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Direct Olefination of Fluorinated Quinoxalines via Cross-Dehydrogenative Coupling Reactions: A New Near-Infrared Probe for Mitochondria

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Abstract. A large library of 5,8-distyrylquinoxaline fluorophores was synthesized in good-to-excellent yields via a palladium-catalyzed oxidative C–H/C–H cross-coupling of electron-deficient fluorinated quinoxalines with electron-rich styrenes. The resulting quinoxaline fluorophores (Qu-Fluors) exhibited tunable color emissions with the quantum yields up to 83% and large Stokes shifts up to 6236 cm^{-1} in dichloromethane. The bioimaging performance of the Qu-Fluors was shown to have potential as near-infrared fluorescent probes for mitochondria.

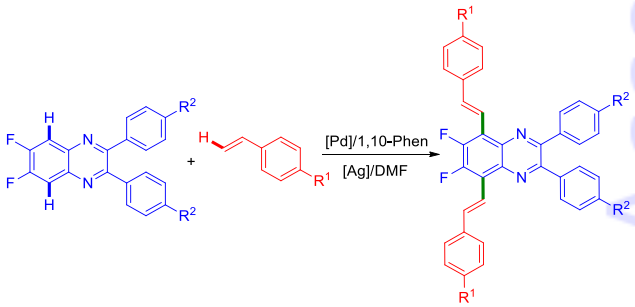
Keywords: Cross-dehydrogenative coupling; Quinoxaline; 1,4-Divinylbenzene; near-infrared probe; Mitochondrial imaging and tracking

Introduction

Electron-poor heteroarenes are key components of organic electronic and photonic materials, including dye-sensitized solar cells (DSCs),[1] polymer solar cells,[2] electron-transport materials,[3] and fluorescent material and dyes.[4] These electron-poor moieties are mostly incorporated into materials via Suzuki or Stille cross-couplings using their organometallic, halide or pseudohalide derivatives. In general, electron-poor organometallic coupling partners result in poor yields.[5] Moreover, in many cases, the synthesis of organometallic and boron derivatives of electron-poor compounds can be challenging.

Recently, C–H activation has been applied to electron-poor building blocks such as 2,1,3-benzothiadiazoles,[6] perylene diimides,[7] naphthalene diimides,[8] thieno[3,4-*c*]pyrrole-4,6-diones,[9] pyridine *N*-oxides,[10] sulphur-containing heterocycles,[11] BODIPY,[12] and polyfluorobenzenes.[13] Some of them are involved in cross-dehydrogenative coupling (CDC) strategy. CDC has recently emerged as an ideal method for the formation of carbon–carbon (C–C)[14] and carbon–heteroatom (C–X) bonds.[15] Because of the substantial benefits for organic synthesis, CDC approaches have garnered significant attention from the chemical community. As an important part of CDC, dehydrogenative Heck reaction, or Fujiwara-Moritani reaction, has attracted more and more attention in the last two decades.[16]

Scheme 1. Direct Oxidative C−H/C−H Cross-Coupling of 6,7-Difluoroquinoxalines with Various Olefins.



As a consequence of the electron-withdrawing abilities and planar structure, quinoxaline (Qu) derivatives, and in particular, 6-fluoroquinoxaline (MFQu) and 6,7-difluoroquinoxaline (DFQu) derivatives have been widely incorporated into small molecules[17] and polymers[18] for solar cells and field-effect transistors such as DSC sensitizers and emitters in organic light-emitting diodes (OLED). 1,4-

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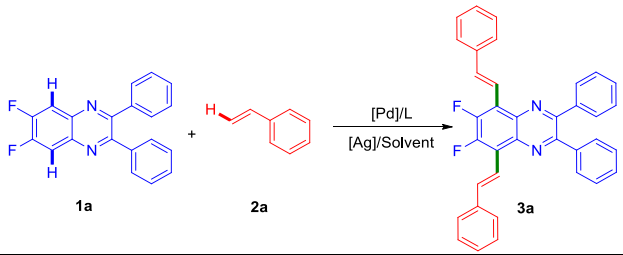
Divinylbenzene derivatives have received significant attention in recent years owing to their highly fluorescent quantum efficiency and have been incorporated into OLED and fluorescent probes.[4,19] Despite the utility of the 1,4-divinylbenzene motif, multi-step syntheses via cross-aldol condensation and Wittig reaction are often required to access 1,4-divinylbenzene derivatives. In addition, the synthesis of required aldehyde starting material suffers from harsh reaction conditions, laborious product isolation procedures, and unsatisfactory yield.

Herein, we report a double direct olefination of quinoxaline derivatives to build 5,8-distyrylquinoxalines via a highly efficient series sp^2 C–H activation CDC process. Furthermore, the properties of the resulting olefinated DFQu derivatives were characterized in yellow to near-infrared light-emitting dyes.

Results and Discussion

Table 1. Optimization of reaction conditions for the one-pot synthesis of **3a**[a].



Entry	[Pd]	[Ag]	Solvent	Yield (**3a**)[b]
1	$Pd(OAc)_2$	$AgNO_3$+ Ag_2CO_3[c]	DMF	87%
2	$Pd(OAc)_2$	Ag_2CO_3	DMF	trace
3	$Pd(OAc)_2$	$AgNO_3$	DMF	72%
4	$Pd(OAc)_2$	AgOAc	DMF	37%
5	$Pd(OAc)_2$	Ag_2O	DMF	trace
6	$Pd(OAc)_2$	AgF	DMF	89%
7	$Pd(OAc)_2$	AgTFA	DMF	52%
8	$Pd(OAc)_2$	AgTs	DMF	20%
9	$Pd(OAc)_2$	AgOTf	DMF	45%
10	$Pd(OAc)_2$	AgF	DMSO	36%
11	$Pd(OAc)_2$	AgF	DMA	40%
12	$Pd(OAc)_2$	AgF	NMP	43%
13[d]	$Pd(TFA)_2$	AgF	DMF	92%
14[d, e]	$Pd(TFA)_2$	AgF	DMF	49%
15[d, f]	$Pd(TFA)_2$	AgF	DMF	51%

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), [Pd] (5 mol%), [Ag] (5 equiv.), 1,10-Phen (10 mol%), solvent (2 mL), in a sealed tube at 130 °C under N_2 atmosphere for 12 h. [b]Yield of isolated product. [c]$AgNO_3$ (5 equiv.) and Ag_2CO_3 (5 equiv.). [d]under N_2 atmosphere for 7 h. [e]2,2'-bipyridine was used as ligand. [f]4,4'-di-*t*-butyl-2,2'-bipyridine was used as ligand. DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide, NMP = *N*-methylpyrrolidone, DMSO = dimethyl sulfoxide.

The reaction conditions were optimized using 6,7-difluoro-2,3-diphenylquinoxaline **1a** and styrene **2a** as the model substrates (Table 1). First, 5,8-distyrylquinoxaline was obtained in 87% yield by reacting **1a** with **2a** in the presence of $Pd(OAc)_2$ (5 mol%), using $AgNO_3$ (5 equiv.) and Ag_2CO_3 (5 equiv.) as the oxidants, 1,10-phenanthroline as ligand and DMF as the solvent at 130 °C (entry 1). Several types of Ag reagents including Ag_2CO_3, $AgNO_3$, AgOAc, Ag_2O, AgF, AgTFA, AgOTs, and AgOTf were screened; AgF provided the best yield (89%), while no desired product was obtained using Ag_2CO_3 and Ag_2O (Table 1, Entries 2–9). The equivalent of AgF was also investigated; 5.0 equiv of AgF resulted in 89% yield, while 4 equiv AgF significantly lowered the yield (see the Supporting Information). Furthermore, after screening several different solvents, the yield did not increase (Table 1, Entries 10–12). When $Pd(TFA)_2$ was used as the catalyst instead of $Pd(OAc)_2$, the reaction time reduced from 12 h to 7 h, and the desired product was obtained in a higher yield compared to that using $Pd(OAc)_2$ (92% and 89%, respectively) (Table 1, Entries 6 and 13). Other pyridine-containing ligands such as 2,2'-bipyridine and 4,4'-di-*t*-butyl-2,2'-bipyridine were screened; however, no detectable increase in the yield of **3a** was observed (Table 1, Entries 14 and 15).

Under the optimized reaction conditions, the substrate scope of this method was investigated (Scheme 2). Diverse styrenes **2a**–**l** (see the Supporting Information) were investigated in this reaction with 6,7-difluoro-2,3-diphenylquinoxalines **1a**–**c**, affording the corresponding products in good-to-excellent yields. The yields decreased slightly in the presence of electron-donating substituents on the aryl ring of styrene (**3a**: 92% compared to **3d**: 82%). The yield slightly decreased in the presence of electron-donating substituents on the 2,3-diphenyl of quinoxaline (**3a**: 92% compared to **3e**: 89%). In contrast, yields improved in the presence of electron-withdrawing substituents on the 2,3-diphenyl of quinoxaline (**3o**: 84% compared to **3p**: 79%). To further demonstrate the utility and versatility of this method, several 5-substituted 6,7-difluoro-2,3-diphenylquinoxaline **1d–f** were employed. As shown in Scheme 3, the desired products **4a**–**c** were obtained in good yields. It is worth mentioning that 5-bromo-6,7-difluoroquinoxaline coupled to styrene via the 8-H preferentially over the 5-Br (Scheme 3c).

With a divergent library of 5,8-distyrylquinoxalines in hand, the photophysical properties including absorptions, emissions, and quantum yields were measured (for details, see the Supporting Information). It is worth noting that these quinoxaline fluorophores, named Qu-Fluors, present color-tunable emissions (λ_{em}: 496−660 nm in CH_2Cl_2) with large Stokes shifts (up to 6236 cm^{-1} in CH_2Cl_2)

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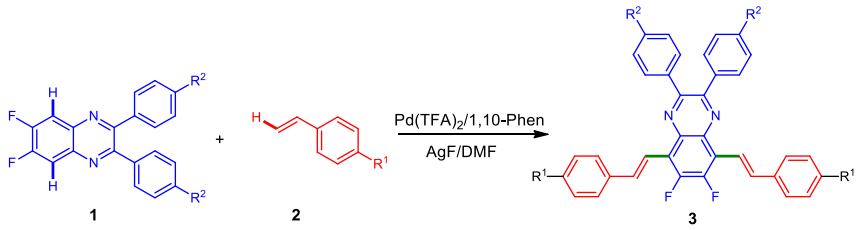
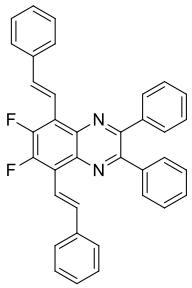
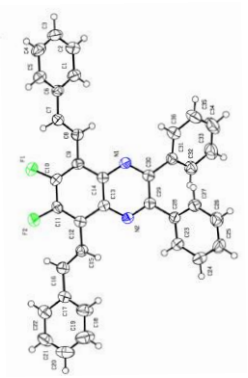
Scheme 2. Direct Oxidative C−H/C−H Cross-Coupling of 6,7-Difluoroquinoxalines with Various Olefins and Photophysical Data of the Resulting Products[a]

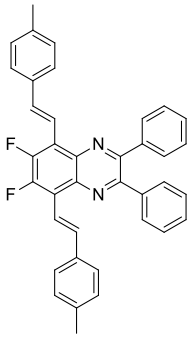




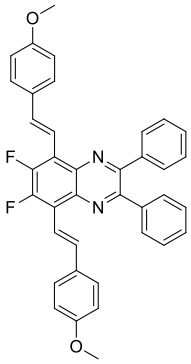
3a 92%[b]
409 nm[c]
504 nm[d] (57.55)[e]



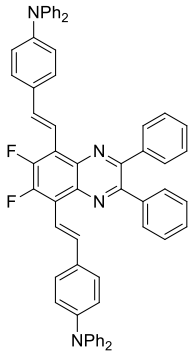
3a: X-ray
CCDC: 1524300



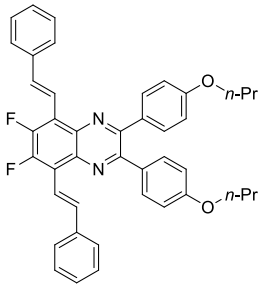
3b 88%
422 nm
518 nm (59.40)



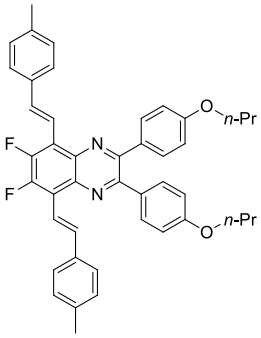
3c 85%
435 nm
544 nm (83.26)



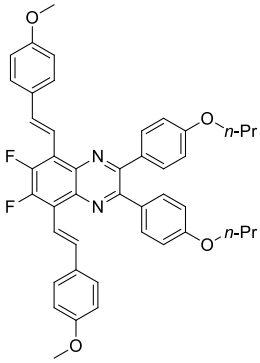
3d 82%
484 nm
616 nm (58.46)



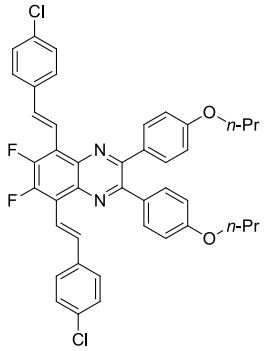
3e 89%
405nm
499 nm (37.13)



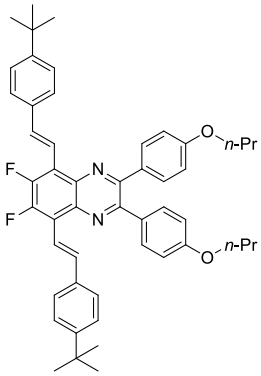
3f 86%
408 nm
512 nm (51.47)



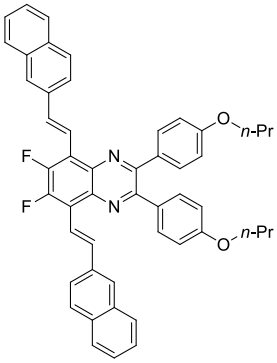
3g 85%
425 nm
535 nm (78.85)



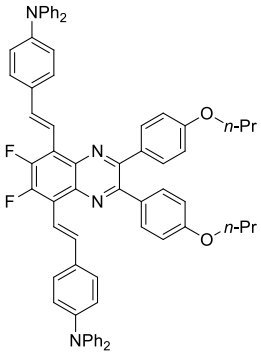
3h 87%
399 nm
496 nm (36.72)



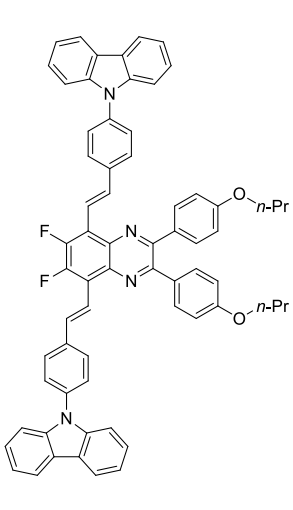
3i 81%
410 nm
512 nm (56.21)



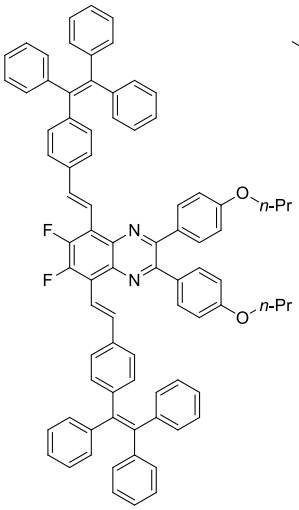
3j 82%
419 nm
512 nm (61.79)



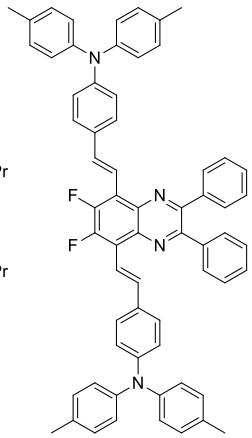
3k 83%
476 nm
605 nm (81.25)



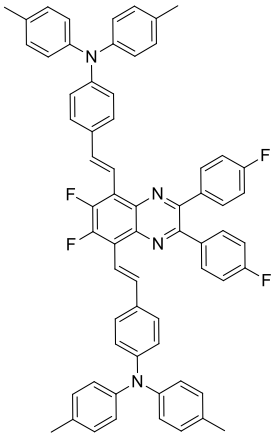
3l 84%
418 nm
530 nm (70.55)



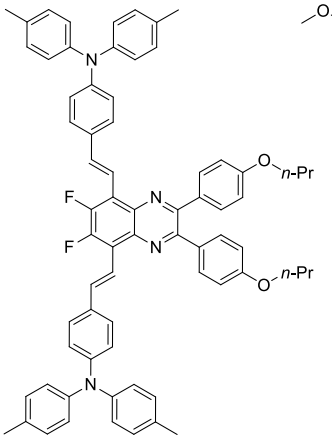
3m 83%
425 nm
541 nm (21.77)



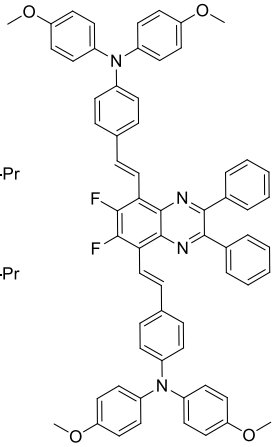
3n 81%
500 nm
631 nm (66.81)



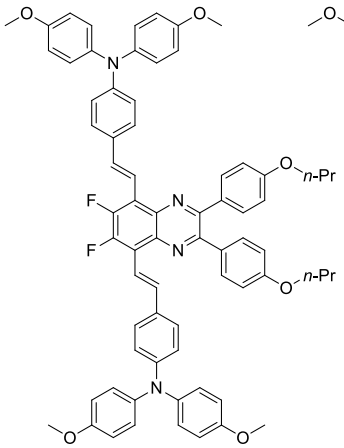
3o 84%
504 nm
638 nm (58.99)



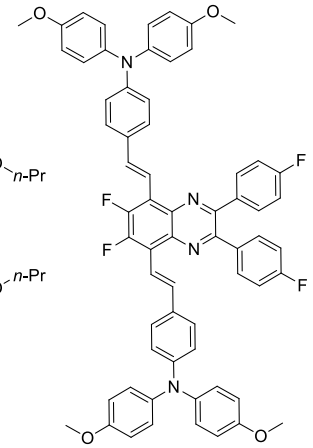
3p 79%
493 nm
622 nm (77.91)



3q 82%
506 nm
652 nm (8.09)



3r 78%
502 nm
641 nm (16.38)



3s 82%
511 nm
660 nm (4.27)

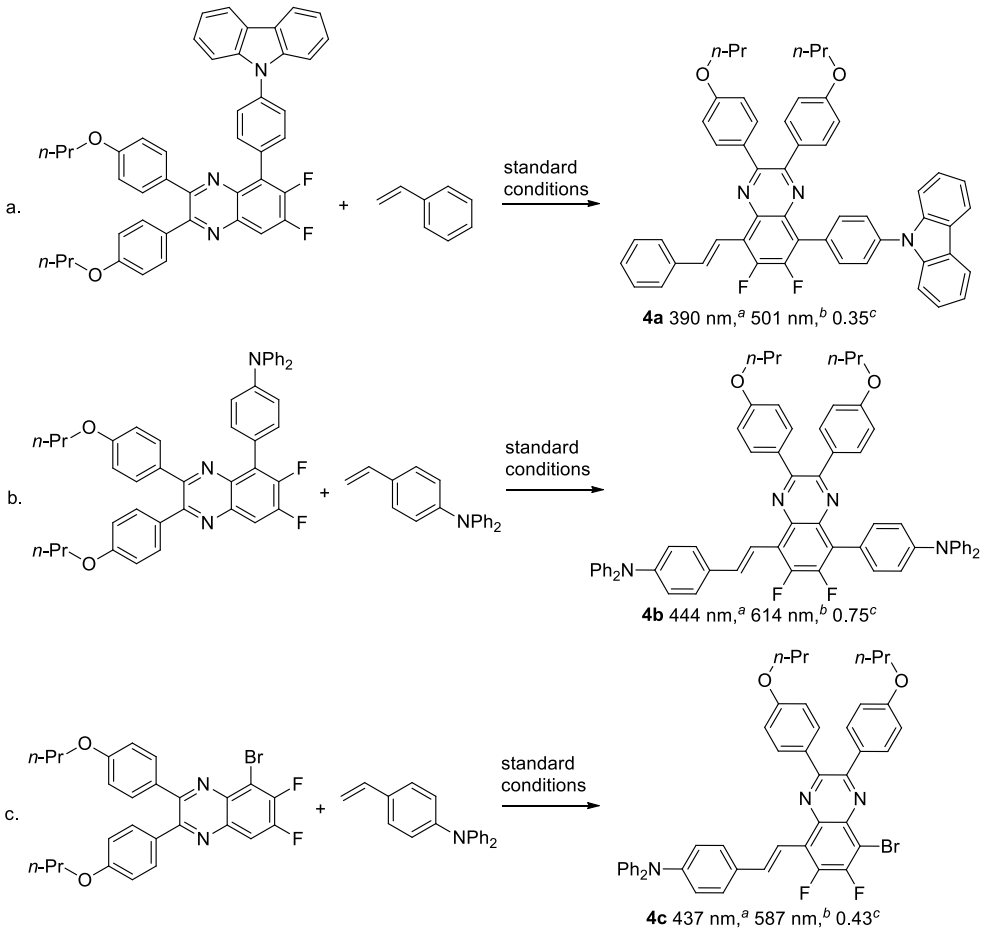
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $Pd(TFA)_2$ (5 mol%), AgF (500 mol%), 1,10-Phen (10 mol%), DMF (2 mL), in a sealed tube at 130 °C under N_2 atmosphere for 7 h. [b]Isolated yield. [c]Absorption maximum in CH_2Cl_2 at 10.0 μM. [d]Emission maximum in CH_2Cl_2 at 10.0 μM. [e]Absolute quantum yield in CH_2Cl_2 at 10.0 μM determined with an integrating sphere system.

and high fluorescence quantum yields (up to 0.83 in CH_2Cl_2).

To clarify the fluorescence-structure relationship of Qu-Fluors, the representative data are listed in Tables 2 and 3. First, as listed in Table 2, the emission wavelengths and quantum yields of Qu-Fluors significantly depend on the styrene substituent (R^1). The quantum yields increased significantly (from 0.37 to 0.81) in the presence of electron-donating substituents on the aryl ring of styrene except compound **3d**. In addition, an increase in the electron-donating ability from Cl (**3h**) to 4-diphenylamino (**3k**) enables bathochromic shifts of emission wavelengths from 496 to 605 nm. Second, the quantum yields of Qu-Fluors also significantly depend on the substituent (R^2) on the 2,3-diphenyl of quinoxaline (Table 3). Slightly higher quantum yields were obtained in the presence of electron-donating substituents on the 2,3-diphenyl of quinoxaline (**3o**: 0.59 compared to **3p**: 0.78). An increase in the electron-withdrawing ability from *n*-propoxy (**3p** and **3r**) to F (**3o** and **3s**) enables bathochromic shifts of emission wavelengths from 622 and 641 to 638 and 660 nm, respectively.

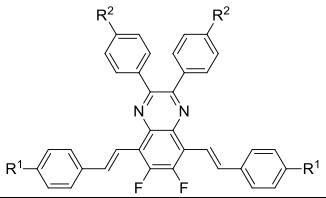
Near-infrared/far red (NIR/FR) fluorophores (λ_{em} = 650–900 nm) play a crucial role in fluorescent bioimaging owing to their low light scattering, minimal photodamage, and deep tissue penetration; therefore, minimizing background interference and improving image sensitivity.[19] With two near-

Scheme 3. Direct Oxidative C−H/C−H Cross-Coupling of 5-Substituted 6,7-Difluoroquinoxalines with Various Olefins and Photophysical Data of the Resulting Products.



[a]Absorption maximum in CH_2Cl_2 at 10.0 μM. [b]Emission maximum in CH_2Cl_2 at 10.0 μM. [c]Absolute quantum yield in CH_2Cl_2 at 10.0 μM.

Table 2. Effect of Substituents (R^1 and R^2) on the Photophysical Property of Qu-Fluors[a]



Compd	R^1	R^2	λ_{abs} (nm)	λ_{em} (nm)	Stokes shift (cm^{-1})	Φ_F
3a	H	H	409	504	4609	0.58
3b	CH_3	H	422	518	4392	0.59
3c	OCH_3	H	435	544	4606	0.83
3e	H	*n*-PrO	405	499	4651	0.37
3f	CH3	*n*-PrO	408	512	4979	0.52
3g	OCH_3	*n*-PrO	425	535	4838	0.79
3h	Cl	*n*-PrO	399	496	4901	0.37
3i	*t*-Butyl	*n*-PrO	410	512	4859	0.56
3j	Naphthalen-2-yl	*n*-PrO	419	512	4335	0.62
3k	NPh_2	*n*-PrO	476	605	4479	0.81
3l	Carbazol-9-yl	*n*-PrO	418	530	5056	0.71

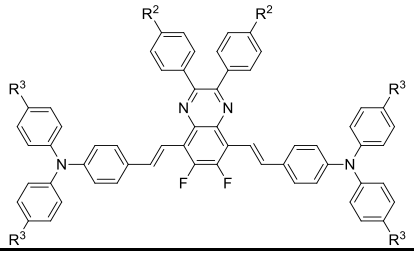
[a]Photophysical properties in CH_2Cl_2 at 10.0 μM.

infrared emission fluorescence materials (**3q** and **3s**) in hand, **3s** was explored for the confocal fluorescent imaging of SiHa cell. Living SiHa cells were cultivated with **3s** (2 μM) in minimum eagle's medium (DMEM, containing 10% of fetal bovine serum (FBS), 100 IU mL^{-1} of penicillin, and 100 mg mL^{-1} of streptomycin) for 30 min at 37 °C and then washed twice with phosphate buffered solution. To our delight, **3s** successfully penetrated the cell membranes and labeled SiHa cells with a bright red luminescence, displaying strong fluorescence in cytosol (Figure 1a). The emission in cytosol sketched filament morphologies, indicating that **3s** may concentrate in mitochondria. In addition, **3s** showed a large Stokes shift of 149 nm, which can be used to avoid imaging interference between excitation and emission.

In almost all eukaryotic cells, mitochondria play vital roles as the energy factories of eukaryotic cells[21] and are also involved in signaling, controlling the cell cycle, and regulating metabolism, cellular differentiation, cell growth and death.[22] Consequently, fluorescent probes that can selectively illuminate cellular mitochondria are in high demand for monitoring the morphological changes and study

10.1002/adsc.201700237

Table 3. Effect of Substituents (R^2 and R^3) on the Photophysical Property of Qu-Fluors[a]



Compd	R^3	R^2	λ_{abs} (nm)	λ_{em} (nm)	Stokes shift (cm^{-1})	Φ_F
3d	H	H	484	616	4427	0.58
3k	H	*n*-PrO	476	605	4479	0.81
3n	CH_3	H	500	631	4152	0.67
3p	CH_3	*n*-PrO	493	622	4207	0.78
3o	CH_3	F	504	638	4167	0.59
3q	OCH_3	H	506	652	4425	0.08
3r	OCH_3	*n*-PrO	502	641	4320	0.16
3s	OCH_3	F	511	660	4417	0.04

[a]Photophysical properties in CH_2Cl_2 at 10.0 μM.

important cellular processes.[23] Recently, many mitochondria-targeted fluorescent probes have been developed.[24] To further explore the imaging potential of **3s**, co-staining experiment with SiHa cells using a mitochondria-specific dye, MitoTracker Green FM (MTG), was performed. The morphological observations showed that **3s** might be localized in mitochondria. Notably, the images from channel 1 (red luminescence from **3s**) and channel 2 (green luminescence from MTG) overlapped very well (Figure 2). The Pearson's coefficient (R_r = 0.94) was calculated using Image-Pro Plus software, clearly demonstrating the specific accumulation of **3s** into the mitochondria of living cells.

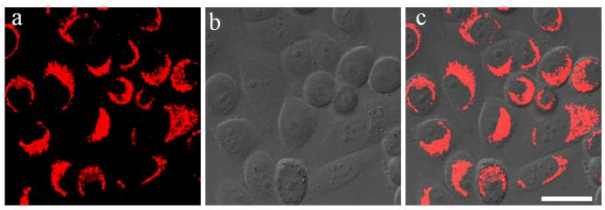


Figure 1. (a) Confocal fluorescence images of SiHa cells cultured with **3s** (2.0 μM, 30 min) (λ_{ex} = 561 nm, λ_{em} =580−700 nm); (b) DIC; (c) merged image of (a and b), bar = 20 μm

Mitochondrial matrix is well known to supply a high-viscosity environment; therefore, we speculated that **3s** can target mitochondria owing to its specific selectivity to viscosity. Thus, the emission spectra of **3s** in various viscosity solvents were recorded, as shown in Figure 3, and the mix solvent of glycerinum (Gly) and dimethyl formamide (DMF) was chosen to simulate viscosity environment. As shown in Figure 3, the emission intensities of **3s** obviously increased with increasing volume fraction of Gly. Thus, **3s** could response to high-viscosity environment, probably ascribed to the fact that certain sticky mitochondria matrix restricted intramolecular rotation of **3s** and further enhanced its fluorescence in mitochondria of SiHa cells, fulfilling our speculation. Moreover, we think that this property of **3s** would benefit its application in improving signal-to-noise ratio.[24d]

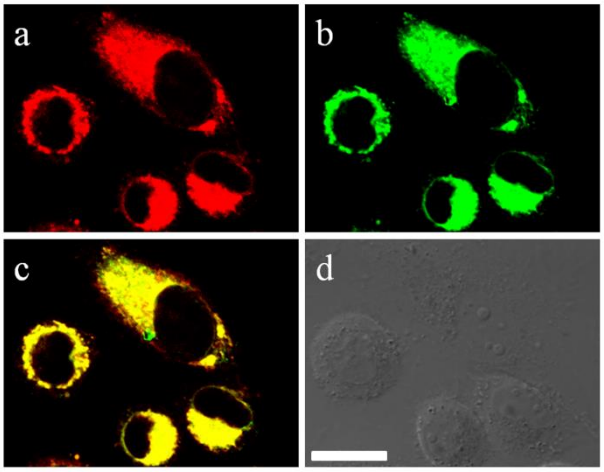


Figure 2. (a) fluorescent image of SiHa cells stained with 3s (2.0 μM, 30 min) (λ_{ex} = 561 nm, λ_{em} = 580-700nm); (b) fluorescent image of SiHa cells stained with MTG (200 nM, 30 min) (λ_{ex} = 473 nm, λ_{em} =500-550nm); (c) merged image of (a and b); (d):DIC, bar = 20 μm

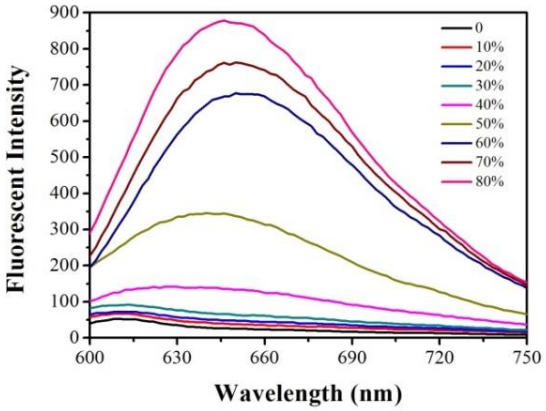


Figure 3. FL spectra of **3s** (25 μM) in DMF/Gly mixtures (λ_{ex} = 500 nm, Gly fraction Vol%)

Conclusion

In conclusion, we developed the first palladium-catalyzed direct olefination of DFQus via a cross-dehydrogenative coupling reaction. A series of symmetrical and unsymmetrical DFQu-olefin

structures were obtained in good to excellent yields under mild reaction conditions with excellent functional group compatibility. The directly coupled fluorophores, named Qu-Fluors, exhibited tunable color emissions with good quantum yields and large Stokes shifts. *In vitro* imaging was explored to demonstrate the potential of the novel Qu-Fluors as the NIR FL probes for bioimaging applications. This versatile methodology offers valuable opportunities for further studies into the properties of quinoxaline motif in optoelectronic materials.

Experimental Section

General information

6,7-difluoro-2,3-diphenylquinoxaline and styrene were prepared according to literature procedures.[1-5] Other reagents were commercially available and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC). ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz, 400 MHz, and 500 MHz, using $CDCl_3$, CD_2Cl_2 and DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were run in the same instrument at 75 MHz, 100 MHz, and 125 MHz. HRMS spectra were determined on a Q-TOF6510 spectrograph (Agilent). UV-vis absorption spectra and fluorescence spectra measurements were performed with a Hitachi UV-4100 spectrometer and a Hitachi F-7000 spectrometer, respectively. The double-stranded DNA-specific dye Hoechst 33342 and MTG were purchased from Molecular Probes. PBS buffer solution: 10 mM NaCl, $Na_2HPO_4{\cdot}12H_2O$, $NaH_2PO_4{\cdot}2H_2O$, pH = 7.40. Viability of the cells was assayed using cell proliferation Kit I with the absorbance of 492 nm being detected using a PerkinElmer Victor plate reader. Mitochondrial fluorescence detection was carried out with flow cytometry (ImageStreamX MarkII). The data were obtained using INSPIRE software and analyzed using IDEAS Application v6.0 software.

Typical Procedure for the Synthesis of Compounds 3: A sealable tube (10 mL) was charged with $Pd(TFA)_2$ (3.4 mg, 0.01 mmol), AgF (126 mg, 1.00 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), compound **1** (0.20 mmol) and compound **2** (0.80 mmol). DMF (2 mL) was added and the tube evacuated and backfilled with N_2 three times. The mixture was gradually heated to 130 °C for 7 h, cooled to room temperature. CH_2Cl_2 (60 mL) was added to dilute the mixture. The combined organics were washed with saturated brine (25 mL), dried over $MgSO_4$, subjected to filtration, and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with CH_2Cl_2/hexane to deliver the compound **3**.

6,7-Difluoro-2,3-diphenyl-5,8-di((E)-styryl)quinoxaline 3a: A purification by flash chromatography in petroleum ether : dichloromethane = 5 : 1 gave the title compound as a yellow-green solid (96 mg, 92%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.20 (2H, J = 17.1 Hz, d), 8.02 (2H, J =17.1 Hz, d), 7.67 (8H, m), 7.46 (12H, m); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 152.85 ($^{1,2}J_{C,F}$ = 256.5, 18.0 Hz, dd), 152.03, 139.32, 138.19, 137.31 ($^{2,3}J_{C,F}$ = 37.5, 6.0 Hz, dd), 131.37, 129.36, 129.15, 128.79, 128.63, 127.32, 121.02 ($^{3,4}J_{C,F}$ = 6.0, 3.75 Hz, dd), 117.97; ^{19}F NMR (282 MHz, CD_2Cl_2): δ -133.05 (s); HRMS calcd for $C_{36}H_{24}F_2N_2$ $(M+H)^+$ 523.19803; found: 523.1981.

Typical Procedure for the Synthesis of Compounds 4: A sealable tube (10 mL) was charged with $Pd(TFA)_2$ (3.4 mg, 0.01 mmol), AgF (63 mg, 0.50 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), compound **1** (0.20 mmol) and compound **2** (0.40 mmol). DMF (2 mL) was added and the tube evacuated and backfilled with N_2 three times. The mixture was gradually heated to 130 °C for 7 h, cooled to room temperature. CH_2Cl_2 (60 mL) was added to dilute the mixture. The combined organics were washed with saturated brine (25 mL), dried over $MgSO_4$, subjected to filtration, and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with CH_2Cl_2/hexane to deliver the compound **4**.

(*E*)-4-(6,7-Difluoro-2,3-bis(4-propoxyphenyl)-8-styryl-quinoxalin-5-yl)-*N*,*N*-diphenylaniline 4a: A purification by flash chromatography in petroleum ether : dichloromethane = 5 : 1 gave the title compound as a yellow-green solid (132 mg, 85%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.20 (6H, m), 7.81 (2H, J = 8.4 Hz, d), 7.73 (6H, m), 7.54 (6H, m), 7.36 (3H, m), 6.95 (2H, m), 6.83 (2H, m), 4.01 (2H, t), 3.94 (4H, t), 1.90 (4H, m), 1.09(6H, m); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 160.18, 160.09, 151.71, 151.08, 140.66, 137.79, 137.59, 137.06, 136.93, 136.11, 135.99, 133.27, 131.29, 131.26, 131.18, 130.87, 129.72, 128.78, 128.43, 128.23, 126.95, 125.99, 123.86, 123.75, 123.47, 121.40, 120.21, 120.08, 117.61, 114.27, 114.12, 109.96, 69.62, 69.55, 22.56, 22.50, 10.24, 10.18; ^{19}F NMR (282 MHz, $CDCl_3$): δ -132.44 (1F, J = 19.8 Hz, d), -134.59 (1F, J = 19.8 Hz, d); HRMS calcd for $C_{52}H_{41}F_2N_3O_2$ $(M+H)^+$ 778.32396; found: 778.3239.

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