Visible-light Photocatalyzed *peri*-[3+2] Cycloaddition of Azaarenes

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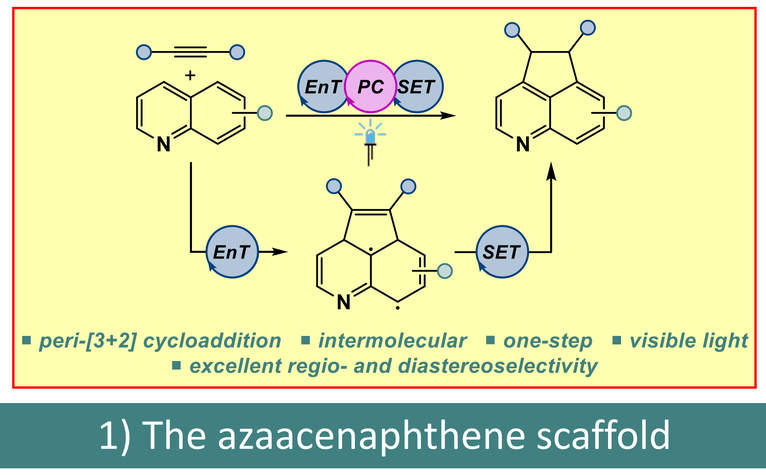
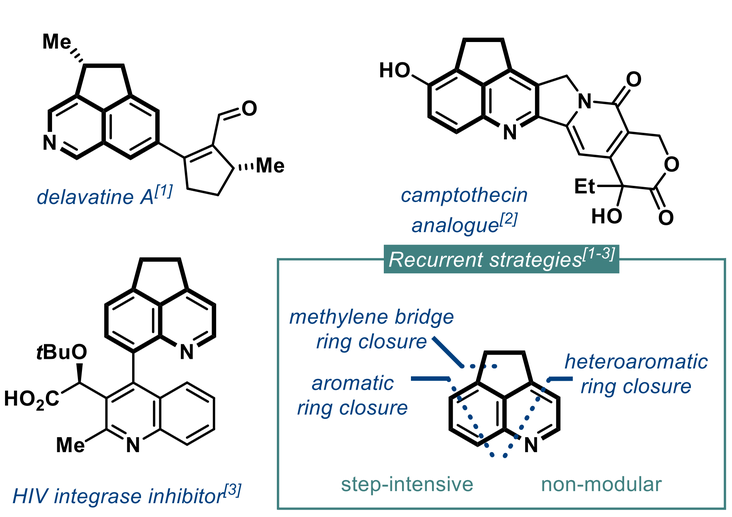
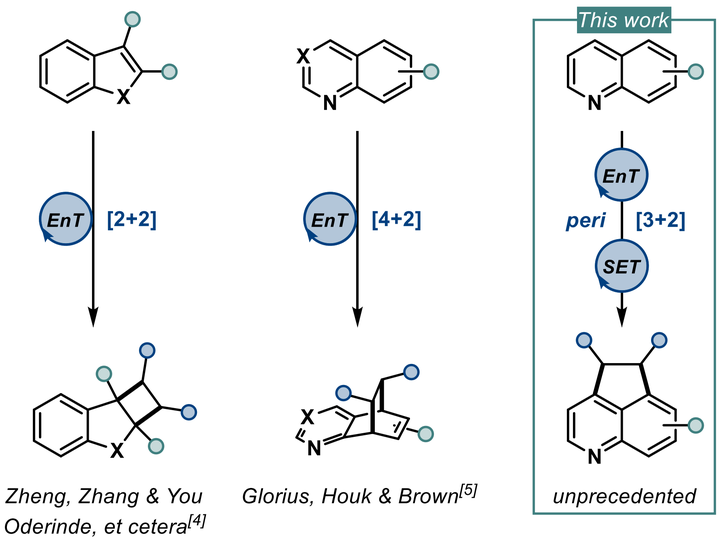


Azaacenaphthenes are relevant structural motifs found in several natural products and pharmaceuticals yet are challenging to access. Currently, the preparation of these compounds is achieved by step-intensive de-novo synthesis or intramolecular cyclization of prefunctionalized substrates. Herein, we present a visible-light photocatalyzed *peri*-[3+2] cycloaddition reaction between alkynes and azaarenes forming azaacenaphthenes in a single reaction step. Detailed DFT calculations and experimental studies support the proposed mixed EnT/SET reaction mechanism.

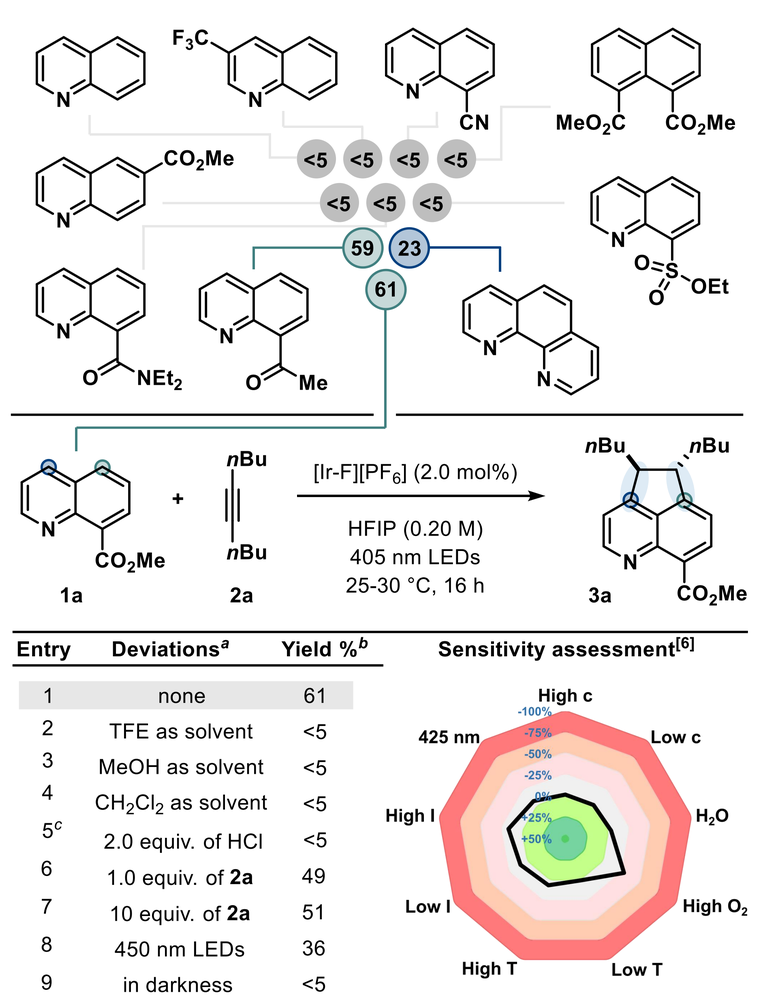
1) The azaacenaphthene scaffold



2) EnT-based cycloadditions of azaarenes



3) Reaction development

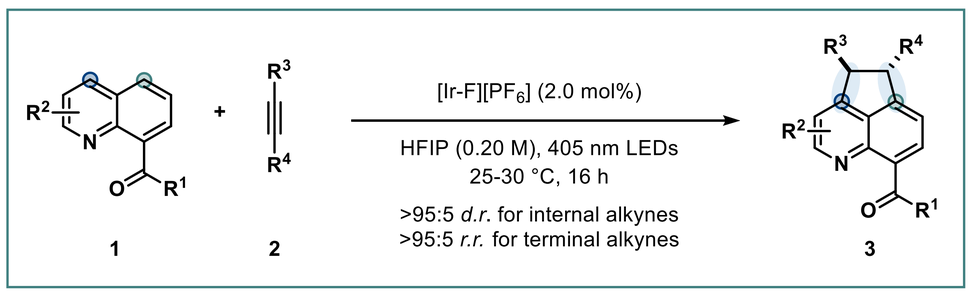


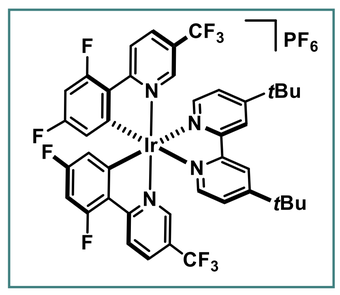
Entry	Deviations[a]	Yield %[b]
1	none	61
2	TFE as solvent	<5
3	MeOH as solvent	<5
4	CH_2Cl_2 as solvent	<5
5[c]	2.0 equiv. of HCl	<5
6	1.0 equiv. of **2a**	49
7	10 equiv. of **2a**	51
8	450 nm LEDs	36
9	in darkness	<5
10	without [Ir-F]	<5

Sensitivity assessment[6]

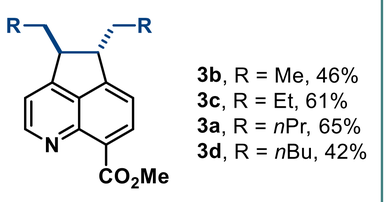
[a]Standard reaction conditions: azaarene **1a** (0.10 mmol, 1.0 equiv.), alkyne **2a** (0.50 mmol, 5.0 equiv.), [Ir-F][PF_6] (2.0 µmol, 2.0 mol%), HFIP (0.50 mL, 0.20 M), 405 nm LEDs (18 W), 25-30 °C, 16 h. [b]Yields were obtained by ^{1}H NMR spectroscopy using mesitylene as internal standard. [c]4 M HCl in 1,4-dioxane was used.

4) Substrate scope (selected examples)



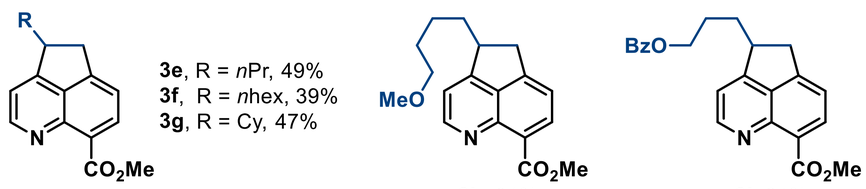


Internal alkynes

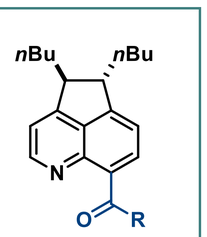


3b, R = Me, 46%
3c, R = Et, 61%
3a, R = *n*Pr, 65%
3d, R = *n*Bu, 42%

Terminal alkynes

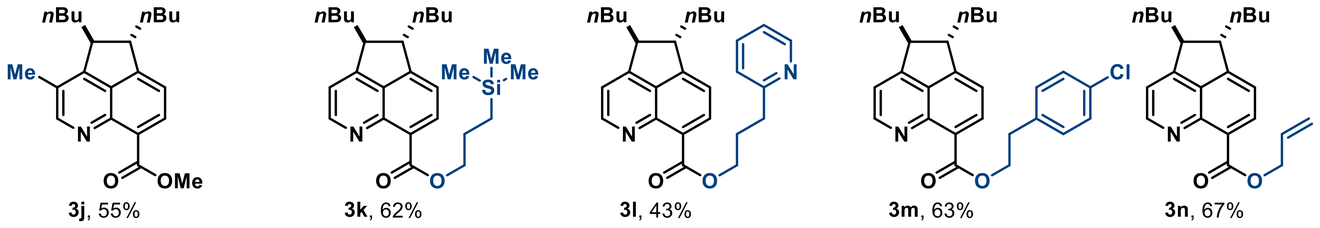


3e, R = *n*Pr, 49%
3f, R = *n*hex, 39%
3g, R = Cy, 47%
3h, 31%
3i, 24%



3q, R = Me, 53%
3r, R = Cy, 63%

Azaarenes

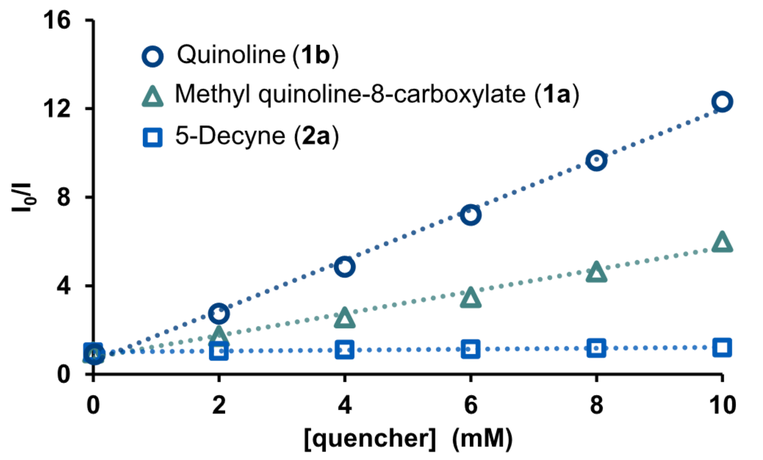


3j, 55%
3k, 62%
3l, 43%
3m, 63%
3n, 67%
3o, R = H, 38%[d]
3p, Me, 39%[d]

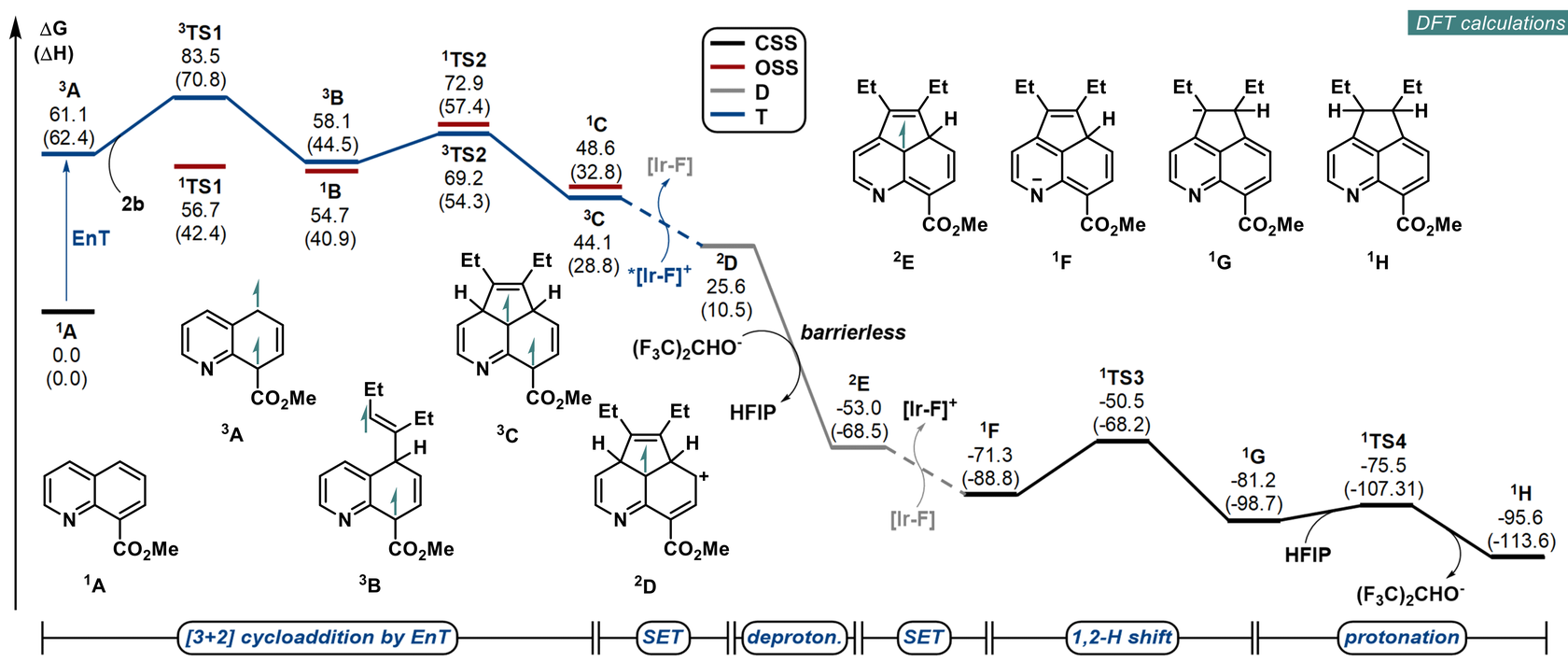
[d]10 equiv. alkyne **2a** and 4.0 mol% [Ir-F][PF_6] were used. The reaction time was increased to 48 h.

5) Mechanistic investigation

Stern–Volmer quenching analysis



DFT calculations



Photocatalyst screening

Entry	Photocatalyst	$E_{1/2}^{II/III*}$ / V	$E_{1/2}^{III*/IV}$ / V	E_T / (kcal/mol)	Yield / % (conv. / %)[e]
1[f]	benzophenone	n.d.	n.d.	69.1	<5 (30)
2	thioxanthone	+1.18	−1.11	63.4	11 (38)
3	[Ir(dF(Me)ppy)$_2$(dtbbpy)][PF_6]	+0.97	−0.92	62.9	28 (47)
4	[Ir-F][PF_6]	+1.21	−0.89	61.8	61 (>95)
5	*fac*-[Ir(ppy)$_3$]	+0.31	−1.73	58.1	<5 (11)
6	[Ir(ppy)$_2$(dtbbpy)][PF_6]	+0.66	−0.96	49.2	<5 (17)
7	[Ru(bpy)$_3$][PF_6]$_2$	+0.77	−0.81	46.5	<5 (7)
8	[Mes_2Acr(*t*Bu)$_2$][BF_4]	+2.00	n.d.	n.d.	<5 (10)

[e]Standard reaction conditions using the indicated photocatalyst. NMR yields given. [f]Irradiation at 365 nm. 20 mol% of benzophenone was used.

‡ These authors contributed equally to this work.

References:

[1] For selected total synthesis approaches towards delavatine A: a) Palani, V.; Hugelshofer, C. L.; Kevlishvili, I.; Liu, P.; Sarpong, R.; *J. Am. Chem. Soc.* **2019**, 141 (6), 2652–2660. b) Zhang, Z.; Wang, J.; Li, J.; Yang, F.; Liu, G.; Tang, W.; He, W.; Fu, J.-J.; Shen, Y.-H.; Li, A.; Zhang, W.-D.; *J. Am. Chem. Soc.* **2017**, 139 (15), 5558–5567. c) Peez, T.; Luy, J.-N.; Harms, K.; Tonner, R.; Koert, U.; *Chem. Eur. J.* **2018**, 24 (67), 17686–17690. [2] Sugimori, M.; Ejima, A.; Ohsuki, S.; Uoto, K.; Mitsui, I.; Matsumoto, K.; Kawato, Y.; Yasuoka, M.; Sato, K.; *J. Med. Chem.* **1994**, 37 (19), 3033–3039. [3] Tsantrizos, Y. S.; Bailey, M. D.; Bilodeau, F.; Carson, R. J.; Cou-lombe, R.; Fader, L.; Halmos, T.; Kawai, S.; Landry, S.; Laplante, S.; Morin, S.; Parisien, M; Poupart, M.-A.; Simoneau, B.; Patent WO 2009062285, May 22, **2009**. [4] For selected dearomative [2+2]-photocycloaddition reactions: a) Zhu, M.; Zheng, C.; Zhang, X.; You, S.-L.; *J. Am. Chem. Soc.* **2019**, 141 (6), 2636–2644. b) Oderinde, M. S.; Mao, E.; Ramirez, A.; Pawluczyk, J.; Jorge, C.; Cornelius, L. A. M.; Kempson, J.; Vetrichelvan, M.; Pitchai, M.; Gupta, A.; Meanwell, N. A.; Mathur, A.; Murali Dhar, T. G.; *J. Am. Chem. Soc.* **2020**, 142 (6), 3094–3103. [5] Ma, J.; Chen, S.; Bellotti, P.; Guo, R.; Schäfer, F.; Heusler, A.; Zhang, X.; Daniliuc, C.; Brown, M. K.; Houk, K. N.; Glorius, F.; *Science* **2021**, 371 (6536), 1338-1345. [6] Pitzer, L.; Schäfers, F.; Glorius, F.; *Angew. Chem. Int. Ed.* **2019**, 58 (25), 8572–8576.

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