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Visible-Light-Mediated Synthesis of Pyrazines from Vinyl Azides Utilizing a Photocascade Process

Asik Hossain
Santosh K. Pagire
Oliver Reiser*

Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, 93053 Regensburg, Germany
oliver.reiser@chemie.uni-regensburg.de

Dedicated to Professor Albert Padwa on the occasion of his 80th birthday

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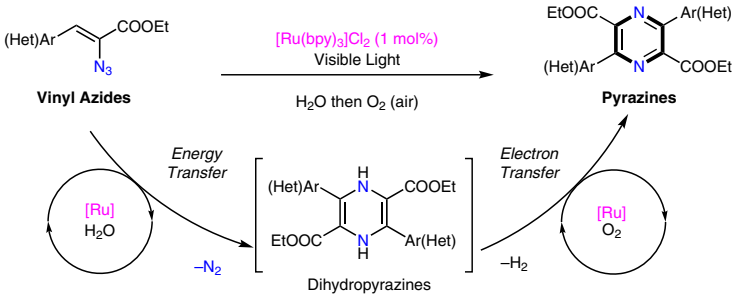

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Abstract A convenient method for the synthesis of substituted pyrazines from vinyl azides has been developed. This method is enabled by a dual-energy and electron-transfer strategy by visible-light photocatalysis. Initially, vinyl azides are activated by a triplet sensitization process from an excited ruthenium photocatalyst in the presence of water to form dihydropyrazines, followed by a single-electron-transfer (SET) process under oxygen (air) atmosphere that leads to the tetrasubstituted pyrazines in good to excellent yields.

Keywords visible-light photocatalysis, pyrazines, synthetic methods, vinyl azides, photocascade process

Visible-light photocatalysis has been widely employed in challenging organic transformations.[1,2] In principle, the photocatalyst gets excited by visible light, which subsequently activates a colorless organic substrate either by direct energy transfer (ET)[3,4] or by single-electron-transfer (SET)[5,6] processes. By the independent use of these two activation modes, a great number of synthetic transformations have been established from various scientific groups including our own.[7] However, the utilization of ET followed by SET modes aiming at photocascade processes is not well established.[8,9] A first example was reported by Xiao and coworkers[9] in the reaction between vinyl azides and alkynes to obtain polysubstituted pyrroles. Similarly, we have also combined ET- and SET-based pathways for the activation of vinyl bromides in the presence of oxygen.[10] As a further example for employing the same photocatalyst in different reaction modes, we report here the visible-light-photocatalyzed transformation of vinyl azides into pyrazines, which are important nitrogen-containing heterocycles with interesting biological activities and great utility as precursors in organic synthesis.[11–13]

For example, the synthesis of dragmacidin A[12] and 2,5-bis(6′-bromo-3′-indolyl)piperazine[11] (Figure 1) is achieved from the corresponding symmetrical pyrazines as key intermediates.[14]

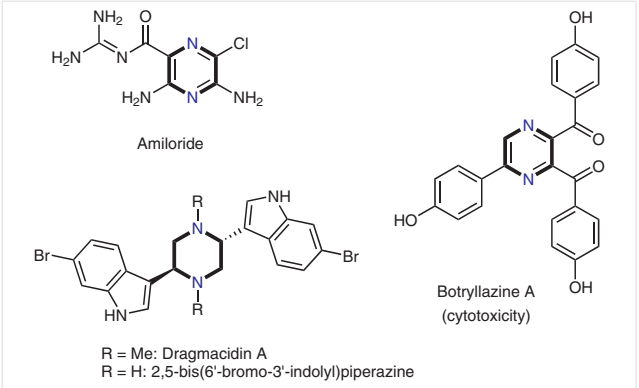
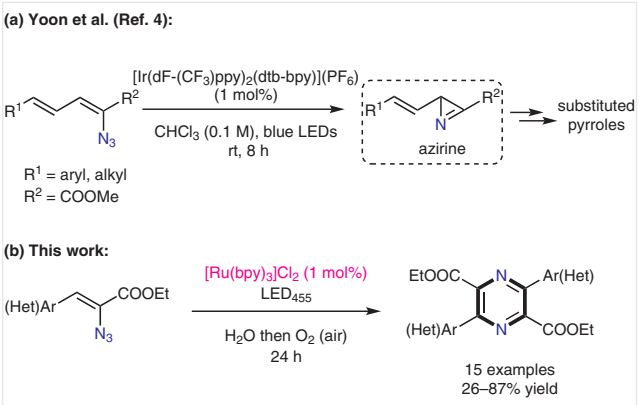


Figure 1 Representative biologically active pyrazine derivatives

Various methods are known for the synthesis of pyrazines,[15] however, their synthesis from vinyl azides by thermal[16] or photochemical[17] approaches is not well-explored, despite the fact that the latter are well-known precursors for the synthesis of N-containing heterocycles such as indoles,[16] pyrroles,[17] pyridines,[18] phenanthridines,[19] and isoquinolines[20] for decades.[21]

Recently, Yoon and coworkers reported the photocatalytic, visible-light sensitization of dienylazides to azirines as key intermediates, which further rearrange to substituted pyrroles (Scheme 1a, top).[4] In this context, we report here a conceptually different strategy for the synthesis of pyrazines from readily accessible vinyl azides (Scheme 1b, bottom).



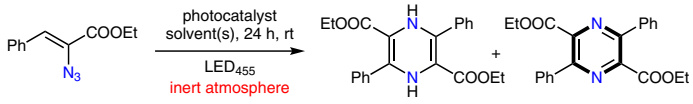
Scheme 1 Photochemical activation of vinyl azides

We began our studies by exposing vinyl azide **2a**, being readily available from the corresponding ethyl cinnamate **4a** (see Supporting Information) to blue light (λ_{max} = 455 nm) employing 1 mol% of typical photocatalysts:[2] Using $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ ($E_{Ir(IV)/Ir(III)^*}$ –0.89 V vs. SCE; *T* = 2300 ns; dF = difluoro, ppy = 2-phenylpyridine, dtb-bpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl) in an acetonitrile/water (4:1) mixture at room temperature under inert atmosphere, we were pleased to observe the formation of a mixture of dihydropyrazine **3a′** and the desired pyrazine **3a** (**3a′/3a** = 6:1) in an overall isolated yield of 85% after 24 hours (Table 1, entry 1). Reducing the amount of water resulted in inferior yields (see Supporting Information for details).

Similarly, other known photocatalysts such as *fac*-$[Ir(ppy)_3]$ ($E_{Ir(IV)/Ir(III)^*}$ –1.73 V vs. SCE; *T* = 1900 ns; ppy = 2-phenylpyridine), $[Ir(dtbbpy)(ppy)_2]PF_6$ ($E_{Ir(IV)/Ir(III)^*}$ = –0.96 V vs. SCE; *T* = 557 ns; ppy = 2-phenylpyridine, dtb-bpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl), $[Ru(bpy)_3]Cl_2$ ($E_{Ru(III)/Ru(II)^*}$ = –0.81 V vs. SCE; *T* = 1100 ns; bpy = 2,2′-bipyridine), Na_2-Eosin Y ($E_{EY^{\bullet+}/EY^*}$ = –1.11 V vs. SCE, *T* = 24000 ns),[22] also provide comparable yields of **3a′** and **3a** (Table 1, entries 2–4), while $[Cu(dap)_2]Cl$ ($E_{Cu(II)/Cu(I)^*}$ = –1.43 V vs. SCE; *T*= 270 ns; dap = 2,9-bis(*p*-anisyl)-1,10-phenanthroline, Table 1, entry 5) did not promote the transformation. This might be due to the short excited state lifetime (*T* = 270 ns)[23] of $[Cu(dap)_2]Cl$ which does not allow an efficient ET from excited state $Cu(I)^*$ to the substrate and makes at the same time the photocatalytic activation of the vinyl azides by SET unlikely, given the high efficiency of SET-triggered Atom Transfer Radical Addition (ATRA) reactions by $[Cu(dap)_2]Cl$.[5,24] Finally, a series of control experiments (Table 1, entries 7–9) indicated the necessity of light, photocatalyst, and water.

Aiming at an operationally simple procedure towards pyrazines **3**, we were looking for a suitable oxidant for the dehydrogenation of dihydropyrazines **3′**. Indeed, carrying out the photoreaction of **2a** under oxygen atmosphere (open to air), thus utilizing oxygen as the terminal oxidant,[25] and employing 1 mol% $[Ru(bpy)_3]Cl_2$ gave rise to the desired product **3a** in 61% yield (Table 2, entry 1) along with 15% benzaldehyde as a byproduct. In contrast, iridium photocatalysts (Table 2, entries 3–5) or Na_2-Eosin Y (1 mol%, Table 2, entry 6) provided **3a** in lower amounts, however, the

Table 1 Reaction Optimization under Nitrogen Atmosphere[a]

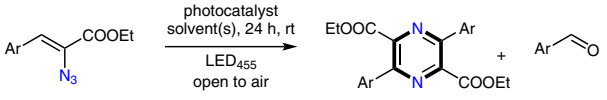


Entry	Photocatalyst (1 mol%)	Solvent(s)	Yield of **3a**′ + **3a** (%)[b]
1	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	MeCN/H_2O (4:1)	85 (6:1)
2	$[Ir(ppy)_3]$	MeCN/H_2O (4:1)	77 (7:1)
3	$[Ir(dtbbpy)(ppy)_2]PF_6$	MeCN/H_2O (4:1)	80 (6:1)
4	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	79 (8:1)
5	$[Cu(dap)_2]Cl$, 535 nm	MeCN/H_2O (4:1)	NR[f]
6	Na_2-Eosin Y, 535 nm	MeCN/H_2O (4:1)	77 (8:1)
7[c]	none	MeCN/H_2O (4:1)	<15
8[d]	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	NR
9[e]	$[Ru(bpy)_3]Cl_2$	dry MeCN	ND[g]

[a] Reaction conditions: Substrate **2a** (0.5 mmol), photocatalyst (1 mol%), N_2, MeCN (1.60 mL), H_2O (0.40 mL), 24 h, rt, LED_{455}.
[b] Isolated yields.
[c] Without a photocatalyst.
[d] Dark reaction.
[e] No water.
[f] NR: no reaction.
[g] ND: not detected.

undesired benzaldehyde was obtained in larger quantities. In line with our mechanistic proposal (Figure 2), the addition of MeOH instead of water does not provide the desired product (Table 2, entry 6). Moreover, the use of an oxygen balloon (excess of oxygen) decreases the yield to 34% and the undesired benzaldehyde is obtained in a major amount (Table 2, entry 8). Further optimization studies revealed that the addition of other oxidant such as $K_2S_2O_8$ does not provide any product (Table 2, entry 9), indicating the importance of oxygen. Other additives such as Na_2CO_3 or trifluoroacetic acid, which were assumed to promote the opening of the azirine intermediate (Figure 2), also have negative effect on the reaction (Table 2, entries 10 and 11) and gave complex mixtures.

Table 2 Reaction Optimization under Oxygen Atmosphere[a]



2a (Ar = Ph)
2e (Ar = *o*-MeOC$_6$H$_4$)

3 **1**

Entry	Photocatalyst (1 mol%)	Solvent(s)	Yield of **3** + (**1**) (%)[b]
1	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	61 (15)[c]
2[d]	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	52 (31)
3	$[Ir(ppy)_3]$	MeCN/H_2O (4:1)	53 (23)
4	$[Ir(dtbbpy)(ppy)_2]PF_6$	MeCN/H_2O (4:1)	40 (35)
5	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	MeCN/H_2O (4:1)	5 (65)
6	Na_2-Eosin Y, 535 nm	MeCN/H_2O (4:1)	42 (36)
7	$[Ru(bpy)_3]Cl_2$	MeCN/MeOH (4:1)	ND[i]
8[e]	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	34 (45)
9[f]	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	ND
10[g]	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	ND
11[h]	$[Ru(bpy)_3]Cl_2$	MeCN/H_2O (4:1)	ND

[a] Reaction conditions: Substrate **2a** (0.5 mmol), photocatalyst (1 mol%), N_2, MeCN (1.60 mL), H_2O/MeOH (0.40 mL), 24 h, rt, LED_{455}.
[b] Isolated yields.
[c] Yield of aldehyde in parenthesis.
[d] **2e** was employed instead of **2a**.
[e] With additional oxygen balloon.
[f] $K_2S_2O_8$(1 equiv).
[g] Na_2CO_3(1 equiv).
[h] Trifluoroacetic acid (1 equiv).
[i] ND: not detected. For detailed optimization, see Supporting Information.

Employing the optimized reaction conditions (Table 2, entry 1) we explored the scope of the reaction. Since $[Ru(bpy)_3]Cl_2$ gave rise to comparatively low amounts of the undesired aldehyde-cleavage products under aerobic conditions, we modified slightly the protocol by simply degassing the reaction mixture via nitrogen bubbling, but then running the reaction open to air. The benefit of this modification was especially apparent for vinyl azides bearing electron-donating arene substituents such as **2e** (cf. Table 2, entry 2 and Scheme 2), giving rise to significantly increased yield and complete suppression of aldehyde cleavage products. A wide range of functional groups on the aryl moiety of the vinyl azides **2** are tolerated well, including weak and strong electron-donating and electron-withdrawing groups, *ortho* and extended π-substituents (Scheme 2). In only two cases aldehyde byproducts (**1a** (15%) and **1d** (18%) were observed in significant amounts. It should be pointed out that all our attempts to separate the two reaction steps, that is, running the transformation of **2a/d** to **3a/d′** under nitrogen atmosphere, followed by irradiation of **3a/d′** under aerobic atmosphere did not suppress the formation of **1a** or **1d**. Switching the aryl group to thiophene (**3m**) was met with only limited success, and the replacement of the ester by keto groups did not result in any product formation (**3n** and **3o**).

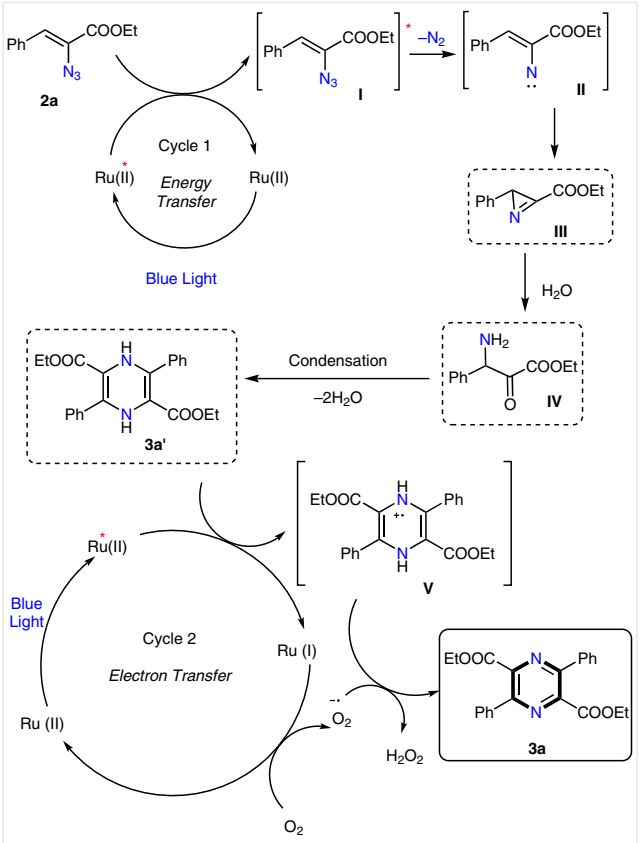
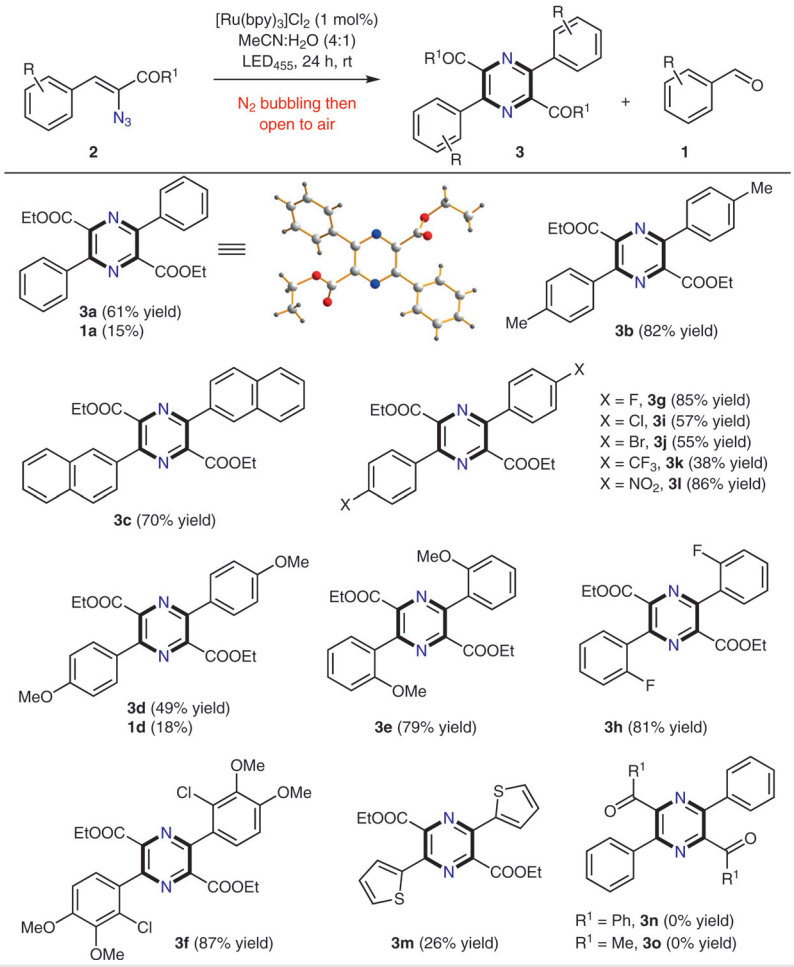
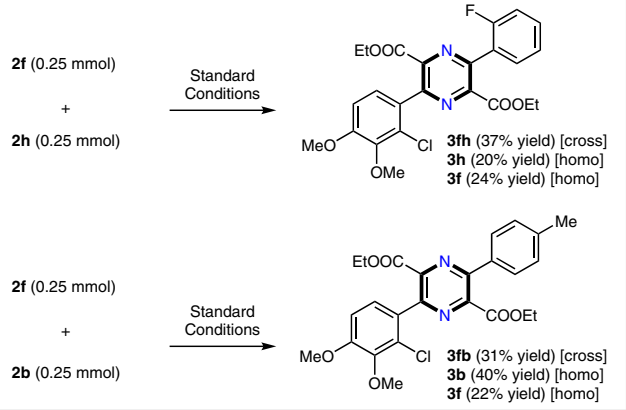


Figure 2 Plausible reaction mechanism for pyrazine formation from vinyl azide

Moreover, the dimerization reaction by employing two different vinyl azides in equimolar amounts (Scheme 3) is possible. However, the homo- and cross-coupled products are all formed with a slight preference for the sterically less



Scheme 2 Substrate scope: substrate **2** (0.50 mmol), $[Ru(bpy)_3]Cl_2$ (1 mol%), MeCN (1.60 mL), water (0.40 mL), rt, LED_{455}, 24 h



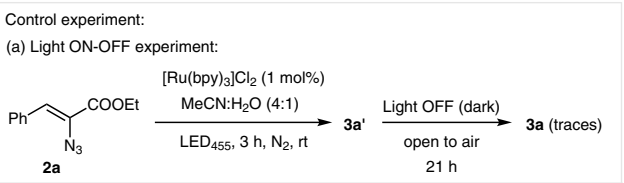
Scheme 3 Cross-coupling between two vinyl azides

encumbered pyrazines. Hence this method allows to accessing unsymmetrical pyrazines from readily available vinyl azides, but only in moderate yields.

Following the mechanistic rationale put forward by Yoon and co-workers for the photochemical activation of dienylazides,[4] the reaction sequence to 1,4-pyrazines developed here starts with an ET from the excited Ru(II)* photocatalyst to vinyl azide **2** (Figure 2). As a result, **2** is converted into the triplet energy state **I**, which upon loss of nitrogen forms a reactive nitrene intermediate **II** that further rearranges to the highly reactive azirine **III**. This azirine **III** may undergo ring opening by water, leading to the formation of α-amino ketone **IV**. The condensation of **IV** to form dihydropyrazine[26] species **3a′** concludes the first transformation of the process.

The formation of **3′** from **2** is considerably faster (approx. 3 h) under the reaction conditions employed then the subsequent oxidation of **3′** to **3** (21 h). In line with control (light on/off) experiments (Scheme 4), nevertheless, the second step should also be a photocatalytic one, that is, being initiated by excited state Ru(II)* which may reductively quench **3′** acting as an electron donor. This results in the

generation of Ru(I) and the N-centered radical cation **V**, which can be oxidized by superoxide anion radical $O_2^{\bullet-}$, being in turn generated from Ru(I) and molecular oxygen.



Scheme 4 Control experiment

To summarize, we have developed a visible light mediated cascade to 1,4-pyrazines, combining energy and electron-transfer-initiated reaction steps operated by the same photocatalyst.[27]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590888.

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(27) **Photochemical Synthesis of Pyrazines: General Procedure**

An oven-dried Schlenk tube (10 mL size) equipped with a stirring bar was charged with $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%) followed by 1.60 mL MeCN and 0.40 mL distilled water. The resulting solution was degassed via nitrogen bubbling for 5 min using a syringe needle. Then vinyl azide **2** (0.50 mmol, 1 equiv) was added under nitrogen. Irradiation with a blue LED (λ_{max} = 455 nm) was carried out for 24 h at rt. The reaction mixture was transferred to a separatory funnel containing distilled water, and extracted three times with EtOAc. After drying the combined organic layers (Na_2SO_4), the resulting solution was concentrated in vacuo. The pure product was obtained either by recrystallization from CH_2Cl_2/pentane or by silica gel column chromatography using hexanes and EtOAc as eluents.

Diethyl 3,6-Diphenylpyrazine-2,5-dicarboxylate (3a)

Following the general procedure, **3a** was prepared from ethyl (*Z*)-2-azido-3-phenylacrylate (**2a**, 109 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 9:1, R_f = 0.20) to afford **3a** as a white solid (57 mg, 61% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.71 (m, 4 H), 7.49–7.47 (m, 6 H), 4.31 (q, *J* = 7.1 Hz, 4 H), 1.16 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 149.9, 144.8, 136.2, 130.0, 128.9, 128.7, 62.5, 13.8. ESI-HRMS: *m/z* calcd for $C_{22}H_{20}N_2O_4$ [M + H]$^+$: 377.1423; found: 377.1502. IR (neat): 3059, 2986, 2925, 2854, 1731, 1449, 1405, 1380, 1293, 1173, 1137, 1094, 1057, 1021, 856, 766, 705 cm^{-1}.

Diethyl 3,6-Di-*p*-tolylpyrazine-2,5-dicarboxylate (3b)

Following the general procedure, **3b** was prepared from ethyl (*Z*)-2-azido-3-(p-tolyl)acrylate (**2b**, 115 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was dissolved in a minimum amount of CH_2Cl_2 followed by the addition of *n*-pentane to initiate crystallization. After 30 min, the solvent mixture was decanted, and the solid was washed twice with *n*-pentane. The residual solvents were removed in vacuo which afforded **3b** as white solid (83 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.1 Hz, 4 H), 7.27 (d, *J* = 7.9 Hz, 4 H), 4.32 (q, *J* = 7.1 Hz, 4 H), 2.41 (s, 6 H), 1.19 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 149.4, 144.6, 140.2, 133.3, 129.5, 128.7, 62.4, 21.5, 13.9. ESI-HRMS: *m/z* calcd for $C_{24}H_{24}N_2O_4$ [M + H]$^+$: 405.1736; found: 405.1814. IR (neat): 2986, 2871, 1723, 1609, 1462, 1442, 1408, 1292, 1247, 1174, 1137, 1095, 1057, 1012, 853, 828, 775, 700 cm^{-1}.

Diethyl 3,6-Di(naphthalen-2-yl)pyrazine-2,5-dicarboxylate (3c)

Following the general procedure, **3c** was prepared from ethyl (*Z*)-2-azido-3-(naphthalen-2-yl)acrylate (**2c**, 134 mg, 0.50 mmol, 1 equiv) and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 4:1, R_f = 0.30) to afford **3c** as a white solid (81 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 2 H), 7.97–7.85 (m, 8 H), 7.59–7.53 (m, 4 H), 4.33 (d, *J* = 7.1 Hz, 4 H), 1.13 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 149.6, 145.1, 134.0, 133.5, 133.2, 129.0, 128.8, 128.6, 127.9, 127.4, 126.8, 125.9, 62.6, 13.9. ESI-HRMS: *m/z* calcd for $C_{30}H_{24}N_2O_4$ [M + H]$^+$: 477.1736; found : 477.1821. IR (neat):3056, 2974, 2927, 2854, 1729, 1686, 1462, 1405, 1381, 1304, 1236, 1169, 1140, 1004, 906, 871, 852, 830, 750 cm^{-1}.

Diethyl 3,6-Fis(4-methoxyphenyl)pyrazine-2,5-dicarboxylate (3d)

Following the general procedure, **3d** was prepared from ethyl (*Z*)-2-azido-3-(4-methoxyphenyl)acrylate (**2d**, 124 mg, 0.50 mmol, 1 equiv) and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 3:1, R_f = 0.28) to afford **3d** as a white solid (53 mg, 49% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 4 H), 6.99–6.96 (m, 4 H), 4.33 (q, *J* = 7.1 Hz, 4 H), 3.85 (s, 6 H), 1.21 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 161.2, 148.5, 144.1, 130.3, 128.5, 114.2, 62.4, 55.5, 13.9. ESI-HRMS: *m/z* calcd for $C_{24}H_{24}N_2O_6$ [M + H]$^+$: 437.1634; found: 437.1740. IR (neat): 2980, 2955, 2926, 2851, 1732, 1607, 1580, 1518, 1414, 1295, 1253, 1177, 1148, 1060, 1017, 841, 811, 786, 752 cm^{-1}.

Diethyl 3,6-Bis(2-methoxyphenyl)pyrazine-2,5-dicarboxylate (3e)

Following the general procedure, **3e** was prepared from ethyl (*Z*)-2-azido-3-(2-methoxyphenyl)acrylate (**2e**, 124 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$(3.7 mg, 0.01 equiv, 1 mol%). The crude product was recrystallized as described for **3b** to afford **3e** as white solid (86 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 2 H), 7.44–7.38 (m, 2 H), 7.14–7.09 (m, 2 H), 6.89 (d, *J* = 8.2 Hz, 2 H), 4.25 (q, *J* = 7.1 Hz, 4 H), 3.73 (s, 6 H), 1.14 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 156.5, 147.6, 145.9, 131.4, 131.2, 126.5, 121.4, 110.1, 61.8, 55.1, 13.9. ESI-HRMS: *m/z* calcd for $C_{24}H_{24}N_2O_6$ [M + H]$^+$: 437.1634; found: 437.1739. IR (neat): 2968,2924, 2843, 1733, 1601, 1495, 1465, 1439, 1411, 1390, 1280, 1248, 1226, 1182, 1149, 1111, 1061, 1014, 854, 759, 697 cm^{-1}.

Diethyl 3,6-Bis(2-chloro-3,4-dimethoxyphenyl)pyrazine-2,5-dicarboxylate (3f)

Following the general procedure, **3f** was prepared from ethyl (*Z*)-2-azido-3-(2-chloro-3,4-dimethoxyphenyl)acrylate (**2f**, 156 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was recrystallized as described for **3b** to afford **3f** as white solid (122 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.5 Hz, 2 H), 6.98 (d, *J* = 8.6 Hz, 2 H), 4.28 (q, *J* = 7.1 Hz, 4 H), 3.94 (s, 6 H), 3.87 (s, 6 H), 1.17 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 154.8, 149.8, 145.5, 145.1, 129.5, 127.8, 126.4, 110.9, 62.5, 60.8, 56.3, 13.9. ESI-HRMS: *m/z* calcd for $C_{26}H_{26}Cl_2N_2O_8$ [M + H]$^+$:

565.1066; found: 565.1143. IR (neat): 3090, 2980, 2938, 2841, 1735, 1590, 1490, 1447, 1412, 1392, 1293, 1269, 1220, 1202, 1099, 1038, 1003, 819, 790, 778 cm^{-1}.

Diethyl 3,6-Bis(4-fluorophenyl)pyrazine-2,5-dicarboxylate (3g)

Following the general procedure, **3g** was prepared from ethyl (*Z*)-2-azido-3-(4-fluorophenyl)acrylate (**2g**, 118 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was recrystallized as described for **3b** to afford **3g** as white solid (87 mg, 85%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 4 H), 7.20–7.15 (m, 4 H), 4.33 (q, *J* = 7.1 Hz, 4 H), 1.20 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 164.1 (d, $^1J_{C-F}$ = 250.6 Hz), 148.8, 144.5, 132.1 (d, $^4J_{C-F}$ = 3.1 Hz), 130.9 (d, $^3J_{C-F}$ = 8.6 Hz), 116.0 (d, $^2J_{C-F}$ = 21.8 Hz), 62.7, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –110.9. ESI-HRMS: *m/z* calcd for $C_{22}H_{18}F_2N_2O_4$ $[M + H]^+$: 413.1235; found: 413.1320. IR (neat): 3084, 2985, 2925, 2854, 1733, 1599, 1512, 1409, 1383, 1289, 1227, 1179, 1155, 1096, 1053, 1012, 845, 815, 766 cm^{-1}.

Diethyl 3,6-Bis(2-fluorophenyl)pyrazine-2,5-dicarboxylate (3h)

Following general procedure, **3h** was prepared from ethyl (*Z*)-2-azido-3-(2-fluorophenyl)acrylate (**2h**, 118 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was recrystallized as described for **3b** to afford **3h** as white solid (83 mg, 81%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.80 (m, 2 H), 7.51–7.44 (m, 2 H), 7.35–7.30 (m, 2 H), 7.16–7.09 (m, 2 H), 4.35 (q, *J* = 7.1 Hz, 4 H), 1.21 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 160.1 (d, $^1J_{C-F}$ = 248.7 Hz), 146.5, 145.4 (d, *J* = 1.9 Hz), 132.0 (d, $^3J_{C-F}$ = 8.5 Hz), 131.7 (d, $^4J_{C-F}$ = 2.3 Hz), 124.9 (d, $^3J_{C-F}$ = 3.3 Hz), 124.7, 115.4 (d, $^2J_{C-F}$ = 21.7 Hz), 62.5, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.6. ESI-HRMS: *m/z* calcd for $C_{22}H_{18}F_2N_2O_4$ $[M + H]^+$: 413.1235; found: 413.1320. IR (neat): 3071, 2985, 2939, 2906, 1730, 1613, 1581, 1490, 1454, 1399, 1384, 1245, 1172, 1140, 1093, 1059, 1014, 859, 757 cm^{-1}.

Diethyl 3,6-Bis(4-chlorophenyl)pyrazine-2,5-dicarboxylate (3i)

Following the general procedure, **3i** was prepared from ethyl (*Z*)-2-azido-3-(4-chlorophenyl)acrylate (**2i**, 126 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was recrystallized as described for **3b** to afford **3i** as white solid (63 mg, 57%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.66 (m, 4 H), 7.47–7.45 (m, 4 H), 4.34 (q, *J* = 7.1 Hz, 4 H), 1.22 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 148.9, 144.5, 136.7, 134.4, 130.2, 129.1, 62.8, 13.9. ESI-HRMS: *m/z* calcd for $C_{22}H_{18}Cl_2N_2O_4$ $[M + H]^+$: 445.0644; found: 445.0713. IR (neat): 2985, 2937, 1728, 1595, 1494, 1426, 1401, 1378, 1277, 1234, 1187, 1158, 1109, 1090, 1053, 1010, 854, 830, 778, 745 cm^{-1}.

Diethyl 3,6-Bis(4-bromophenyl)pyrazine-2,5-dicarboxylate (3j)

Following the general procedure, **3j** was prepared from ethyl (*Z*)-2-azido-3-(4-bromophenyl)acrylate (**2j**, 148 mg, 0.50 mmol, 1 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 3:1, R_f = 0.22) to afford **3j** as a white solid (73 mg, 55% yield).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.58 (m, 8 H), 4.34 (q, *J* = 7.2 Hz, 4 H), 1.22 (t, *J* = 7.2 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 149.0, 144.5, 134.9, 132.0, 130.4, 125.0, 62.8, 13.9. ESI-HRMS: *m/z* calcd for $C_{22}H_{18}Br_2N_2O_4$ $[M + H]^+$: 532.9633; found: 532.9708. IR (neat): 2983, 2925, 2854, 1728, 1588, 1474, 1423, 1399, 1376, 1279, 1234, 1186, 1159, 1051, 1006, 854, 826, 776, 734 cm^{-1}.

Diethyl 3,6-Bis(4-(trifluoromethyl)phenyl)pyrazine-2,5-dicarboxylate (3k)

Following the general procedure, **3k** was prepared from ethyl (*Z*)-2-azido-3-(4-(trifluoromethyl)phenyl)acrylate (**2k**, 143 mg, 0.50 mmol, 1 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 3:1, R_f = 0.30) to afford **3k** as a white solid (48 mg, 38% yield).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.1 Hz, 4 H), 7.76 (d, *J* = 8.3 Hz, 4 H), 4.34 (q, *J* = 7.1 Hz, 4 H), 1.20 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 149.4, 144.9, 139.4, 132.1 (q, *J* = 33.1 Hz), 129.4, 125.7 (q, *J* = 3.6 Hz), 122.1, 62.9, 13.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.2. ESI-HRMS: *m/z* calcd for $C_{24}H_{18}F_6N_2O_4$ $[M + H]^+$: 513.1171; found: 513.1254. IR (neat): 2982, 2965, 2927, 2856, 1721, 1414, 1324, 1254, 1138, 1105, 1072, 1053, 1016, 858, 832, 790, 717 cm^{-1}.

Diethyl 3,6-Bis(4-nitrophenyl)pyrazine-2,5-dicarboxylate (3l)

Following the general procedure, **3l** was prepared from ethyl (*Z*)-2-azido-3-(4-nitrophenyl)acrylate (**2l**, 131 mg, 0.50 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was recrystallized as described for **3b** to afford **3l** as yellow solid (99 mg, 86%).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.38–8.35 (m, 4 H), 7.93–7.90 (m, 4 H), 4.37 (q, *J* = 7.1 Hz, 4 H), 1.24 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 149.08, 149.00, 144.8, 141.8, 130.1, 124.0, 63.2, 14.0. ESI-HRMS: *m/z* calcd for $C_{22}H_{18}N_4O_8$ $[M + H]^+$: 467.1125; found: 467.1198. IR (neat): 3110, 2985, 2958, 2919, 2851, 1721, 1601, 1516, 1466, 1408, 1344, 1296, 1259, 1144, 1100, 1009, 850, 800, 749, 689 cm^{-1}.

Diethyl 3,6-Di(thiophen-2-yl)pyrazine-2,5-dicarboxylate (3m)

Following the general procedure, **3m** was prepared from ethyl (*Z*)-2-azido-3-(thiophen-2-yl)acrylate (**2m**, 112 mg, 0.50 mmol, 1 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 5:1, R_f = 0.52) to afford **3m** as a pale yellow solid (25 mg, 26%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 4 H), 7.12–7.09 (m, 2 H), 4.48 (q, *J* = 7.1 Hz, 4 H), 1.37 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 142.5, 141.9, 139.1, 130.4, 128.6, 128.4, 62.8, 14.0. ESI-HRMS: *m/z* calcd for $C_{18}H_{16}N_2O_4S_2$ $[M + H]^+$: 389.0551; found: 389.0644. IR (neat): 3097, 2991, 2963, 2924, 2853, 1719, 1531, 1435, 1418, 1381, 1330, 1270, 1145, 1109, 852, 830, 706 cm^{-1}.

Diethyl 3-(2-Chloro-3,4-dimethoxyphenyl)-6-(p-tolyl)pyrazine-2,5-dicarboxylate (3fb)

Following the general procedure, **3fb** was prepared from ethyl (*Z*)-2-azido-3-(2-chloro-3,4-dimethoxyphenyl)acrylate (**2f**, 78 mg, 0.25 mmol, 1 equiv), ethyl (*Z*)-2-azido-3-(p-tolyl)acrylate (**2b**, 57.7 mg, 0.25 mmol, 1.00 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 3:1, R_f = 0.25) to afford **3fb** as a white solid (37 mg, 31% yield).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.1 Hz, 2 H), 7.33–7.27 (m, 3 H), 6.97 (d, *J* = 8.6 Hz, 1 H), 4.36–4.25 (m, 4 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 2.42 (s, 3 H), 1.22–1.16 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 164.7, 154.7, 150.5, 148.7, 145.5, 144.9, 144.8, 140.5, 133.2, 129.6, 129.5, 128.9, 127.8, 126.3, 110.8, 62.6, 62.4, 60.8, 56.3, 21.6, 13.97, 13.94. ESI-HRMS: *m/z* calcd for $C_{25}H_{25}ClN_2O_6$ $[M + H]^+$: 485.1401; found: 485.1494. IR (neat): 2982, 2927, 2854, 1739, 1591, 1487, 1450, 1397, 1291, 1277, 1236, 1224, 1198, 1153, 1120, 1077, 1030, 1013, 964, 809, 755 cm^{-1}.

Diethyl 3-(2-Chloro-3,4-dimethoxyphenyl)-6-(2-fluorophenyl)pyrazine-2,5-dicarboxylate (3fh)

Following the general procedure, **3fh** was prepared from ethyl (*Z*)-2-azido-3-(2-chloro-3,4-dimethoxyphenyl)acrylate (**2f**, 78 mg, 0.25 mmol, 1 equiv), ethyl (*Z*)-2-azido-3-(2-fluorophenyl)acrylate (**2h**, 59 mg, 0.25 mmol, 1 equiv) and $[Ru(bpy)_3]Cl_2·6H_2O$ (3.7 mg, 0.01 equiv, 1 mol%). The crude product was purified by column chromatography (silica gel, hexanes–EtOAc = 3:1, R_f = 0.34) to afford **3fh** as a white solid (45 mg, 37% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.82 (m, 1 H), 7.59–7.30 (m, 3 H), 7.16–7.09 (m, 1 H), 6.99–6.97 (m, 1 H), 4.38–4.26 (m, 4 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 1.23–1.16 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 164.5, 160.1 (d, $^1J_{C–F}$ = 248.3 Hz), 154.8, 149.7, 146.5, 145.5, 145.1, 132.0 (d, $^3J_{C–F}$ = 8.5 Hz), 131.7 (d, $^4J_{C–F}$ = 2.2 Hz), 129.4, 127.7, 126.4, 125.0, 124.9 (d, $^3J_{C–F}$ = 3.3 Hz), 124.9, 115.4 (d, $^2J_{C–F}$ = 21.6 Hz), 110.9, 62.5 (2×), 60.8, 56.3, 13.95, 13.92. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.6. ESI-HRMS: *m/z* calcd for $C_{24}H_{22}ClFN_2O_6$ $[M + H]^+$: 489.1150; found: 489.1257. IR (neat): 2981, 2934, 2843, 1723, 1616, 1558, 1490, 1450, 1408, 1296, 1269, 1248, 1224, 1173, 1142, 1099, 1075, 1040, 1016, 812, 758 cm^{-1}.