, 1H), 7.29 (s, 1H), 4.81 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 148.8, 147.3, 142.9, 139.5, 134.3, 127.6, 120.8, 119.9, 36.4 ppm. HRMS (ESI): calcd for $C_{10}H_8N_3O_4S$ $[M+H]^+$: 266.0236, found 266.0230.

*2-(4-nitrobenzyl)quinoxaline (**3r**).* 14 h, 27.6 mg, 52% yield, brown solid; mp: 78-81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.19 (d, *J* = 8.7 Hz, 2H), 8.08 (ddd, *J* = 9.6, 7.9, 1.1 Hz, 2H), 7.77 (tdd, *J* = 8.5, 7.0, 1.6 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 4.48 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 147.2, 145.6, 145.5, 142.3, 141.6, 130.6, 130.1, 129.9, 129.5, 129.3, 124.2, 42.6 ppm. HRMS (ESI): calcd for $C_{15}H_{12}N_3O_2$ $[M+H]^+$: 266.0930, found 266.0926.

*2-((8-nitroquinolin-5-yl)methyl)quinoxaline (**3s**).* 12 h, 46.2 mg, 73% yield, brown solid; mp: 134-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.85 – 8.79 (m, 1H), 8.20 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.11 – 8.03 (m, 2H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.76 (pd, *J* = 7.0, 1.7 Hz, 2H), 7.63 (dd, *J* = 8.5, 4.3 Hz, 1H), 7.53 (dd, *J* = 8.3, 4.3 Hz, 1H), 4.53 (s, 2H) ppm; ^{13}C NMR

(125MHz, $CDCl_3$) δ 153.0, 152.6, 148.6, 145.7, 142.2, 141.7, 139.9, 135.8, 130.5, 130.1, 129.9, 129.9, 129.5, 129.3, 128.3, 127.8, 122.9, 38.1 ppm. HRMS (ESI): calcd for $C_{18}H_{13}N_4O_2$ $[M+H]^+$: 317.1039, found 317.1040.

*2-((4-nitronaphthalen-1-yl)methyl)quinoxaline (**3t**).* 14 h, 50.4 mg, 80% yield, brown solid; mp: 112-115 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 – 8.67 (m, 1H), 8.55 (d, *J* = 8.7 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.08 – 8.04 (m, 2H), 7.75 (dddd, *J* = 14.9, 8.4, 7.0, 1.5 Hz, 2H), 7.70 – 7.66 (m, 1H), 7.60 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 4.89 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 146.6, 145.3, 142.2, 141.5, 141.3, 132.9, 130.48, 129.8, 129.4, 129.3, 129.2, 127.9, 126.2, 125.7, 125.0, 123.9, 123.6, 41.0 ppm. HRMS (ESI): calcd for $C_{19}H_{14}N_3O_2$ $[M+H]^+$: 316.1086, found 316.1080.

*2-((5-nitroisoquinolin-8-yl)methyl)quinoxaline (**3u**).* 12 h, 41.1 mg, 65% yield, brown solid; mp: 126-129 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.80 (d, *J* = 5.3 Hz, 1H), 8.66 (t, *J* = 5.4 Hz, 1H), 8.09 – 8.04 (m, 2H), 8.02 – 7.97 (m, 1H), 7.75 – 7.69 (m, 3H), 7.64 (d, *J* = 6.1 Hz, 1H), 4.58 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 152.4, 146.4, 146.0, 145.4, 142.1, 141.6, 133.0, 131.0, 130.5, 129.9, 129.6, 129.4, 129.2, 128.0, 127.7, 114.6, 38.6 ppm. HRMS (ESI): calcd for $C_{18}H_{13}N_4O_2$ $[M+H]^+$: 317.1039, found 317.1035.

*2-((5-nitroquinolin-8-yl)methyl)quinoxaline (**3v**).* 14 h, 44.2 mg, 70% yield, brown solid; mp: 121-123 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.84 – 8.81 (m, 1H), 8.25 – 8.16 (m, 2H), 8.10 – 8.06 (m, 1H), 8.05 – 8.00 (m, 1H), 7.83 – 7.79 (m, 1H), 7.78 – 7.71 (m, 2H), 7.58 (dd, *J* = 8.7, 4.2 Hz, 1H), 4.58 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 151.8, 147.1, 147.1, 145.5, 142.2, 141.7, 133.1, 131.4, 130.6, 130.5, 129.9, 129.4, 129.3, 129.0, 123.6, 120.6, 38.4 ppm. HRMS (ESI): calcd for $C_{18}H_{13}N_4O_2$ $[M+H]^+$: 317.1039, found 317.1042.

General Procedure for Deuterium Experiment

a. 2-Methylquinoxaline **1a** (1.0 equiv., 0.2 mmol) was added in DMSO (2 mL) and D_2O (0.2 mL) under air. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was quenched by the addition of water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL). Dried by $MgSO_4$ and concentrated to afford the crude product. The deuterium rate was obtained from ^1H NMR (See Supporting Information, S2 and S3).

b. Potassium *tert*-butoxide (2.0 equiv., 0.4 mmol) was added to a solution of 2-methylquinoxaline **1a** (1.0 equiv., 0.2 mmol) in DMSO (2 mL) and D_2O (0.2 mL) under air. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was quenched by the addition of water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL). Dried by MgSO4 and concentrated to afford the crude product. The deuterium rate was obtained from ^{1}H NMR (See Supporting Information, S3 and S4).

General Procedure for KIE Experiment

Potassium *tert*-butoxide (2.0 equiv., 0.4 mmol) was added to a solution of 2-methylquinoxaline **1a** (0.2 mmol), [D]-**1a** (0.2 mmol) and 1,3-dinitrobenzene **2a** (1.0 equiv., 0.4 mmol) in DMSO (2 mL) under air. The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was quenched by the addition of water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL). Dried by $MgSO_4$ and concentrated to afford the crude product. After completion, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:15 to 1:10) to give the product **3a-**D/H. The deuterium rate was obtained from ^{1}HNMR (See Supporting Information, S5).

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Supporting Information

NMR spectra of the products. This material is available free of charge via the Internet at http: //pubs.acs.org.

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