

## Supplementary Information

# Generation and Alkylation of $\alpha$ -Carbamyl Radicals via Organic Photoredox Catalysis

Joshua B. McManus, Nicholas P.R. Onuska and David A. Nicewicz\*

Department of Chemistry, University of North Carolina at Chapel Hill, New  
Venable Laboratories, Chapel Hill, NC 27599-3290, USA

E-mail: nicewicz@unc.edu

### Table of Contents:

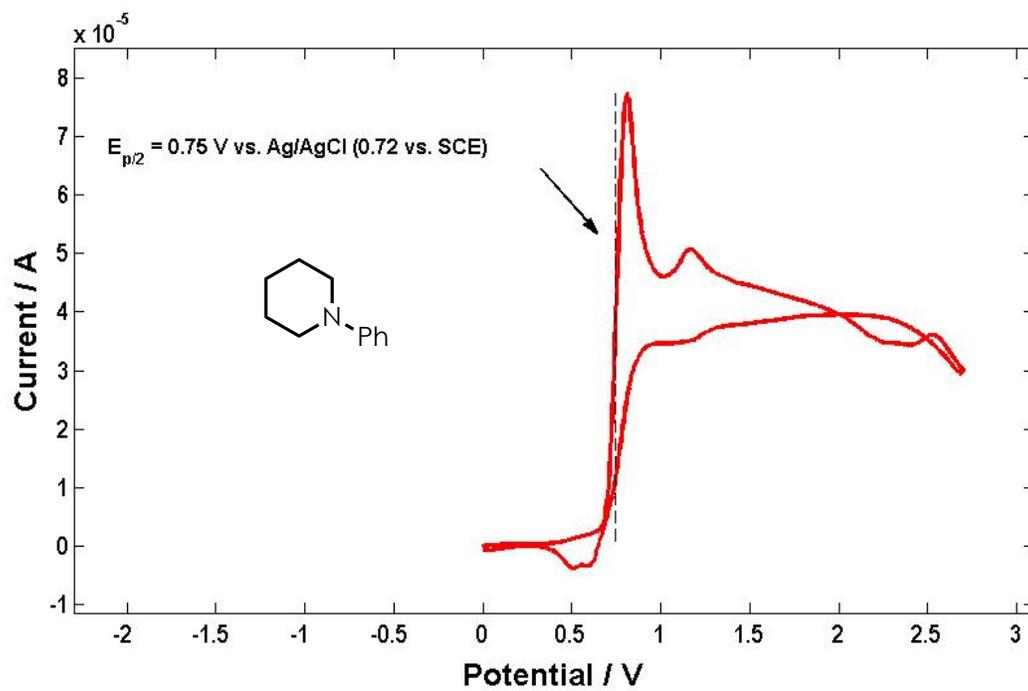
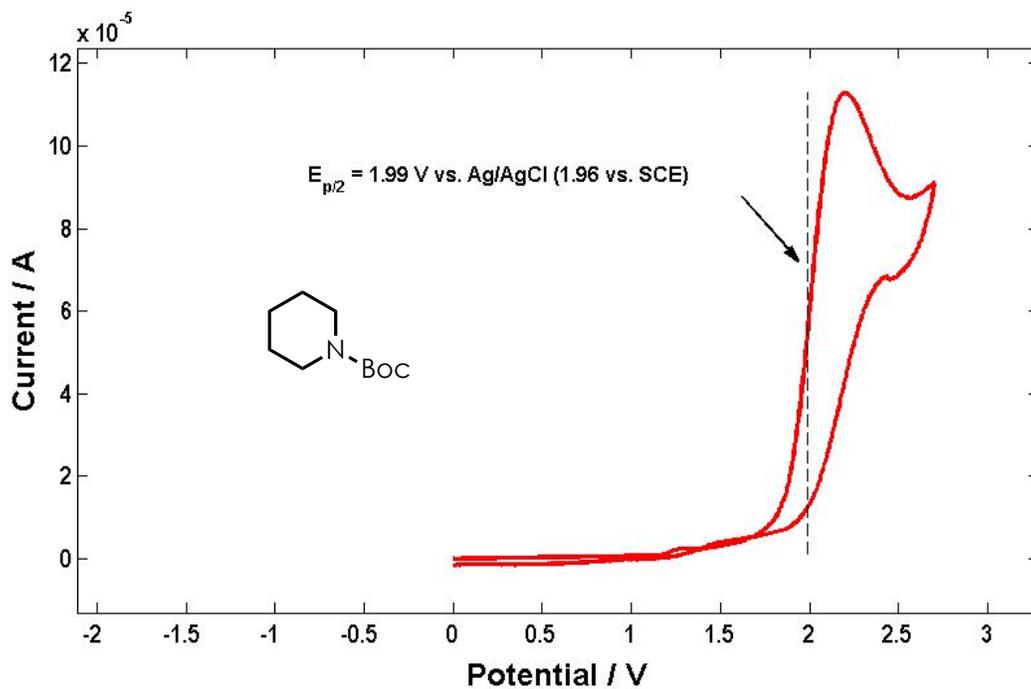
I.	General Information.....	S2
II.	Electrochemical Data.....	S2
III.	Synthesis and Characterization of Catalyst and Substrate.....	S5
IV.	Reaction Optimization.....	S11
V.	Procedure and Data for Product Synthesis.....	S12
VI.	Synthesis of (+)-monomorine I.....	S25
VII.	Stern-Volmer Analysis.....	S26
VIII.	Photochemical Quantum Yield ( $\Phi_r$ ) Determination.....	S28
IX.	Large Scale Flow Synthesis of <i>tert</i> -butyl ( <i>R</i> )-(3,3-dicyano-2-phenylpropyl)(phenyl)carbamate ( <b>26</b> ).....	S29
X.	Computational Details.....	S30
XI.	References.....	S33
XII.	<sup>1</sup> H, <sup>13</sup> C and <sup>19</sup> F NMR Spectra .....	S35

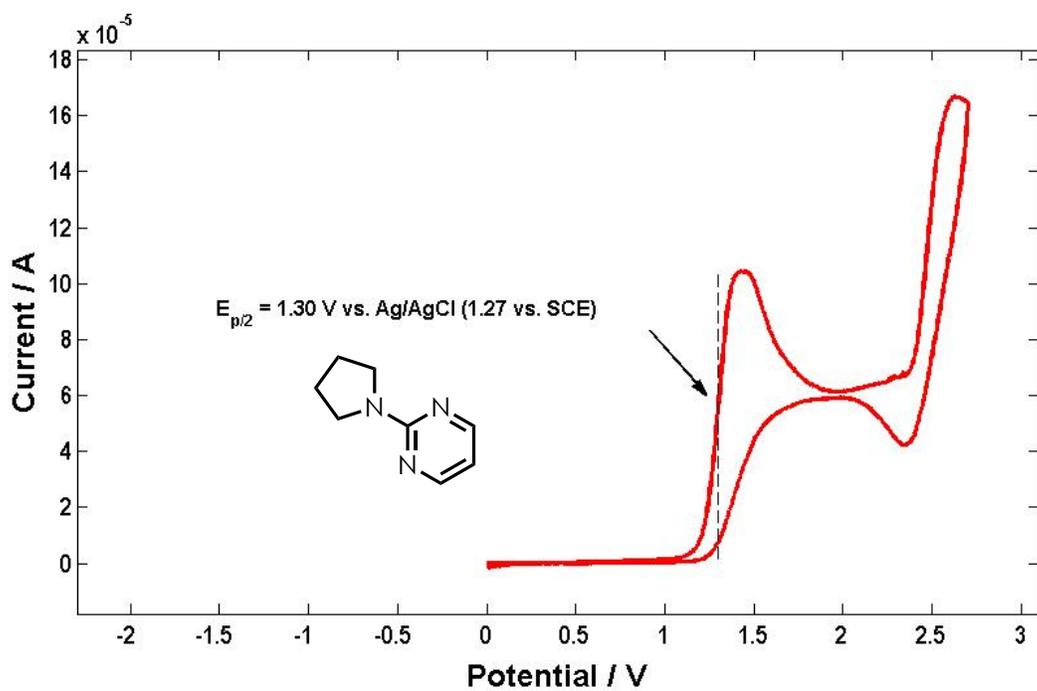
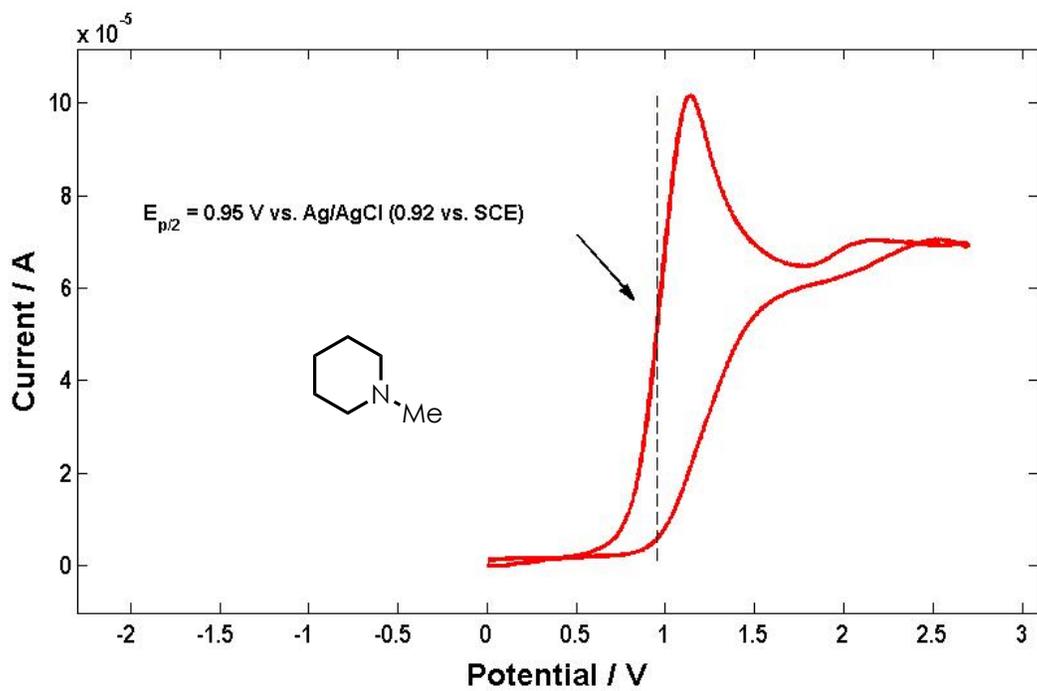
## I. General Information:

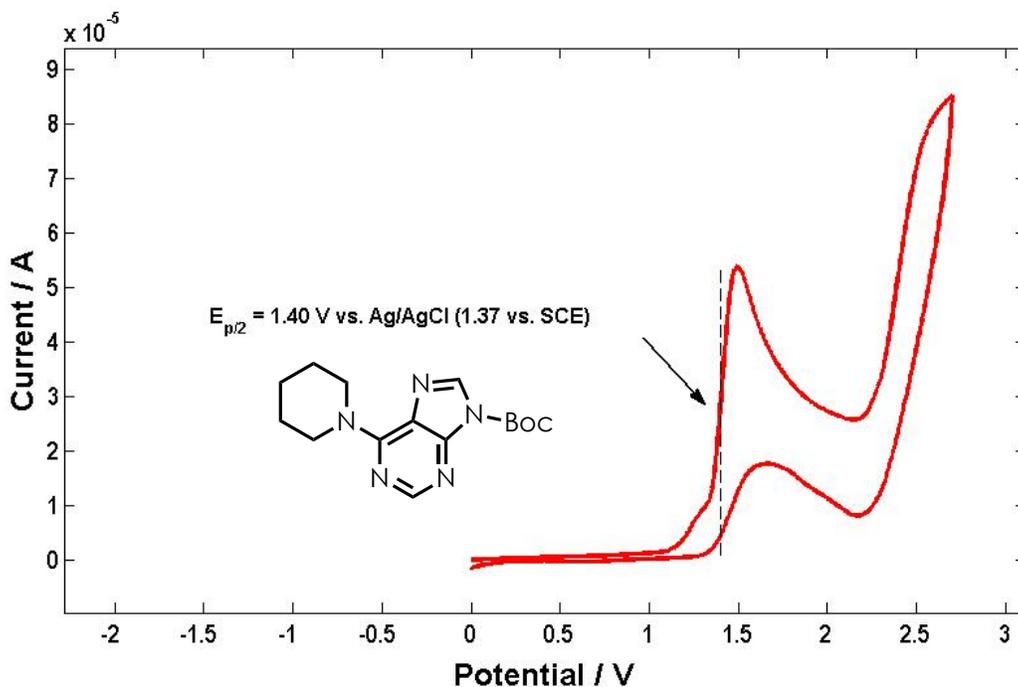
**Methods and Materials:** Proton and carbon magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) were recorded on a Bruker AVANCE III 600 CryoProbe ( $^1\text{H}$  NMR at 600 MHz,  $^{13}\text{C}$  NMR at 151 MHz and  $^{19}\text{F}$  NMR at 565 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dddd = doublet of doublets of doublets of doublets, dt = doublet of triplets, ddt = doublet of doublets of triplets, td = triplet of doublets, tt = triplet of triplets, m = multiplet, q = quartet), coupling constants (Hz), and integration. Electrochemical potentials were Obtained with a standard set of conditions to main internal consistency. Cyclic voltammograms were collected with a Pine WaveNow Potentiostat. Data was analyzed using MATLAB by subtracting a background current prior to identifying the maximum current ( $C_p$ ) and determining the potential ( $E_{p/2}$ ) at half this value ( $C_{p/2}$ ). The obtained value was referenced to  $\text{Ag}|\text{AgCl}$  and converted to SCE by subtracting 0.03 V. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. High Resolution Mass Spectra (HRMS) were obtained using a Thermo LTqFT mass spectrometer with electrospray ionization in positive or negative mode. Optical rotation values were determined using a Jasco DIP-1000 digital polarimeter. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63  $\mu\text{m}$ ) purchased from Silicycle. Irradiation of photochemical reactions was carried out using 2 x 15W PAR38 Royal Blue Aquarium LED flood lamps Model# 6851 purchased from Ecoxotic with an output centered at a wavelength of approximately 455 nm. Irradiance at the reaction vessel was determined using a ThorLabs Digital Optical Power and Energy Meter (part no. PM100D). The reactions were carried out in 2-dram borosilicate glass vials (purchased from Fisher Scientific, catalogue # 03-339-22D) sealed with polypropylene caps equipped with Teflon coated septa (purchased through VWR international, Microliter Product # 15-0060K). All reagents were purchased from Sigma-Aldrich, Fisher Scientific, Oakwood Chemical or TCI corporation and were used without additional purification unless otherwise noted.

## II. Electrochemical Data:

Samples were prepared with 0.1 mmol of analyte in 5 mL of 0.1 M tetra-N-butylammonium hexafluorophosphate in dry, degassed acetonitrile. Measurements employed a glassy carbon working electrode, platinum wire counter electrode, 3.5 M NaCl silver-silver chloride reference electrode, and a scan rate of 100 mV/s. Reductions were measured by scanning potentials in the negative direction and oxidations in the positive direction.

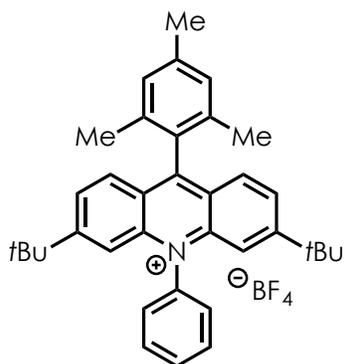






### III. Synthesis and Characterization of Catalyst and Substrates:

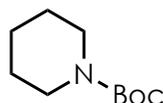
#### Catalyst Synthesis:



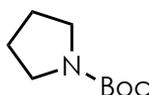
**3,6-Di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate** prepared according to literature precedent: Analytical data matched that reported in the literature.<sup>1</sup>

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.99 (td, *J* = 7.5, 6.7, 1.3 Hz, 2H), 7.94 (s, 1H), 7.94 – 7.90 (m, 1H), 7.83 – 7.74 (m, 6H), 7.44 (dd, *J* = 1.5, 0.7 Hz, 2H), 7.19 (d, *J* = 1.2 Hz, 2H), 2.51 (s, 3H), 1.89 (s, 6H), 1.32 (s, 18H). **<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 163.53, 162.26, 142.14, 140.15, 136.85, 136.17, 131.81, 131.60, 129.31, 128.93, 128.26, 128.03, 127.45, 124.04, 115.08, 36.67, 30.22, 21.32, 20.25. **<sup>19</sup>F NMR** (565 MHz, CDCl<sub>3</sub>) δ -150.85, -154.50.

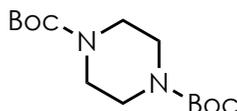
### Preparation of Amine Substrates



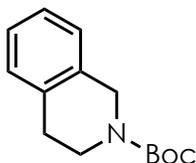
**tert-butyl piperidine-1-carboxylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>1</sup>



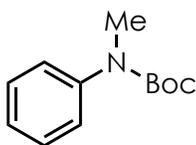
**tert-butyl pyrrolidine-1-carboxylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>2</sup>



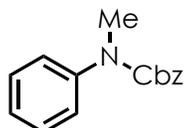
**di-tert-butyl piperazine-1,4-dicarboxylate** was prepared according to the following procedure: Piperazine (10 mmol, 0.86 g) was dissolved in 70mL of DCM. Et<sub>3</sub>N (15 mmol, 2.1 mL) was added to the solution before di-tert-butyl dicarbonate (22 mmol, 4.8 g). The reaction mixture stirred overnight, before being concentrated and purified by column chromatography (10 EtOAc/Hex). Spectral data were in agreement with literature values.<sup>3</sup>



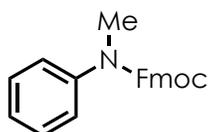
**tert-butyl 3,4-dihydroisoquinoline-2(1H)-carboxylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>4</sup>



**tert-butyl methyl(phenyl)carbamate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>5</sup>



**benzyl methyl(phenyl)carbamate**: was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>6</sup>



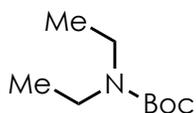
**(9H-fluoren-9-yl)methyl methyl(phenyl)carbamate**: Fmoc-Cl (3.02 g, 11.7 mmol) in dioxane (20 mL) was added slowly to an ice-bath cooled solution of N-methylaniline (0.5 g, 4.67 mmol) in dioxane (50 mL) and 10 % NaHCO<sub>3</sub> (50 mL). The mixture was stirred in the ice-bath for 30 minutes and then warmed to room temperature where it was allowed to stir for 12 hours. The solution was poured into H<sub>2</sub>O, and extracted with Et<sub>2</sub>O (50 mL x 3). The organic layer was separated and washed with H<sub>2</sub>O (3 mL). The organic layer was dried with MgSO<sub>4</sub> and concentrated in vacuo. Reaction mixture was purified by column chromatography (0-10% EtOAc/Hex) to give the desired compound (1.4 g, 4.4 mmol, 94%) as a white solid.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.44 (dt, *J* = 13.0, 7.6 Hz, 5H), 7.39 – 7.20 (m, 6H), 4.48 (d, *J* = 6.9 Hz, 2H), 4.19 (s, 1H), 3.38 (s, 3H).

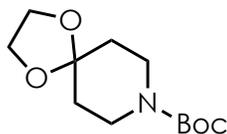
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 155.57, 143.93, 143.18, 141.33, 129.08, 127.67, 127.01, 126.53, 125.20, 119.96, 67.66, 47.19, 37.87.

**IR** (thin film): 1700, 1596, 1497, 1341 1150, 756.

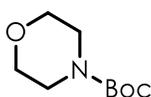
**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 352.130830; found: 352.13019.



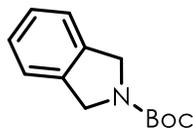
**tert-butyl diethylcarbamate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>7</sup>



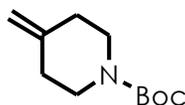
**tert-butyl 1,4-dioxo-8-azaspiro[4.5]decane-8-carboxylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>8</sup>



**tert-butyl morpholine-4-carboxylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>9</sup>

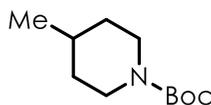


**tert-butyl isoindoline-2-carboxylate** was prepared according to the following procedure: Isoindoline (1.00 g, 8.39 mmol) was stirred with DCM (10 mL). Boc<sub>2</sub>O (2.75 g, 12.6 mmol) was added in one portion, followed by triethylamine (1.8 mL, 12.6 mmol). The reaction mixture was allowed to stir overnight before being concentrated to yield a dark oil. The product was isolated *via* flash column chromatography (15% ethyl acetate/hexane) to yield the desired product as a white solid (2.28 g, quant.). Spectral data were in agreement with literature values.<sup>10</sup>

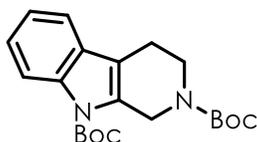


**tert-butyl 4-methylenepiperidine-1-carboxylate** was prepared according to the following procedure: Methyltriphenylphosphonium bromide (1.97 g, 5.52 mmol) was stirred with THF (20 mL) under nitrogen in a flame-dried flask. Potassium tert-butoxide (619 mg, 5.52 mmol) was added in one portion and the reaction mixture became a bright yellow color. The reaction mixture was allowed to stir for 30 minutes at room temperature. tert-butyl 4-oxopiperidine-1-carboxylate (1.00 g, 5.02 mmol) was then added in one portion and the yellow color disappeared. A white precipitate formed and the reaction mixture was allowed to stir overnight. The next day, the reaction mixture was concentrated and the desired product was isolated *via* flash column chromatography (5%

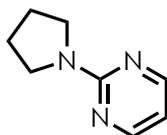
EA/hexanes) as a clear oil (593 mg, 60% yield). Spectral data were in agreement with literature values.<sup>10</sup>



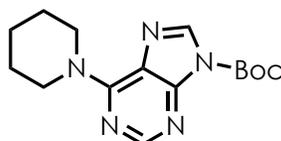
**tert-butyl 4-methylpiperidine-1-carboxylate** was prepared according to the following procedure: tert-butyl 4-methylenepiperidine-1-carboxylate (300 mg, 1.52 mmols) was dissolved in methanol (10 mL) and sparged with argon for 10 minutes. A small portion of Pd/C was added to the flask and the resulting suspension was sparged with hydrogen for 10 minutes. The flask was then stirred for 24 hours under an atmosphere of hydrogen (balloon). The reaction mixture was then filtered through a celite pad and concentrated to yield the desired product as a clear oil (293 mg, 97% yield). Spectral data were in agreement with literature values.<sup>11</sup>



**di-tert-butyl 3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>12</sup>

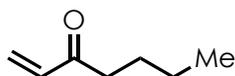


**2-(pyrrolidin-1-yl)pyrimidine** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>13</sup>

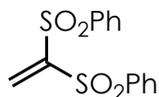


**tert-butyl 6-(piperidin-1-yl)-9H-purine-9-carboxylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>14</sup>

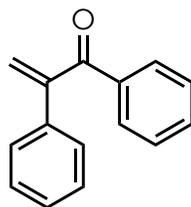
## Preparation of Radical Acceptors



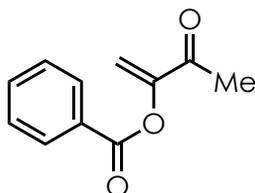
**hept-1-en-3-one** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>15</sup>



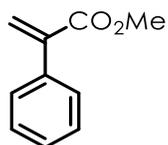
**(ethene-1,1-diyl)disulfonylbenzene** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>16</sup>



**1,2-diphenylprop-2-en-1-one** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>17</sup>

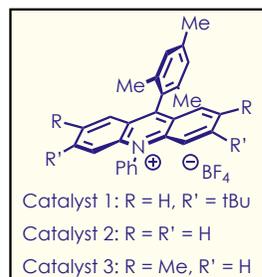
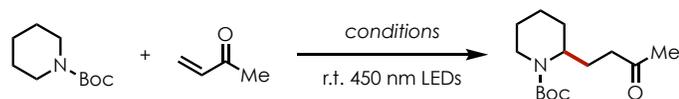


**3-oxobut-1-en-2-yl benzoate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>18</sup>



**methyl 2-phenylacrylate** was prepared according to a published procedure; spectral data were in agreement with literature values.<sup>19</sup>

## Reaction Optimization



entry	catalyst	concentration	solvent	time	X:XX	yield	additive
1	2	0.1	DCE	20	1:1	< 5	-
2	3	0.1	DCE	20	1:1	< 5	-
3	1	0.1	DCE	20	1:1	33	-
4	1	0.1	DCE	20	1:2	39	-
5	1	0.1	DCE	20	1:3	45	-
6	1	0.1	DCE	20	1:4	43	-
7	1	0.1	MECN	20	1:3	28	-
8	1	0.1	PhCF <sub>3</sub>	20	1:3	< 5	-
9	1	0.1	DCM	20	1:3	51	-
10	1	0.1	MeNO <sub>2</sub>	20	1:3	13	-
11	1	0.05	DCM	20	1:3	42	-
12	1	0.033	DCM	20	1:3	35	-
13	1	0.025	DCM	20	1:3	42	-
14	2	0.1	DCM	20	1:3	< 5	-
15	3	0.1	DCM	20	1:3	< 5	-
16	1	0.1	DCE	20	2:1	57	-
17	1	0.1	DCE	20	3:1	68	-
18	1	0.1	DCE	20	4:1	65	-
19	1	0.1	DCM	1	3:1	31	-
20	1	0.1	DCM	2	3:1	57	-
21	1	0.1	DCM	3	3:1	58	-
22	1	0.1	DCM	6	3:1	79	-
23	1	0.1	DCM	9	3:1	63	-
24	1	0.1	DCM	12	3:1	71	-
25	1	0.1	DCM	18	3:1	72	-
26	1	0.1	DCM	36	3:1	58	-
27	1	0.05	DCM	20	1:3	33	HCO <sub>2</sub> H
28	1	0.05	DCM	20	1:3	42	MeCO <sub>2</sub> H
29	1	0.05	DCM	20	1:3	< 5	TsOH·AEH <sub>2</sub> O
30	1	0.05	DCM	20	1:3	43	NH <sub>4</sub> Cl
31	1	0.05	DCM	20	1:3	36	NaBF <sub>4</sub>
32	1	0.05	DCM	20	1:3	28	LiBF <sub>4</sub>
33	1	0.05	DCM	20	1:3	< 5	Sc(OTf) <sub>3</sub>
34	1	0.05	DCM	20	1:3	23	Zn(OTf) <sub>2</sub>
35	1	0.05	DCM	20	1:3	12	Ce(OTf) <sub>3</sub>
36	1	0.05	DCM	20	1:3	12	2,6-lutidine
37	1	0.05	DCM	20	1:3	41	2,6-di-tert-butyl-4-methylpyridine
38	1	0.05	DCM	20	1:3	19	K <sub>2</sub> CO <sub>3</sub>
39	1	0.05	DCM	20	1:3	21	pH 9 buffer

## Procedure and Data for Product Synthesis

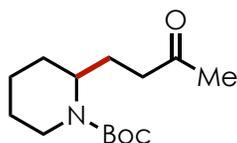
### Reaction Setup



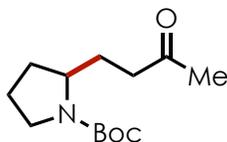
Light intensity at reaction site was determined to be  $96\text{mW}/\text{cm}^2$

### General Procedure

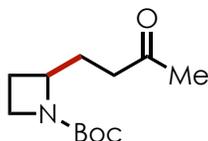
To a 1- or 2-dram vial charged with a Teflon-coated stir was added 3,6-Di-*tert*-butyl-9-mesityl-*N*-phenylacridinium (2.89 mg, 0.005 mmol) and amine substrate (0.3 mmol). The vial was then sealed with a Teflon coated septum cap before 1 mL (0.1 M) of dichloromethane was added via syringe and the mixture sparged with  $\text{N}_2$  for 5 minutes. The Michael acceptor was added (0.1 mmol) and the reactions were stirred for 6 hrs under irradiation with 450 nm LEDs. After completion, the reaction mixture was concentrated in vacuo and purified using silica gel chromatography to afford the desired product.



***tert*-butyl (S)-2-(3-oxobutyl)piperidine-1-carboxylate (2):** Isolated by column chromatography (0-20% EtOAc/Hex), as a yellow oil, 21.2 mg, 83%. Analytical data matched that reported in the literature.<sup>20</sup>



**tert-butyl (S)-2-(3-oxobutyl)pyrrolidine-1-carboxylate (3):** Isolated by column chromatography (0-20% EtOAc/Hex), as a yellow oil, 21.0 mg, 87%. Analytical data matched that reported in the literature.<sup>20</sup>



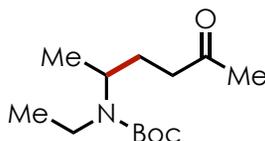
**tert-butyl (R)-2-(3-oxobutyl)azetidine-1-carboxylate (4):** Isolated by column chromatography (0-20% EtOAc/Hex), as a colorless oil, 15.4 mg, 68%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*)  $\delta$  4.22 (p, *J* = 6.5 Hz, 1H), 3.89 – 3.74 (m, 2H), 2.62 – 2.48 (m, 2H), 2.33 – 2.24 (m, 1H), 2.18 (s, 3H), 2.00 (ddq, *J* = 63.6, 14.5, 7.2 Hz, 2H), 1.83 (q, *J* = 9.3, 8.3 Hz, 1H), 1.45 (s, 9H).

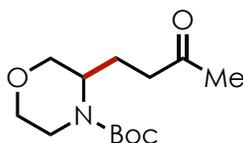
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  208.45, 156.86, 79.34, 61.33, 46.37, 39.42, 29.91, 29.70, 28.44, 21.79.

**IR** (thin film): 2971, 2929, 2892, 1603, 1363, 1249, 1134.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 250.141395; found: 250.14130.



**tert-butyl (S)-ethyl(5-oxohexan-2-yl)carbamate (5):** Isolated by column chromatography (0-20% EtOAc/Hex), as a yellow oil, 9.5 mg, 39%. Analytical data matched that reported in the literature.<sup>21</sup>



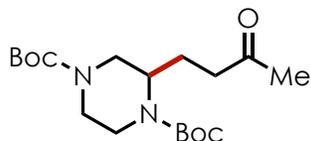
**tert-butyl (R)-3-(3-oxobutyl)morpholine-4-carboxylate (6):** Isolated by column chromatography (40% EtOAc/Hex), as a yellow oil, 15.9 mg, 62%.

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*)  $\delta$  3.94 – 3.86 (m, 1H), 3.80 – 3.70 (m, 2H), 3.64 (d, *J* = 11.7 Hz, 2H), 3.49 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.35 (td, *J* = 11.9, 3.0 Hz, 1H), 3.03 (s, 1H), 2.50 – 2.24 (m, 2H), 2.08 (s, 3H), 1.76 (dtd, *J* = 13.0, 7.5, 5.4 Hz, 1H), 1.39 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, Chloroform-*d*) δ 207.71, 154.72, 80.01, 69.65, 66.91, 39.78, 36.63, 29.97, 29.69, 28.39, 24.68.

**IR** (thin film): 2971, 1686, 1409, 1364, 1165, 1119, 864

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 280.15208; found: 280.15229.



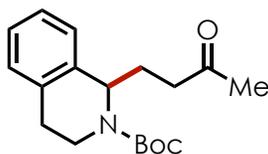
**di-tert-butyl (R)-2-(3-oxobutyl)piperazine-1,4-dicarboxylate (7)**: Isolated by column chromatography (0-20% EtOAc/Hex), as a white solid, 32.1mg, 90%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 4.21 – 3.69 (m, 4H), 2.83 (d, *J* = 135.3 Hz, 3H), 2.55 – 2.29 (m, 2H), 2.12 (d, *J* = 2.8 Hz, 3H), 1.95 – 1.79 (m, 1H), 1.79 – 1.68 (m, 1H), 1.50 – 1.35 (m, 18H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 207.51, 154.91, 154.70, 80.07, 80.02, 47.20, 45.48, 43.95, 42.81, 39.62, 29.96, 28.35, 22.58.

**IR** (thin film): 2974, 1687, 1412, 1364, 1227, 1164, 865.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 379.220922; found: 379.22077.



**tert-butyl 1-(3-oxobutyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (8)**: Isolated by column chromatography (5-25% EtOAc/Hex), as a colorless oil, 30.1mg, 99%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.24 – 7.14 (m, 3H), 7.11 (d, *J* = 5.9 Hz, 1H), 5.20 – 5.00 (m, 1H), 4.30 – 3.86 (m, 1H), 3.32 – 3.04 (m, 1H), 3.01 – 2.82 (m, 1H), 2.72 (d, *J* = 16.3 Hz, 1H), 2.63 (dt, *J* = 17.9, 7.5 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.17 (s, 3H), 2.13 – 1.92 (m, 2H), 1.48 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 208.13, 207.60, 155.19, 154.88, 137.79, 137.57, 134.26, 134.13, 129.07, 128.73, 127.33, 127.13, 126.52, 126.10, 80.04, 79.58, 54.02, 53.51, 40.23, 40.03, 38.33, 36.66, 30.21, 28.47.

**IR** (thin film): 2974, 1684, 1416, 1364, 1159, 748.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 326.173244; found: 326.17301.



**tert-butyl-1-(3-oxobutyl)isoindoline-2-carboxylate (9):** Isolated by column chromatography (15% EtOAc/Hex), as a yellow oil, 63.2 mg (0.3 mmol scale), 73%.

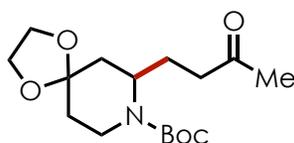
**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.45 – 7.05 (m, 4H), 5.21 – 5.11 (m, 1H), 4.75 (dd, *J* = 35.9, 14.9 Hz, 1H), 4.58 – 4.44 (m, 1H), 2.62 – 2.27 (m, 2H), 2.20 – 1.98 (m, 5H), 1.69 – 1.04 (m, 9H).

**<sup>13</sup>C NMR** (151 MHz, Chloroform-*d*)  $\delta$  208.46, 208.19, 154.55, 140.10, 140.02, 136.95, 136.66, 127.70, 127.62, 127.54, 127.47, 122.58, 122.43, 122.37, 80.08, 79.71, 62.21, 62.08, 52.54, 52.45, 38.60, 37.56, 29.88, 29.57, 29.16, 28.94, 28.52.

(Mixture of rotomers)

**IR** (thin film): 2976, 2360, 1712, 1367, 1276, 764

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 312.157594; found: 312.15741.



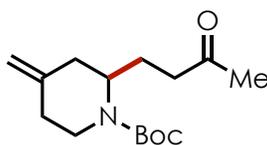
**tert-butyl 7-(3-oxobutyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (10):** Isolated by column chromatography (10-50% EtOAc/Hex), as a orange oil, 23.5 mg, 32%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*)  $\delta$  4.40 – 4.30 (m, 1H), 4.11 – 3.89 (m, 5H), 3.07 – 2.94 (m, 1H), 2.49 – 2.33 (m, 2H), 2.28 – 2.12 (m, 4H), 1.86 (dd, *J* = 13.7, 6.6 Hz, 1H), 1.75 (dtd, *J* = 14.8, 7.6, 4.9 Hz, 1H), 1.71 – 1.59 (m, 3H), 1.53 – 1.43 (m, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  208.34, 154.87, 107.16, 79.70, 77.23, 77.02, 76.80, 64.68, 63.85, 50.15, 40.59, 37.52, 34.63, 30.04, 28.44, 25.10.

**IR** (thin film): 2965, 1684, 1415, 1377, 1165, 1105.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 314.196199; found: 314.19644.



**tert-butyl 4-methylene-2-(3-oxobutyl)piperidine-1-carboxylate (11):** Isolated by column chromatography (15% EtOAc/Hex), as a yellow oil, 8.2 mg, 31%.

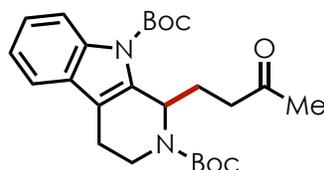
**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*)  $\delta$  4.80 (dd, *J* = 44.1, 1.9 Hz, 1H), 4.45 – 3.76 (m, 2H), 2.75 (s, 1H), 2.36 (tdd, *J* = 17.7, 11.2, 5.8 Hz, 2H), 2.23 – 2.05 (m, 4H), 1.96 – 1.74

(m, 1H), 1.79 – 1.56 (m, 2H), 1.57 – 1.40 (m, 9H), 1.38 – 1.22 (m, 2H), 1.03 – 0.83 (m, 1H).

**<sup>13</sup>C NMR** (151 MHz, Chloroform-*d*) δ 175.92, 155.05, 154.77, 142.20, 111.13, 81.88, 79.65, 79.32, 70.09, 54.95, 50.43, 39.84, 38.56, 34.12, 30.06, 29.70, 28.46, 28.15, 28.04, 23.86, 20.76, 14.02. (Mixture of rotomers)

**IR** (thin film): 2924, 2362, 1687, 1412, 1261, 1162, 764

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 290.173244; found: 290.17302.



**di-tert-butyl (R)-1-(3-oxobutyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate (12):** Isolated by column chromatography (30% EtOAc – 50%

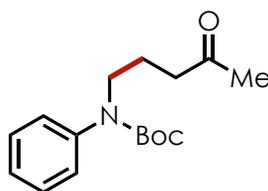
EtOAc/hexanes gradient), as a yellow solid, 17.7 mg, 20% (0.2 mmol scale).

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 8.61 – 8.32 (m, 1H), 7.52 – 7.48 (m, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 5.30 – 5.12 (m, 1H), 4.57 – 4.24 (m, 1H), 3.24 – 3.02 (m, 1H), 2.91 – 2.67 (m, 3H), 2.59 (s, 1H), 2.31 – 2.19 (m, 3H), 2.00 – 1.92 (m, 1H), 1.51 (d, *J* = 11.9 Hz, 18H).

**<sup>13</sup>C NMR** (151 MHz, , Chloroform-*d*) δ 171.18, 155.47, 154.84, 135.96, 134.46, 133.93, 126.72, 121.74, 119.41, 118.00, 110.98, 108.76, 108.16, 80.22, 79.93, 60.42, 50.77, 50.18, 40.02, 38.77, 37.57, 30.13, 29.72, 28.49, 21.48, 21.08, 14.22. (Mixture of rotomers)

**IR** (thin film): 3009, 2360, 1689, 1276, 1261

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 465.236024; found: 465.23453.



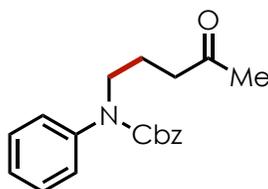
**tert-butyl (4-oxopentyl)(phenyl)carbamate (13):** Isolated by column chromatography (5-20% EtOAc/Hex), as a yellow oil, 27.0 mg, 97%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.35 (t, *J* = 7.7 Hz, 2H), 7.25 – 7.16 (m, 3H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.12 (s, 3H), 1.83 (p, *J* = 7.2 Hz, 2H), 1.44 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 207.51, 154.91, 154.70, 80.07, 80.02, 77.27, 77.05, 47.20, 45.48, 43.95, 42.81, 39.62, 29.96, 28.35, 22.58.

**IR** (thin film): 2975, 1602, 1390, 1298, 1158, 756.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 300.157544; found: 300.15728.



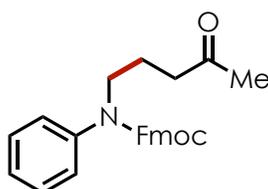
**benzyl (4-oxopentyl)(phenyl)carbamate (14):** Isolated by column chromatography (0-30% EtOAc/Hex), as a yellow oil, 25.2 mg, 81%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.41 – 7.18 (m, 10H), 5.16 (s, 2H), 3.72 (t, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 2.08 (s, 3H), 1.88 – 1.76 (m, 2H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 207.90, 155.49, 141.54, 136.65, 129.08, 128.40, 127.86, 127.55, 127.26, 126.81, 67.17, 49.58, 40.40, 29.91, 22.35.

**IR** (thin film): 2974, 1700, 1494, 1403, 1294, 697.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 334.141396; found: 334.14086.



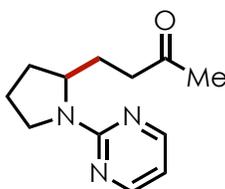
**(9H-fluoren-9-yl)methyl (4-oxopentyl)(phenyl)carbamate (15):** Isolated by column chromatography (0-40% EtOAc/Hex), as white solid, 31.4 mg, 79%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.38 (ddt, *J* = 25.3, 17.6, 7.5 Hz, 6H), 7.27 – 7.14 (m, 5H), 4.60 – 4.24 (m, 2H), 4.13 (d, *J* = 38.2 Hz, 1H), 3.67 (s, 2H), 2.45 (s, 2H), 2.13 (s, 3H), 1.75 (d, *J* = 57.4 Hz, 2H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 207.92, 155.52, 143.80, 141.27, 134.70, 129.19, 127.75, 127.58, 127.04, 126.91, 125.10, 119.84, 67.30, 49.56, 47.13, 40.45, 29.98, 22.31.

**IR** (thin film): 3084, 2946, 1702, 1405, 1295, 740.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 422.172695; found: 422.17197.



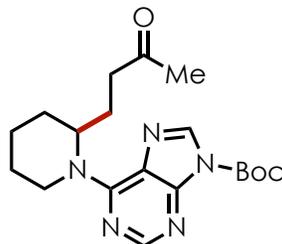
**4-(1-(pyrimidin-2-yl)pyrrolidin-2-yl)butan-2-one (16):** Isolated by column chromatography (0-55% EtOAc/Hex), as an orange solid, 21.9 mg, 100%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 8.24 (td, *J* = 4.0, 3.5, 1.6 Hz, 2H), 6.41 (tdd, *J* = 4.8, 4.0, 3.3, 1.6 Hz, 1H), 4.20 – 4.09 (m, 1H), 3.59 – 3.45 (m, 2H), 2.51 – 2.39 (m, 2H), 2.13 – 2.07 (m, 3H), 2.06 – 1.86 (m, 4H), 1.77 – 1.65 (m, 2H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 208.68, 160.52, 157.51, 109.20, 56.69, 47.02, 40.70, 30.26, 29.69, 27.59, 23.34.

**IR** (thin film): 2691, 2872, 1711, 1580, 1494, 1338, 798.

**HRMS** (+ESI): *m/z* calculated for [M+H]<sup>+</sup>: 220.144439; found: 220.14434.



**tert-butyl (S)-6-(2-(3-oxobutyl)piperidin-1-yl)-9H-purine-9-carboxylate (17):**

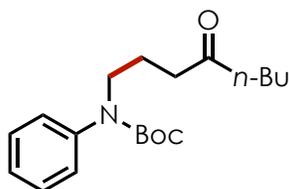
Isolated by column chromatography (0-55% EtOAc/Hex), as a yellow oil, 22.6 mg, 60.5%.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.15 (s, 1H), 6.01 – 4.96 (m, 2H), 3.11 (s, 1H), 2.56 – 2.33 (m, 2H), 2.25 (dtt, *J* = 16.1, 11.7, 5.9 Hz, 1H), 2.04 (s, 3H), 1.69 (s, 16H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 208.33, 154.49, 154.32, 150.99, 146.11, 136.46, 119.93, 86.22, 40.19, 30.03, 29.69, 29.13, 27.97, 25.86, 23.66, 19.20.

**IR** (thin film): 2931, 1749, 1714, 1580, 1258, 1138.

**HRMS** (+ESI): *m/z* calculated for [M+H]<sup>+</sup>: 374.218666; found: 374.21807.



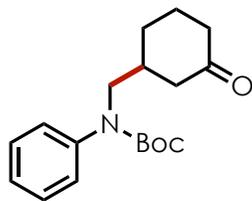
**tert-butyl (4-oxooctyl)(phenyl)carbamate (18):** Isolated by column chromatography (0-8% EtOAc/Hex), as a colorless oil, 26.0 mg, 82.0%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.34 (t, *J* = 7.8 Hz, 2H), 7.24 – 7.17 (m, 3H), 3.65 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.83 (p, *J* = 7.3 Hz, 2H), 1.53 (p, *J* = 7.5 Hz, 2H), 1.34 – 1.25 (m, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).

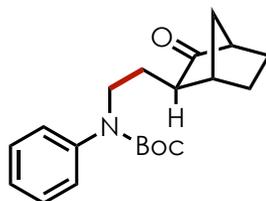
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 210.42, 154.77, 142.34, 128.77, 127.02, 126.05, 80.13, 49.20, 42.57, 39.58, 28.32, 25.93, 22.60, 22.33, 13.85.

**IR** (thin film): 2957, 2931, 1693, 1389, 1365, 1298, 1157, 697.

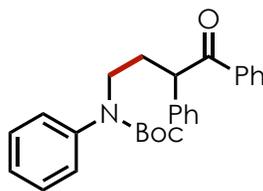
**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 342.203995; found: 342.20246.



**tert-butyl (S)-((3-oxocyclohexyl)methyl)(phenyl)carbamate (19):** Isolated by column chromatography (0-20% EtOAc/Hex), as a white solid, 16.2 mg, 53%.  
**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*)  $\delta$  7.35 (t,  $J = 7.8$  Hz, 2H), 7.25 – 7.21 (m, 1H), 7.19 (d,  $J = 7.8$  Hz, 2H), 3.73 – 3.61 (m, 2H), 2.45 (ddt,  $J = 13.6, 4.0, 2.0$  Hz, 1H), 2.36 (dddt,  $J = 14.2, 4.9, 3.4, 1.6$  Hz, 1H), 2.27 (td,  $J = 13.5, 6.2$  Hz, 1H), 2.05 (dddd,  $J = 30.4, 15.8, 11.7, 7.5, 3.8$  Hz, 3H), 1.90 (dtd,  $J = 13.6, 3.8, 1.9$  Hz, 1H), 1.60 (tdt,  $J = 13.0, 8.3, 4.1$  Hz, 3H), 1.43 (s, 10H).  
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  210.87, 154.94, 142.30, 128.89, 127.14, 126.26, 80.39, 77.23, 77.02, 76.81, 54.79, 45.68, 41.38, 38.14, 28.90, 28.29, 24.94.  
**IR** (thin film): 2928, 1696, 1390, 1365, 1280, 1164, 698.  
**HRMS** (+ESI):  $m/z$  calculated for [M+Na]<sup>+</sup>: 326.173244; found: 326.17313.



**tert-butyl (2-((1R,2S,4S)-3-oxobicyclo[2.2.1]heptan-2-yl)ethyl)(phenyl)carbamate (20):** Isolated by column chromatography (0-20% EtOAc/Hex), as a colorless oil, 31.8mg, 100%.  
**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*)  $\delta$  7.34 (t,  $J = 7.8$  Hz, 2H), 7.25 – 7.14 (m, 3H), 3.75 (ddd,  $J = 14.5, 9.7, 5.1$  Hz, 1H), 3.64 (ddd,  $J = 13.9, 9.4, 6.3$  Hz, 1H), 2.66 – 2.58 (m, 2H), 2.03 – 1.90 (m, 2H), 1.82 (dtd,  $J = 13.1, 8.5, 5.3$  Hz, 1H), 1.67 (dt,  $J = 10.3, 1.8$  Hz, 1H), 1.63 – 1.56 (m, 3H), 1.53 – 1.35 (m, 11H).  
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  219.21, 154.64, 142.29, 128.81, 127.07, 126.12, 80.19, 51.33, 50.30, 48.69, 38.30, 37.12, 28.34, 25.35, 25.30, 21.21.  
**IR** (thin film): 2964, 2358, 1743, 1696, 1391, 1154.  
**HRMS** (+ESI):  $m/z$  calculated for [M+Na]<sup>+</sup>: 352.188894; found: 352.18875.



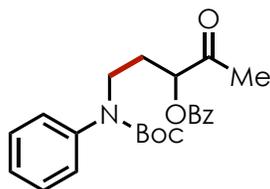
**tert-butyl (4-oxo-3,4-diphenylbutyl)(phenyl)carbamate (21):** Isolated by column chromatography (0-8% EtOAc/Hex), as a white solid, 31.2 mg, 91%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.97 – 7.87 (m, 2H), 7.51 – 7.45 (m, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.17 (m, 8H), 4.65 (t, *J* = 7.2 Hz, 1H), 3.78 – 3.59 (m, 2H), 2.54 – 2.41 (m, 1H), 2.15 – 2.00 (m, 1H), 1.38 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 198.95, 154.69, 142.34, 139.14, 136.53, 132.85, 129.01, 128.79, 128.72, 128.45, 128.14, 127.12, 126.93, 125.98, 80.23, 51.00, 48.14, 32.69, 28.25.

**IR** (thin film): 2976, 2365, 1693, 1391, 1165, 755.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 438.204544; found: 438.20440.



**1-((tert-butoxycarbonyl)(phenyl)amino)-4-oxopentan-3-yl benzoate (22):**

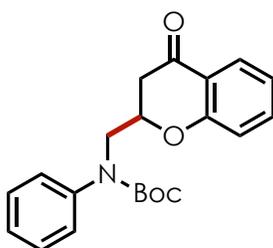
Isolated by column chromatography (0-21% EtOAc/Hex), as a colorless oil, 29.0mg, 73%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 8.08 – 8.01 (m, 2H), 7.63 – 7.58 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.25 – 7.17 (m, 3H), 5.28 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.88 (dddd, *J* = 33.7, 14.0, 8.6, 6.0 Hz, 2H), 2.33 – 2.06 (m, 5H), 1.43 (d, *J* = 5.1 Hz, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 204.72, 165.89, 154.53, 142.10, 133.46, 129.82, 129.16, 128.92, 128.47, 126.88, 126.26, 80.56, 76.85, 46.35, 29.18, 28.27, 26.08.

**IR** (thin film): 2975, 1718, 1693, 1270, 1164, 711.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 420.178723; found: 420.17858.



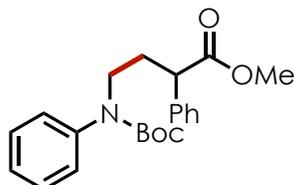
**tert-butyl (R)-((4-oxochroman-2-yl)methyl)(phenyl)carbamate (23):** Isolated by column chromatography (0-20% EtOAc/Hex), as a yellow solid, 23.0 mg, 65%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.30 (s, 1H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 4.70 (dtd, *J* = 12.6, 6.2, 3.5 Hz, 1H), 4.09 – 3.98 (m, 2H), 2.82 – 2.65 (m, 2H), 1.45 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 191.47, 161.04, 154.78, 142.49, 136.02, 128.88, 127.34, 126.96, 126.48, 121.48, 120.98, 117.93, 80.88, 75.85, 53.34, 40.68, 28.27.

**IR** (thin film): 2975, 1689, 1463, 1365, 1148, 761.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 376.152508; found: 376.15231.



**methyl 4-((*tert*-butoxycarbonyl)(phenyl)amino)-2-phenylbutanoate (24):**

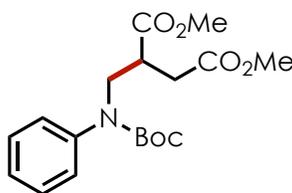
Isolated by column chromatography (10% EtOAc/Hex), as a clear oil, 25.3 mg, 69%.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.41 – 7.07 (m, 10H), 3.73 – 3.52 (m, 6H), 2.34 (dtd, *J* = 13.7, 8.3, 5.6 Hz, 1H), 2.16 – 2.00 (m, 1H), 1.44 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, Chloroform-*d*) δ 173.82, 154.59, 142.29, 138.43, 128.78, 128.71, 127.83, 127.37, 126.94, 126.03, 80.27, 52.06, 48.97, 48.06, 32.03, 28.31.

**IR** (thin film): 2976, 1734, 1694, 1390, 1158, 697

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 392.183610; found: 392.18361.



**dimethyl 2-(((*tert*-butoxycarbonyl)(phenyl)amino)methyl)succinate (25):**

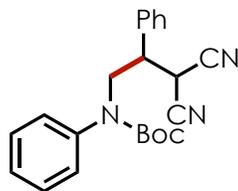
Isolated by column chromatography (20% EtOAc/Hex), as a clear oil, 26.5 mg, 76%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.35 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.17 (m, 3H), 4.06 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.87 (dd, *J* = 14.2, 6.6 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.10 (ddd, *J* = 11.5, 9.2, 5.7 Hz, 1H), 2.77 (dd, *J* = 17.0, 9.3 Hz, 1H), 2.52 (dd, *J* = 17.0, 4.7 Hz, 1H), 1.43 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, Chloroform-*d*) δ 173.31, 171.93, 154.65, 141.75, 128.82, 127.30, 126.43, 51.99, 51.80, 50.80, 40.67, 33.35, 28.22.

**IR** (thin film): 2978, 1736, 1697, 1367, 1160, 751

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 374.157988; found: 374.15780



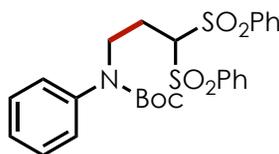
**tert-butyl (R)-(3,3-dicyano-2-phenylpropyl)(phenyl)carbamate (26):** Isolated by column chromatography (0-18% EtOAc/Hex), as a white solid, 33.8mg, 94%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.43 – 7.36 (m, 3H), 7.36 – 7.27 (m, 4H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 4.42 (dd, *J* = 14.4, 8.0 Hz, 1H), 4.19 (d, *J* = 5.9 Hz, 1H), 4.13 (dd, *J* = 14.4, 7.0 Hz, 1H), 3.56 (q, *J* = 7.0 Hz, 1H), 1.44 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 154.73, 141.34, 134.76, 129.21, 129.18, 129.11, 128.30, 126.91, 126.82, 112.00, 111.52, 81.55, 77.33, 77.12, 76.91, 51.50, 45.25, 28.21, 27.44.

**IR** (thin film): 2978, 1688, 1159, 1392, 1366, 2253, 697.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 362.186303; found: 362.18776.



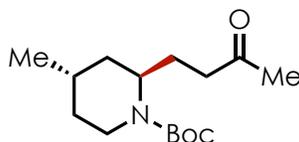
**tert-butyl (3,3-bis(phenylsulfonyl)propyl)(phenyl)carbamate (27):** Isolated by column chromatography (20-50% EtOAc/Hex), as a white solid, 51.0 mg, 99%.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 7.8 Hz, 4H), 7.69 – 7.64 (m, 2H), 7.55 – 7.47 (m, 4H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.24 (m, 1H), 7.21 – 7.14 (m, 2H), 4.96 (s, 1H), 4.04 (t, *J* = 5.9 Hz, 2H), 2.45 (q, *J* = 5.8 Hz, 2H), 1.44 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 155.07, 142.42, 142.42, 137.72, 134.40, 129.61, 129.07, 128.98, 127.29, 126.37, 80.85, 80.23, 48.38, 28.26, 25.41.

**IR** (thin film): 2976, 1682, 1328, 1312, 1147, 1079, 728.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 538.133429; found: 538.13377.



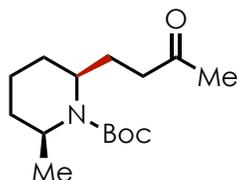
**tert-butyl-4-methyl-2-(3-oxobutyl)piperidine-1-carboxylate (28):** Isolated as a single diastereomer by column chromatography (5% EtOAc/Hex), as a yellow oil, 13.2 mg, 49%. Crude NMR showed >20:1 d.r.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 4.33 – 4.05 (m, 1H), 3.91 (dd, *J* = 69.9, 13.1 Hz, 1H), 2.67 (dt, *J* = 46.5, 16.7 Hz, 1H), 2.44 – 2.24 (m, 2H), 2.07 (d, *J* = 2.9 Hz, 3H), 1.94 – 1.87 (m, 1H), 1.76 – 1.42 (m, 3H), 1.38 (s, 9H), 1.18 (tq, *J* = 13.0, 5.7 Hz, 2H), 1.01 – 0.87 (m, 1H), 0.81 (d, *J* = 6.5 Hz, 3H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 208.64, 208.62, 155.13, 79.39, 79.20, 50.53, 49.69, 40.55, 40.31, 39.32, 38.03, 37.70, 34.33, 34.08, 30.06, 30.05, 28.53, 25.48, 25.41, 24.30, 23.35, 22.34 (Mixture of rotomers).

**IR** (thin film): 2925, 1684, 1414, 1364, 1246, 1156, 1087.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 292.188345; found: 292.18717.



**tert-butyl (2*S*,6*S*)-2-methyl-6-(3-oxobutyl)piperidine-1-carboxylate ((*S*)-**

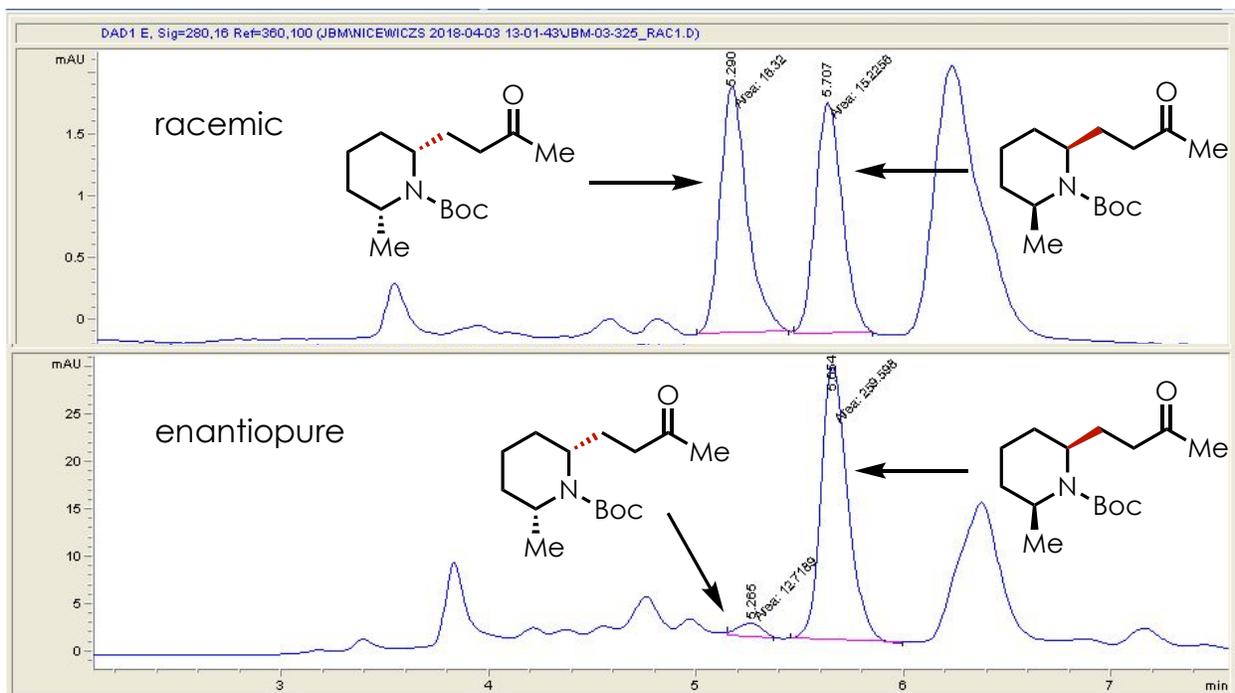
**29**): Isolated as a single diastereomer by column chromatography (0-20% EtOAc/Hex), as a colorless oil, 17.0 mg, 20%. HPLC analysis was performed on an Agilent 1200 Series PDA system equipped with Chiralpak IA column using a flow rate of 1 mL/min with a 95:5 ratio of hexanes and isopropanol as eluent. Retention time of the enantiopure sample matched that of the racemic standard. Starting material ee was 97% and ee of product after the completion of the reaction was 90%. Crude NMR showed >10:1 d.r.

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 4.33 (p, *J* = 7.1 Hz, 1H), 4.12 (qd, *J* = 7.5, 3.8 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.41 (ddd, *J* = 17.4, 9.5, 5.4 Hz, 1H), 2.16 (s, 3H), 1.90 – 1.76 (m, 2H), 1.72 – 1.55 (m, 4H), 1.48 (s, 10H), 1.19 (d, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 208.43, 155.40, 79.16, 49.27, 45.67, 41.47, 30.17, 29.97, 28.73, 28.51, 28.19, 20.54, 14.12.

**IR** (thin film): 2970, 2934, 1679, 1362, 1173, 1079.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 292.188345; found: 292.18784.



## Synthesis of monomorine I



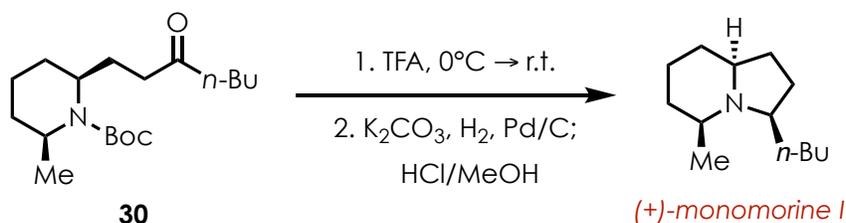
***tert*-butyl (2*S*,6*S*)-2-methyl-6-(3-oxoheptyl)piperidine-1-carboxylate (30):** To a 2 dram vial was added *tert*-butyl (*S*)-2-methylpiperidine-1-carboxylate (59.8 mg, 0.3 mmol), catalyst 1 (2.87 mg, 0.005 mmol) and 1 mL of DCM. The solution was sparged with N<sub>2</sub> then irradiated with blue light. During irradiation, a degassed 1 mL solution of butyl vinyl ketone (11.2 mg, 0.1 mmol) and catalyst 1 (2.87 mg, 0.005 mmol) was added over 8 hours via syringe pump. The solution then stirred for an additional 2 hours under irradiation before being concentrated and purified by column chromatography (8% Et<sub>2</sub>O/Hex) to give compound 30 as a single diastereomer (11:1 d.r. by crude NMR) as an orange oil (54% by NMR vs. HMDS).

**<sup>1</sup>H NMR** (600 MHz, Chloroform-*d*) δ 4.38 – 4.27 (m, 1H), 4.15 – 4.07 (m, 1H), 2.53 – 2.34 (m, 4H), 1.90 – 1.51 (m, 10H), 1.49 (s, 9H), 1.31 (ddt, *J* = 19.0, 11.6, 5.5 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 210.92, 155.39, 79.13, 42.64, 42.49, 40.56, 30.19, 28.82, 28.52, 28.17, 26.04, 23.33, 22.37, 20.52, 14.14, 13.86.

**IR** (thin film): 2932, 2871, 1712, 1680, 1362, 1174, 1079.

**HRMS** (+ESI): *m/z* calculated for [M+Na]<sup>+</sup>: 334.235298; found: 334.23522.



**(+)-monomorine I:** Compound 30 (65 mg, 0.077 mmol) was taken up in 1.2 mL of trifluoroacetic acid at 0°C. The reaction was allowed to warm to room temperature where it stirred for an additional 6 hours. The reaction mixture was then concentrated in vacuo to afford the crude TFA salt.

The crude product was combined with K<sub>2</sub>CO<sub>3</sub> (43.26 mg, 0.313 mmol) and 10 wt% palladium on carbon (10 mg, 9.4 μmol). The mixture was taken up in 10 mL of anhydrous MeOH and cooled to 0°C. The solution was then purged 3x with H<sub>2</sub> and allowed to warm to room temperature. The reaction then stirred for 14 hours under 1 atm of H<sub>2</sub> then passed through a silica plug and acidified with 2 mL of 3N methanolic HCl. The solution was concentrated in vacuo to give

monomorphine I hydrochloride as a white solid (45.4 mg, 93.8%). The HCl salt was purified by column chromatography (0-15% MeOH/DCM).  $[\alpha]^{26}_D = +29.1$  (c 0.0043, *n*-Hexane). The spectral data of the free base was in agreement with literature values.<sup>29</sup>

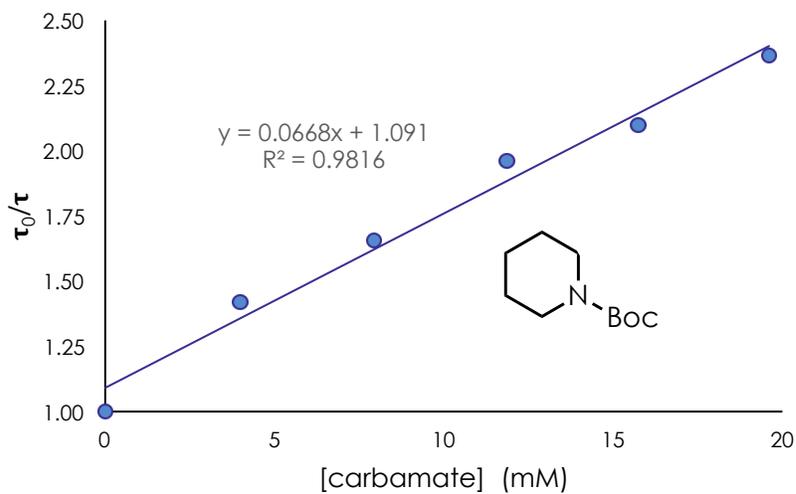
### Stern Volmer Analysis

Emission lifetime measurements were taken at ambient temperature using a Edinburgh FLS920 spectrometer and fit to single exponential decay according to a modification of the method previously described by our laboratory.<sup>22</sup> Measurements were made by the time-correlated single photon counting (TCSPC) capability of the instrument with pulsed excitation light (444.2 nm, typical pulse width = 95 ps) generated by a Edinburgh EPL-445 ps pulsed laser diode operating at a repetition rate of 5 MHz. The maximum emission channel count rate was less than 5% of the laser channel count rate, and each data set collected greater than 10000 counts on the maximum channel. The lifetime of fluorescence was determined by reconvolution fit with the instrument response function using the Edinburgh FS900 software. In all cases, after reconvolution, fluorescence decay was satisfactorily fit with a monoexponential function of the form:

$$I_t = I_0 e^{-t/\tau}$$

where  $I$  is the intensity (counts), and  $\tau$  is the mean lifetime of fluorescence.

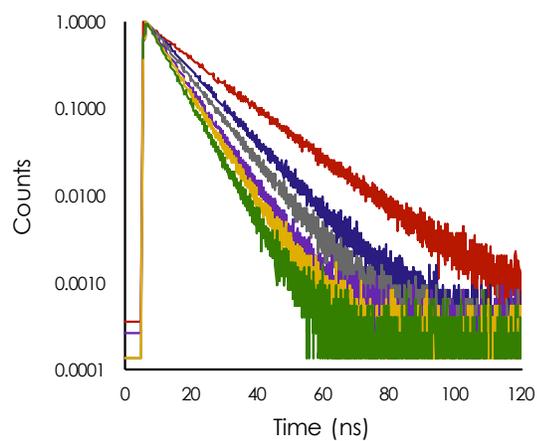
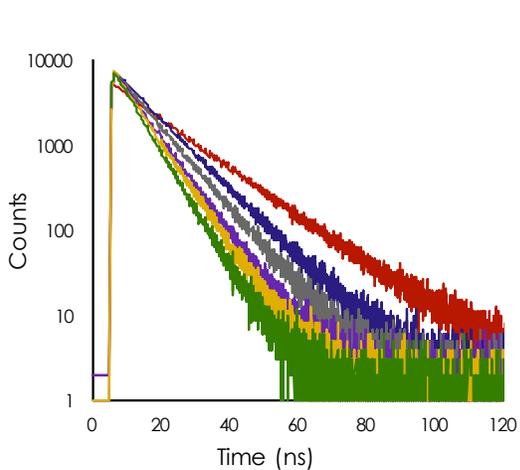
Stern-Volmer analysis on the quenching of fluorescence lifetime was carried out in DCM with detection at 500 nm (15 nm bandwidth), where the concentration of acridinium was  $1.6 \times 10^{-5}$  M. The quenching constant was determined with quencher concentrations in the range of 0 M to  $2.0 \times 10^{-2}$  M. Bimolecular quenching constants,  $k_q$ , were determined from the corresponding Stern-Volmer constant.<sup>30</sup> Quenching constants were determined for ***t*-Bu<sub>2</sub>-Mes-Acr<sup>+</sup>** with a representative Boc-amine. Comparison of UV-Vis absorption spectra taken before and after lifetime quenching studies verified that the acridinium was unchanged. UV-Vis spectra were taken on a Hewlett-Packard 8453 Chemstation spectrophotometer.



spike	catalyst concentration (M)	Quencher concentration (M)	lifetime (ns)	normalization
0	0.00016000	0.000000	14.9	1.000
1	0.00015936	0.003984	10.5	1.419
2	0.00015873	0.007937	9	1.656
3	0.00015810	0.011858	7.6	1.961
4	0.00015748	0.015748	7.1	2.099
5	0.00015686	0.019608	6.3	2.365

Raw Data

Normalized Data

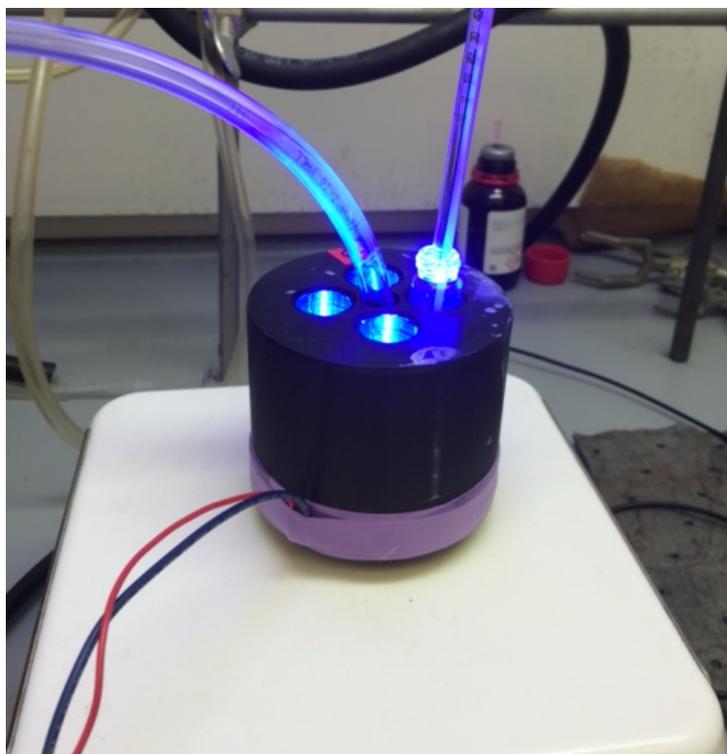


### Photochemical Quantum Yield ( $\Phi_r$ ) Determination:

A flame-dried vial was charged with acridinium catalyst (0.005 mmol, 5 mol%), DCM (1 mL), Boc-piperidine (0.3 mmol) and methyl vinyl ketone (0.1 mmol). The reaction mixture was then sparged with nitrogen for 10 minutes before being sealed and irradiated using a single blue LED for 2 hours (see below).

After this time, the reaction mixture was concentrated and the yield of the desired product was determined by proton NMR using HMDS as an internal standard (18.5% yield). This process was repeated for a reaction time of 3 hours, resulting in a 35.1% yield of the desired alkylation product. The photon flux for this light source had been previously determined to be  $1.50 \times 10^{-6}$  mol photons  $s^{-1}$  after two trials (std. dev.= $5 \times 10^{-8}$  mol photons  $s^{-1}$ ) using potassium ferrioxalate as a chemical actinometer (see reference for details).<sup>23</sup>

Based on these values, the quantum yield ( $\Phi_r$ ) for this reaction was determined to be  $0.19 \pm 0.03$  % ( $n=2$ ). This value suggests that a rapid chain mechanism is not the dominant pathway under these conditions.

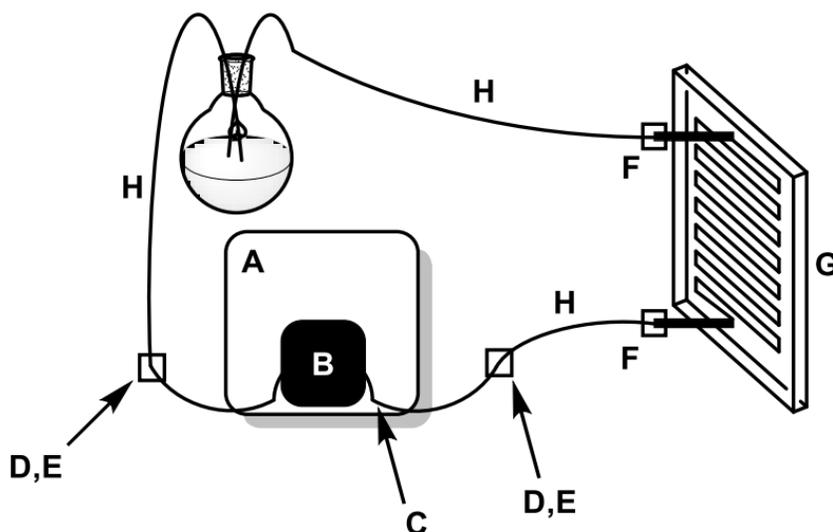


**Figure S1:** Photoreactor setup used in the quantum yield determination studies. This photoreactor allows for irradiation using a single 450 nm LED to ensure consistent photon flux. Individual reaction vials (1-dram) can be placed into the LED slots. The same slot was used for photon flux measurements, and quantum yield determination. The reactor is cooled by flowing air through the reactor and

out a heat sink mounted on the bottom. Reactor temperature was maintained below 40°C throughout the reactions. Stirring is accomplished by setting the reactor on a standard stir plate.

CREE XT-E Royal Blue LEDs were used pre-soldered to MCPCB (metal core printed circuit board); purchased from [www.rapidled.com](http://www.rapidled.com) (<http://www.rapidled.com/cree-xt-e-royal-blue-led/>)

### Large Scale Flow Synthesis of *tert*-butyl (*R*)-(3,3-dicyano-2-phenylpropyl)(phenyl)carbamate



- A.** Masterflex L/S Variable-Speed Drive (Cole-Parmer # EW-07528-30)
- B.** Masterflex L/S Rigid PTFE-Tubing Pump Head (Cole-Parmer # EW-77390-00)
- C.** Masterflex PTFE-tubing 4mm O.D. (Cole-Parmer # EW-77390-50)
- D.** 4MM PTFE Male NPT Compression Adapter (Cole-Parmer # WU-31321-62)
- E.** 1/8" O.D. to 1/8" PTFE Female NPT Compression Adapter (Cole-Parmer # EW-31320-50)
- F.** 1/4-28 flangeless fitting/ferrule for 1/8" O.D. tubing (Sigma-Aldrich SUPELCO # 58686)
- G.** Microreactor (Little Things Factory Gmbh # XXL-ST-02)
- H.** PTFE Tubing 1/16" I.D., 1/8" O.D. (Cole-Parmer # WU-06605-27)

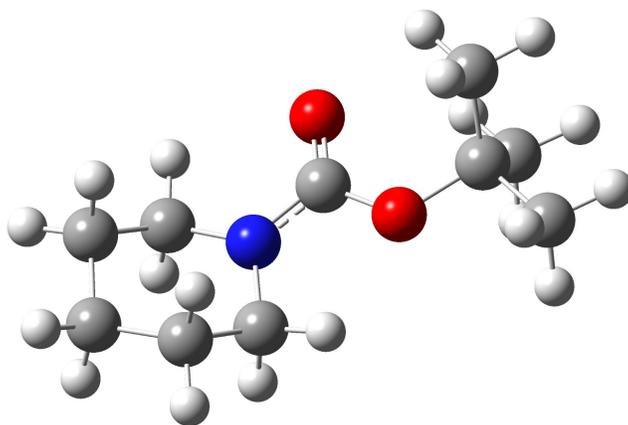
A flame-dried, 100 mL round bottom flask was charged with *tert*-butyl methyl(phenyl)carbamate (3.11 g, 15.0 mmol, 3 equiv.), benzylidenemalononitrile (771 mg, 5.00 mmol, 1 equiv.), 3,6-Di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate (143 mg, 0.25 mmol, 0.05 equiv.) and dichloroethane (50 mL). Dichloroethane was used due to the potential volatility of dichloromethane, The resulting mixture was sparged with nitrogen for 20 minutes. The flow cell was purged with dichloroethane which was

sparging with nitrogen prior to the introduction of the reaction mixture. Two 15W PAR38 blue LED floodlamps were positioned on either side of the microreactor (**G**). Tubing was introduced into the flask using a commercially available rubber septum which had been punctured. A nitrogen line was introduced into the headspace of the flask to ensure the complete exclusion of oxygen from the reaction mixture. The Masterflex L/S Variable-Speed Drive was set to 20 rpm and the occlusion bed of the pump head was adjusted as per the manufacturer's instructions. The floodlamps were then switched on and the reaction mixture was allowed to flow through the reactor for 18 hours. The temperature remained at ~35 °C during the reaction, as measured at the center of the lamps, close to the flow cell using a conventional alcohol thermometer. At this point, TLC indicated that the reaction had reached completion. Solvent was removed under reduced pressure and the resulting residue was purified *via* flash column chromatography (10-15% EtOAc/hexanes), yielding the desired product as a pale yellow solid (95%, 1.71 g).

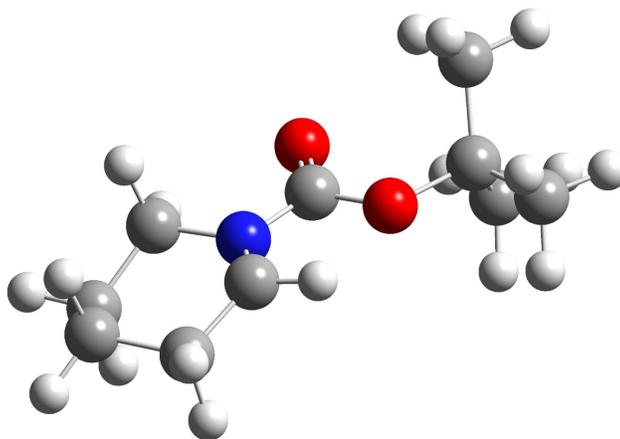
#### **Computational Details:**

All computations were performed in the Gaussian 16 software package,<sup>23</sup> and were performed at the UB3LYP level of theory<sup>24,25</sup> using the 6-311+G(d) basis set.<sup>26,27</sup> Bond dissociation energies were estimated by calculating the relative energy differences of the optimized geometries of the starting molecule and corresponding radical plus the energy of a hydrogen atom in the gas phase. All obtained geometries were verified as minima by ensuring that they possess no negative vibrational frequencies. All transition states were verified by ensuring that they possessed one negative vibrational mode. Transition state energies were calculated using CPCM solvent modeling for dichloromethane/ pKa values for cation radicals were calculated using these computed bond dissociation energies and experimentally determined oxidation potentials according to the methods described by Arnold and coworkers.<sup>28</sup> The energy of a gas phase hydrogen atom was calculated to be -0.502156 hartrees. Visual representations of the optimized geometries of the ground state of Boc-piperidine and the corresponding radical, as well as their single point energies are given below.

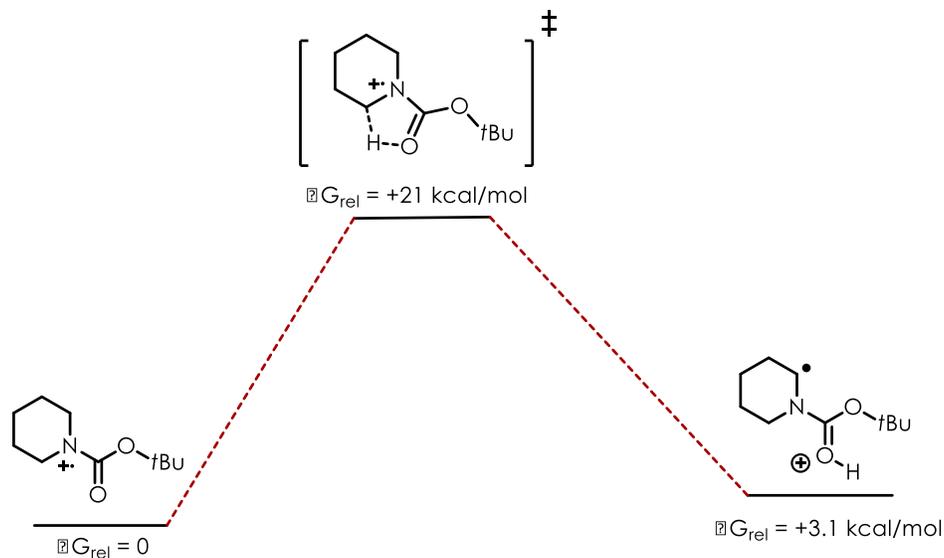
Boc-piperidine (Energy = -597.893854 Hartrees)



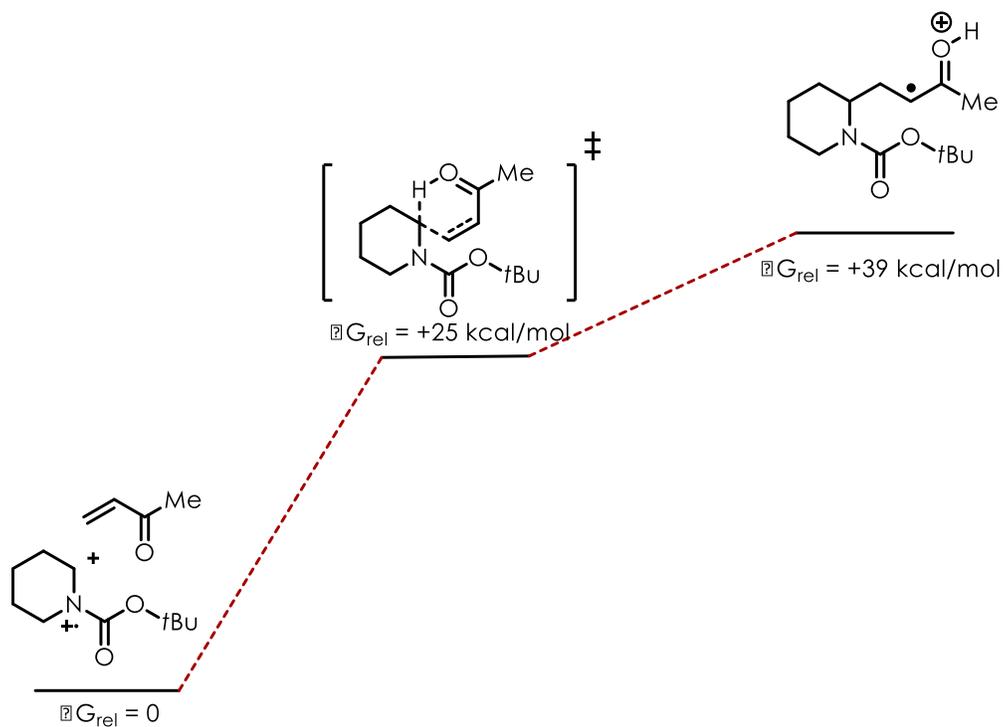
Boc-piperidine radical (Energy = -597.238650 Hartrees)



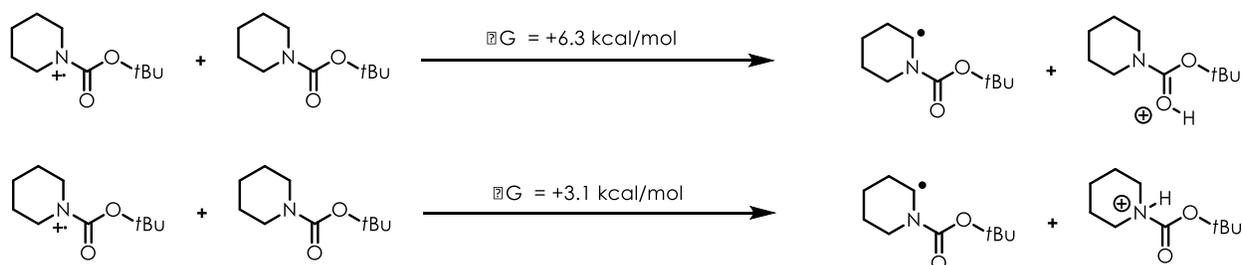
**Calculated BDE = 96.04 kcal/mol**  
**Calculated cation radical pKa ~ 5**



**Figure S2: Relative free energies for intramolecular deprotonation mechanism**



**Figure S3: Relative free energies for concerted alkylation/proton transfer mechanism with methyl vinyl ketone**



**Figure S4: Overall free energy differences for possible intermolecular deprotonations of the carbamate cation radical**

## References

- (1) Takasu, N.; Oisaki, K.; Kanai, M. *Org. Lett.* **2013**, 15, 1918–1921.
- (2) Taylor, N. J.; Emer, E.; Preshlock, S.; Schedler, M.; Tredwell, M.; Verhoog, S.; Mercier, J.; Genicot, C.; Gouverneur, V. *Derisking. J. Am. Chem. Soc.* **2017**, 139, 8267–8276.
- (3) Deb, B.; Debnath, S.; Deb, A.; Maiti, D. K.; Majumdar, S. *Tetrahedron Lett.* **2017**, 58, 629–633.
- (4) Schrittwieser, J. H.; Resch, V.; Wallner, S.; Lienhart, W.-D.; Sattler, J. H.; Resch, J.; Macheroux, P.; Kroutil, W. *J. Org. Chem.* **2011**, 76 (16), 6703–6714.
- (5) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *J. Org. Chem.* **2015**, 80, 1258–1263.
- (6) McCammant, M. S.; Thompson, S.; Brooks, A. F.; Krska, S. W.; Scott, P. J. H.; Sanford, M. S. *Org. Lett.* **2017**, 19, 3939–3942.
- (7) Millet, A.; Dailler, D.; Larini, P.; Baudoin, O. *Angew. Chem. Int. Ed.* **2014**, 53, 2678–2682.
- (8) Minakawa, M.; Yamada, Y. M. A.; Uozumi, Y. *RSC Adv* **2014**, 4, 36864–36867.
- (9) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, 7, 8283–8286.
- (10) Bagh, B.; Broere, D. L. J.; Sinha, V.; Kuijpers, P. F.; van Leest, N. P.; de Bruin, B.; Demeshko, S.; Siegler, M. A.; van der Vlugt, J. I. *J. Am. Chem. Soc.* **2017**, 139, 5117–5124.
- (11) Cochrane, E. J.; Hassall, L. A.; Coldham, I. *J. Org. Chem.* **2015**, 80, 5964–5969.
- (12) Kawada, H.; Kador, P. F. *J. Med. Chem.* **2015**, 58, 8796–8805.
- (13) Aarhus, T. I.; Fritze, U. F.; Hennum, M.; Gundersen, L.-L. *Tetrahedron Lett.* **2014**, 55, 5748–5750.
- (14) McLeod, M. C.; Singh, G.; Plampin, J. N.; Rane, D.; Wang, J. L.; Day, V. W.; Aubé, J. *Nat. Chem.* **2014**, 6, 133–140.
- (15) Quintard, A.; Alexakis, A.; Mazet, C. *Angew. Chem. Int. Ed.* **2011**, 50, 2354–2358.

- (16) Gembus, V.; Bonnet, J.-J.; Janin, F.; Bohn, P.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2010**, *8*, 3287.
- (17) Sanabria, R.; Herrera, R.; Aguilar, R.; González-Romero, C.; Jiménez-Vázquez, H. A.; Delgado, F.; Söderberg, B. C.; Tamariz, J. *Helv. Chim. Acta* **2008**, *91*, 1807–1827.
- (18) Felpin, F.-X.; Miqueu, K.; Sotiropoulos, J.-M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. - Eur. J.* **2010**, *16*, 5191–5204.
- (19) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001**, *66*, 2302–2311.
- (20) Angioni, S.; Ravelli, D.; Emma, D.; Dondi, D.; Fagnoni, M.; Albin, A. *Adv. Synth. Catal.* **2008**, *350*, 2209–2214.
- (21) Romero, N. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 17024–17035.
- (22) Griffin, J. D.; Cavanaugh, C. L.; Nicewicz, D. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 2097–2100.
- (23) Gaussian 16, Revision B.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
- (24) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- (25) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785–789.
- (26) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654.
- (27) McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639–5648.
- (28) Nicholas, A. M. de P.; Arnold, D. R. *Can. J. Chem.* **1982**, *60*, 2165–2179.
- (29) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928.
- (30) Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*; 3rd ed.; Springer: New York, 2006.

# Spectral Data

