Alkyl radical addition to aliphatic and aromatic *N*-acylhydrazones using an organic photoredox catalyst

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Materials and Methods

New scintillation vials were employed in radical addition reactions, and all other reactions were performed in oven dried glassware with magnetic stirring. Radical addition reactions were performed under static argon atmosphere. DMSO used for reactions was purchased in a bottle sealed under argon, used without further purification. THF was degassed with argon and passed through columns of activated alumina prior to use. Argon was passed through columns of CaSO₄ and R3-11 catalyst for removal of water and oxygen, respectively. Reagents were used without further purification. CDCl₃ for NMR spectroscopy was passed through a column of basic alumina. Thin layer chromatography employed glass 0.25 mm silica gel plates with UV indicator. TLC plates were visualized with either UV lamp or phosphomolybdic acid stain. Flash chromatography columns were packed with 230-400 mesh silica gel loaded as a slurry in eluting solvent. Crude material was loaded onto columns for purifying radical addition products were buffered with ~1% Et₃N in loading slurries and eluting solvents. HRMS was run by independent

facility at the University of Iowa. Melting point ranges were obtained using a Meltemp apparatus and are uncorrected.

Photoreactor Assembly

The photoreactor¹ depicted at right was built with 470 nm LED strips (60 LED/m, 1 m) purchased from superbrightleds.com and fitted with 12V power supplies. Two LED strips were adhered to the inside of a crystallizing dish, the outside of which was



covered with duct tape. During photoredox reactions, the reactor was surrounded by aluminum foil to contain the light, and the temperature was stabilized through use of either a small fan or compressed air.

Synthesis of *N*-acylhydrazones

Compounds **1a-b** and **6a-h** were synthesized by known procedures, and characterization data matched prior reports.¹⁻²



3-(Hexylidene)amino-2-oxazolidinone (1c): To a mixture of 3-amino-2-oxazolidinone (0.4286 g, 4.20 mmol, 1.00 eq) and MgSO₄ (0.75 g) in 10 mL of CH_2Cl_2 was added hexanal (1.00 mL, 8.14 mmol, 1.94 eq),

followed by *p*-TsOH·H₂O (100 mg, 0.526 mmol, 0.125 eq). After 19h, filtration, concentration, and gradient flash chromatography (hexanes and EtOAc, 6:1 hex:EtOAc \rightarrow 1:1) furnished the title compound (0.4956 g, 64% yield) as a colorless oil. HRMS(ESI) *m/z* calcd for C₉H₁₆N₂O₂Na 207.1109 ([M+Na]⁺), found 207.1120; ¹H NMR (300 MHz, CDCl₃) δ 7.05-7.02 (t, *J* = 5.7 Hz, 1H), 4.51-4.46 (m, 2H), 3.80-3.75 (m, 2H), 2.43-2.36 (td, *J* = 7.5, 9.5 Hz, 2H), 1.56-1.50 (m, 2H), 1.36-1.30 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 154.8, 149.0, 61.4, 42.4, 32.8, 31.5, 26.7, 22.5, 14.1.

3-(2-Methylpropylidene)amino-2-oxazolidinone (1d): Using the procedure for the synthesis of **1c**, from 3-amino-2-oxazolidinone (0.1954 g, 1.91 mmol, 1.00 eq) and isobutyraldehyde (0.90 mL, 9.9 mmol, 5.2 eq) was obtained the title compound (0.1833 g, 61% yield) as a colorless solid. mp 51-53°C; HRMS(ESI) *m/z* calcd for $C_7H_{12}N_2O_2Na$ 179.0796 ([M+Na]⁺), found 179.0791; ¹H NMR (300 MHz, CDCl₃) δ 6.90 (d, *J* = 6.1 Hz, 1H), 4.48 (t, J = 8.1 Hz, 2H), 3.76 (t, J = 8.1 Hz, 2H), 2.78-2.62 (m, 1H), 1.13 (d, J = 6.9 Hz, 6H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 154.7, 153.5, 61.3, 42.3, 31.9, 20.2.

3-(2,2-Dimethylpropylidene)amino-2-oxazolidinone (1e): Using the procedure for the synthesis of **1c**, from 3-amino-2-oxazolidinone (0.4135 g, 4.05 mmol, 1.00 eq) and pivalaldehyde (0.80 mL, 7.4 mmol, 1.82 eq) was obtained the title compound (0.5808 g, 84% yield) as a colorless solid. mp 142-144°C; HRMS(ESI) *m/z* calcd for $C_8H_{14}N_2O_2Na$ 193.0953 ([M+Na]+), found 193.0946; ¹H NMR (300 MHz, CDCl₃) δ 6.97 (s, 1H), 4.47 (t, *J* = 7.8 Hz, 2H), 3.76 (t, *J* = 7.8 Hz, 2H), 1.15 (s, 9); ¹³C NMR {¹H} δ 156.2, 154.7, 61.3, 42.5, 35.3, 27.7.

Synthesis of Ammonium Biscatecholatoalkylsilicate Salts and 4CzIPN

Alkylsilicate salts were prepared from the corresponding trimethoxysilanes, and characterization data matched that reported previously.³

The photocatalyst 4CzIPN was prepared and characterized as previously reported.⁴

General Procedure A: Radical Additions to Hydrazones

A scintillation vial containing hydrazone (0.1 M in DMSO), and MgCl₂ was capped under Ar and allowed to stir. After 1 h, the appropriate bis(catecolato)alkylsilicate was added along with catalyst 4CzIPN. The vial was capped under Ar, sealed with Parafilm or electrical tape, and irradiated at 470 nm with the LED photoreactor (p. S2) at ca. 30°C. After 42–48 h, the reaction mixture was partitioned between EtOAc and H₂O. The organic phase was washed with 10% aq KOH and brine, dried (either Na₂SO₄ or MgSO₄), and concentrated. Percent conversion was determined by ¹H NMR integration of the crude product (detailed in next section). Gradient flash

chromatography (hexanes/EtOAc or hexanes/Et₂O, buffered with ~1% Et₃N) afforded the target compounds.

O N	Cy—[Si(cat) ₂] _{<i>i</i>-Pr₂NH₂}	
Ph	Lewis Acid, 15 mol% 4CzIPN, solvent, 470 nm LED	HN Cy
1a		2a

 Table S1. Additional Conditions Screened for Radical Addition

entry	Lewis Acid (2 eq.)	Eq. silicate	Solvent	Time (h)	% conv. ^a
1	none	2	DMSO	24	40
2	none	2	DMSO	49	48
3	ZnBr ₂	1	DMSO	18	27
4	Zn(OTf) ₂	1	DMSO	18	27
5	CuCl ₂	1	DMSO	18	0
6	ZnBr ₂	2	DMSO	18	63
7	ZnBr ₂	4	DMSO	18	64
8	3 eq. ZnBr ₂	2	DMSO	18	49
9	Sc(OTf) ₃	2	DMSO	18	23
10	AlCl ₃	2	DMSO	18	40
11	MgCl ₂	2	DMSO	18	59
12	MgBr ₂	2	DMSO	18	54
13	Mg(OTf) ₂	2	DMSO	18	31
14	InCl ₃	2	DMSO	18	33
15	ZnBr ₂	2	DMF	16	28
16	MgCl ₂	2	DMF	16	44
17	MgCl ₂	1.2	EtOH	23	10
18	MgCl ₂	2.6	DMSO	48	86
19	MgCl ₂	1.3	DMSO	22	63
20	MgCl ₂	3	DMSO	48	22 ^b
21	MgCl ₂	3	DMSO	48	68 ^c
22	MgCl ₂	3	DMSO	47	88 (60 ^d)
23	MgCl ₂	2	DMSO	24	73

^{*a*} Determined by ¹H NMR integration. ^{*b*} 1 mol% catalyst loading. ^{*c*} 5 mol% catalyst loading. ^{*d*} Isolated yield.

Determination of Percent Conversion of 2a

Percent conversions of hydrazone **1a** to radical addition product **2a** are reported in Table S1. Insignificant amounts of other products from **1a** were observed, so that the percent conversion could be reasonably estimated from ¹H NMR integrals of oxazolidinone peaks from **1a** and **2a**. An example is presented below. Integrals for peaks A (product **2a**, 1H) and B (reactant **1a**, 2H), corresponding to oxazolidinone hydrogens, are substituted in the equation below. Note that the hydrogens on the oxazolidinone are non-equivalent due to diastereotopicity in **2a**.



estimated % conversion = $\frac{\text{Int Peak A}}{\text{Int Peak A} + (0.5 * \text{Int Peak B})} * 100$

Experimental Details of Radical Addition Reactions

3-[(Cyclohexylphenylmethyl)amino]-2-oxazolidinone (2a): Using General Procedure A, from hydrazone **1a** (0.0233 g, 0.123 mmol, 1.00 eq), MgCl₂ (0.0256 Ph Cy g, 0.269 mmol, 2.19 eq), diisopropylammonium bis(catecholato)cyclohexylsilicate (0.1670g, 0.389 mmol, 3.16 eq), and 4CzIPN (0.0148 g, 0.0187 mmol, 0.150 eq) was obtained the title compound (0.0203 g, 60% yield) as a colorless solid. mp 91-93°C; HRMS(ESI) *m/z* calcd for C₁₆H₂₂N₂O₂Na 297.1579 ([M+Na]⁺), found 297.1577; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.24 (m, 5H), 4.67-4.60 (br s, 1H), 4.10 (td, *J* = 8.8, 4.7 Hz, 1H), 4.03-3.90 (m, apparent q, *J* = 8.8 Hz, 1H), 3.95 (dd, *J* = 7.6, 2.1 Hz, 1H), 3.48-3.35 (m, apparent q, 1H), 3.05-2.95 (td, *J* = 8.2, 4.1 Hz, 1H), 2.01-1.87 (m, 1H), 1.86-1.73 (m, 1H), 1.73-1.54 (m, 3H), 1.51-1.37 (m, 1H), 1.33-1.01 (m, 4H), 0.92-0.76 (m, 1H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 158.8, 140.9, 128.8, 128.1, 127.5, 69.6, 61.4, 47.9, 41.9, 30.2, 29.1, 26.4, 26.2 (2C).

3-((1-Cyclohexyl-3-phenylpropyl)amino)oxazolidin-2-one (2b): Using General Procedure A, from hydrazone **1b** (0.0433 g, 0.198 mmol, 1.00 eq), MgCl₂ (0.0417 g, 0.438 mmol, 2.21 eq), diisopropylammonium bis(catecholato)cyclohexylsilicate (0.2551 g, 0.594 mmol, 3.00 eq), and 4CzIPN (0.0247 g, 0.0313 mmol, 0.158 eq) was obtained the title compound (0.0168 g, 28% yield) as amorphous solid. mp 61-64°C; HRMS(ESI) *m/z* calcd for C₁₈H₂₆N₂O₂Na 325.1892 ([M+Na]⁺), found 325.1900; ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.25 (m, 2H), 7.23-7.15 (m, 3H), 4.30-4.23 (m, apparent t, *J* = 7.8 Hz, 2H), 4.16 (br d, *J* = 4.1 Hz, 1H), 3.62-3.52 (m, 2H), 2.85-2.76 (m, 1H), 2.75-2.68 (m, apparent t, *J* = 7.8 Hz, 2H), 1.87-1.57 (m, 7H), 1.57-1.44 (m,1H), 1.30-1.00 (m, 5H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 159.3, 142.4, 128.5, 125.9, 63.6, 61.3, 48.4, 39.5, 32.6, 31.0, 29.3, 27.9, 26.8, 26.7 (2C).

3-((1-Cyclohexylhexyl)amino)oxazolidin-2-one (2c): Using General
 Procedure A, from hydrazone 1c (0.0428 g, 0.232 mmol, 1.00 eq), MgCl₂
 (0.0474 g, 0.498 mmol, 2.15 eq), diisopropylammonium

bis(catecholato)cyclochexylsilicate (0.2995 g, 0.697 mmol, 3.00 eq), and 4CzIPN (0.0318 g, 0.0403 mmol, 0.174 eq) was obtained the title compound (0.0136 g, 22% yield) as a pale yellow oil. HRMS(ESI) *m/z* calcd for C₁₅H₂₈N₂O₂Na 291.2048 ([M+Na]⁺), found 291.2051; ¹H NMR (300 MHz, CDCl₃) δ 4.29 (m, apparent t, *J* = 7.8 Hz, 2H), 4.11 (br s, 1H), 3.61 (m, apparent t, *J* = 7.8 Hz, 2H), 2.82-2.74 (m, 1H), 1.81-1.73 (m, 1H), 1.72-1.62 (m, 1H), 1.51-0.97 (m, 17H), 0.88 (t, *J* = 6.9 Hz, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃) δ 159.2, 64.2, 61.3, 48.7, 39.6, 32.4, 29.3, 29.1, 28.0, 26.9 (2C), 26.8, 26.1, 22.7, 14.2.

3-((1-Cyclohexyl-2-methylpropyl)amino)oxazolidin-2-one (2d): Using General Procedure A, from hydrazone **1d** (0.0347 g, 0.222 mmol, 1.00 eq), **MgCl**₂ (0.0450 g, 0.473 mmol, 2.13 eq), diisopropylammonium bis(catecholato)cyclochexylsilicate (0.2873 g, 0.669 mmol, 3.01 eq), and 4CzIPN (0.0275 g, 0.0348 mmol, 0.157 eq) was obtained the title compound (0.0099 g, 19% yield) as amorphous solid. mp 69-71°C; HRMS(ESI) *m/z* calcd for C₁₃H₂₄N₂O₂Na 263.1735 ([M+Na]⁺), found 263.1734; ¹H NMR (300 MHz, CDCl₃) δ 4.27 (m, apparent t, *J* = 7.9 Hz, 2H), 4.07 (br d, *J* = 4.0 Hz, 1H), 3.62 (m, apparent t, *J* = 7.9 Hz, 2H), 2.53 (m, appparent q, *J* = 4.3 Hz, 1H), 1.93-1.83 (m, 1H), 1.80-1.60 (m, 5H), 1.31-1.06 (m, 6H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 159.0, 69.0, 61.2, 48.2, 39.5, 30.9, 29.4, 28.8, 27.1, 26.9, 26.7, 20.5, 18.8.

3-((1-Phenylbutyl)amino)oxazolidin-2-one (3): Using General Procedure A, from hydrazone **1a** (0.0355 g, 0.187 mmol, 1.00 eq), MgCl₂ (0.0422 g, 0.443 mmol, 2.37 eq), diisopropylammonium bis(catecholato)propylsilicate (0.2192 g, 0.563 mmol, 3.01 eq), and 4CzIPN (0.0263 g, 0.0333 mmol, 0.178 eq) was obtained the title compound (0.0197 g, 45% yield) as a yellow oil. HRMS(ESI) *m/z* calcd for C₁₃H₁₈N₂O₂Na 257.1266 ([M+Na]⁺), found 257.1273; ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.23 (m, 5H), 4.43 (br s, 1H), 4.20-4.12 (m, 2H), 4.00 (m, apparent q, *J* = 8.2 Hz, 1H), 3.43 (m, apparent q, *J* = 8.8 Hz, 1H), 3.04 (ddd, *J* = 8.4, 8.4, 5.3 Hz, 1H), 1.79-1.54 (m, 2H), 1.37-1.08 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 158.9, 141.9, 128.5, 128.1, 127.8, 64.3, 61.5, 48.1, 37.3, 19.2, 14.2.

3-((1,3-Diphenylpropyl)amino)oxazolidin-2-one (4): Using General Procedure A, from hydrazone **1a** (0.0438 g, 0.230 mmol, 1.00 eq), MgCl₂ Ph Ph (0.0491 g, 0.516 mmol, 2.24 eq), diisopropylammonium bis(catecholato)(2phenylethyl)silicate (0.3202 g, 0.709 mmol, 3.08 eq), and 4CzIPN (0.0284 g, 0.0360 mmol, 0.157 eq) was obtained the title compound (0.0144 g, 21% yield) as a yellow oil. HRMS(ESI) m/z calcd for C₁₈H₂₁N₂O₂ 297.1603 ([M+H]⁺), found 297.1602; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.27 (m, 5H), 7.26-7.09 (m, 5H), 4.45 (br s, 1H), 4.25-4.18 (m, 1H), 4.17-4.09 (m, 1H), 4.02 (m, apparent q, J = 8.2 Hz, 1H), 3.43 (m, apparent q, J = 8.2 Hz, 1H), 3.06 (ddd, J = 8.4, 8.4, 6.1 Hz, 1H), 2.61-2.41 (m, 2H), 2.17-1.89 (m, 2H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 158.9, 141.7, 141.3, 128.6, 128.5, 128.4, 128.2, 128.0, 126.1, 64.2, 61.5, 48.1, 36.8, 32.2.

3-((5-Methyl-1-phenylhexan-3-yl)amino)oxazolidin-2-one (5): Using General Procedure A, from hydrazone 1b (0.0426 g, 0.195 mmol, 1.00 eq), Ph' MgCl₂ (0.0413 g, 0.434 mmol, 2.23 eq), diisopropylammonium bis(catecholato)isobutylsilicate (0.2370 g, 0.587 mmol, 3.01 eg), and

4CzIPN (0.0247 g, 0.0313 mmol, 0.161 eg) was obtained the title compound (0.0076 g, 14% yield) as a yellow oil. HRMS(ESI) m/z calcd for C₁₆H₂₄N₂O₂Na 299.1735 ([M+Na]⁺), found 299.1727; ¹H NMR (300 MHz, CDCl₃) & 7.32-7.26 (m, 2H), 7.23-7.15 (m, 3H), 4.28 (m, apparent t, J = 7.8 Hz, 2H), 4.14 (br s, 1H), 3.60 (m, apparent t, J = 7.8 Hz, 2H), 3.13-3.02 (m, 1H), 2.81-2.59 (m, 2H), 1.84-1.65 (m, 3H), 1.34 (m, apparent t, J = 6.8 Hz, 2H), 0.94 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 159.5, 142.4, 128.5, 128.5, 126.0, 61.4, 56.9, 48.8, 41.9, 34.8, 31.5, 25.0, 23.1, 22.9.

Ph N'-(Cyclohexyl(phenyl)methyl)benzohydrazide (7a): Using General Procedure HN^{_NH} A, from hydrazone 6a (0.0295 g, 0.132 mmol, 1.00 eq), MgCl₂ (0.0269 g, 0.282 Ph mmol, 2.15 eq), diisopropylammonium bis(catecholato)cyclohexylsilicate (0.0882 g, 0.205 mmol, 1.55 eq), and 4CzIPN (0.0059 g, 0.00747 mmol, 0.0566 eq) was obtained the title compound (0.0307 g, 75% yield) as a colorless solid. Product identity was confirmed by comparison of ¹H NMR to literature reports.²



N'-(Cyclohexyl(p-tolyl)methyl)benzohydrazide (7b): Using General Procedure A, from hydrazone 6b (0.0298 g, 0.125 mmol, 1.00 eq), MgCl₂ (0.0275 g, 0.289 mmol, 2.31 eq), diisopropylammonium bis(catecholato)cyclohexylsilicate (0.1604 g, 0.373 mmol, 2.98 eq), and 4CzIPN (0.0164 g, 0.0208 mmol, 0.166 eq) was obtained the title compound (0.0377 g, 94% yield) as a colorless solid. mp 152-153°C; HRMS(ESI) *m/z* calcd for C₂₁H₂₆N₂ONa 345.1943 ([M+Na]⁺), found 345.1948; ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.54 (m, 1H), 7.53-7.51 (m, 1H), 7.49-7.41 (m, 1H), 7.40-7.32 (m, 2H), 7.25-7.18 (m, 3H), 7.17-7.11 (m, 2H), 5.40 (br d, *J* = 7.3 Hz, 1H), 3.80 (d, *J* = 7.7 Hz, 1H), 2.35 (s, 3H), 2.09-2.00 (m, 1H), 1.85-175 (m, 1H), 1.75-1.55 (m, 2H), 1.51-1.39 (m, 1H), 1.34-1.02 (m, 4H), 0.93-0.72 (m, 2H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 166.9, 138.0, 137.1, 133.2, 131.8, 129.1, 128.7, 128.5, 126.9, 70.4, 42.4, 30.2, 29.5, 26.5, 26.3 (2C), 21.3.

Ph N'-((4-Chlorophenyl)(cyclohexyl)methyl)benzohydrazide (7c): Using General Procedure A, from hydrazone 6c (0.0335 g, 0.129 mmol, 1.00 eq), MgCl₂ (0.0268 g, 0.281 mmol, 2.18 eq), diisopropylammonium bis(catecholato)cyclohexylsilicate (0.1677 g, 0.390 mmol, 3.02 eq), and

4CzIPN (0.0167 g, 0.0211 mmol, 0.164 eq) was obtained the title compound (0.0373 g, 84% yield) as a colorless solid. mp 173-176°C; HRMS(ESI) *m/z* calcd for C₂₀H₂₃N₂OCINa 365.1397 ([M+Na]⁺), found 365.1383; ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.55 (m, 1H), 7.54-7.52 (m, 1H), 7.51-7.43 (m, 1H), 7.41-7.36 (m, 2H), 7.35-7.31 (m, 1H), 7.31-7.27 (m, 3H), 7.26-7.22 (m, 1H), 5.40 (br s, 1H), 3.84 (d, *J* = 7.3 Hz, 1H), 2.06-1.94 (m, 1H), 1.86-1.75 (m, 1H), 1.74-1.56 (m, 2H), 1.51-1.38 (m, 1H), 1.35-1.04 (m, 4H), 0.95-0.76 (m, 2H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 167.2, 139.7, 133.1, 132.9, 132.0, 129.9, 128.8, 128.6, 126.9, 70.0, 42.4, 30.1, 29.3, 26.4, 26.2 (2C).

 $\begin{array}{lll} & \begin{array}{l} & \label{eq:hermiddle} \text{N}^{-}(1-\text{Cyclohexyl-3-phenylpropyl)benzohydrazide (7d): Using General HN^{,NH} & Procedure A, from hydrazone 6d (0.0669 g, 0.265 mmol, 1.00 eq), MgCl_2 \\ & \begin{array}{l} & \begin{array}{l} & \begin{array}{l} & \begin{array}{l} & \begin{array}{l} & \end{array}{l} & \end{array}{l} & \begin{array}{l} & \end{array}{l} & \begin{array}{l} & \end{array}{l} & \end{array}{l} & \end{array}{l} & \begin{array}{l} & \end{array}{l} & \end{array}{l} & \begin{array}{l} & \end{array}{l} & \end{array}{l} & \end{array}{l} & \begin{array}{l} & \end{array}{l} & \end{array}{l} & \end{array}{l} & \begin{array}{l} & \end{array}{l} & \begin{array}{l} & \end{array}{l} \\{l} & \end{array}{l} \\{l} & \end{array}{l} \\{l} & \end{array}{l} \\ length{l} & \end{array}{l} \\ length{l} & \end{array}{l} & \end{array}{l} \\ length{l} & \end{array}{l} \end{array} \\ length{l} & \end{array}{l} \\ length{l} \\ le$

Ph *N'*-(1- Cyclohexyl-2-methylpropyl)benzohydrazide (7e): Using General $HN^{/NH}$ Procedure A, from hydrazone 6e 0.0399 g (0.210 mmol, 1.00 eq), MgCl₂ (0.0462 g, 0.485 mmol, 2.31 eq), diisopropylammonium bis(catecholato)cyclohexylsilicate (0.1394 g, 0.324 mmol, 1.55 eq), and 4CzIPN (0.0114 g, 0.0144 mmol, 0.0687 eq) was obtained the title compound (0.0146 g, 25% yield) as a yellow oil. HRMS(ESI) *m/z* calcd for C₁₇H₂₇N₂O 275.2123 ([M+H]⁺), found 275.2122; ¹H NMR (300 MHz, CDCl₃) δ 7.78-7.74 (m, 2H), 7.61-7.54 (m, 1H), 7.53-7.41 (m, 3H), 4.70 (br s, 1H), 2.51 (dd, *J* = 4.9, 4.9 Hz, 1H), 2.04-1.86 (m, 2H), 1.85-1.49 (m, 4H), 1.37-1.12 (m, 6H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 166.6, 133.3, 131.9, 128.9, 126.9, 71.5, 39.9, 31.6, 29.4, 29.1, 27.0, 26.8, 26.7, 21.3, 18.7.

Ph N'-(Cyclohexyl(o-tolyl)methyl)benzohydrazide (7f): Using General
 HN NH
 Procedure A, from hydrazone 6f (0.0574 g, 0.241 mmol, 1.00 eq), MgCl₂
 (0.475 g, 0.499 mmol, 2.07 eq), diisopropylammonium
 bis(catecholato)cyclohexylsilicate (0.3197 g, 0.744 mmol, 3.09 eq), and

4CzIPN (0.320 g, 0.0405 mmol, 0.168 eq) was obtained the title compound (0.0727 g, 94% yield) as an amorphous solid. mp 130-132 °C; HRMS(ESI) *m/z* calcd for C₂₁H₂₆N₂ONa 345.1943 ([M+Na]⁺), found 345.1938; ¹H NMR (300 MHz, CDCl₃) δ 7.55-7.42 (m, 4H), 7.39-7.32 (m, 2H), 7.28-7.21 (m, 2H), 7.20-7.10 (m, 2H), 4.23 (d, *J* = 8.1 Hz, 1H), 2.26 (s, 3H), 2.19-2.08 (m, 1H), 1.87-1.79 (m, 1H), 1.75-1.59 (m, 3H), 1.40-1.00 (4H), 0.99-0.81 (m, 2H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 167.1, 139.7, 137.4, 133.0, 131.7, 130.3, 128.6, 126.8, 126.7, 126.2, 29.8, 29.5, 26.4, 26.3, 26.1, 19.9.



N'-((2-Chlorophenyl)(cyclohexyl)methyl)benzohydrazide (7g): Using
General Procedure A, from hydrazone 6g (0.0443 g, 0.171 mmol, 1.00 eq),
MgCl₂ (0.0395g, 0.415 mmol, 2.46 eq), diisopropylammonium
bis(catecholato)cyclohexylsilicate (0.2319 g, 0.540 mmol, 3.16 eq), and

4CzIPN (0.0247 g, 0.313 mmol, 0.183 eq) was obtained the title compound (0.0494 g, 84% yield) as amorphous solid. mp 128-129°C; HRMS(ESI) *m/z* calcd for C₂₀H₂₄N₂OCl 343.1577 ([M+H]⁺), found 343.1576; ¹H NMR (300 MHz, CDCl₃) δ 7.65-7.59 (m, 1H), 7.58-7.53 (m, 2H), 7.50-7.42 (m, 1H), 7.40-7.28 (m, 4H), 7.24-7.15 (m, 2H), 5.49 (br s, 1H), 4.50 (d, *J* = 7.4 Hz, 1H), 2.13-2.03 (m, 1H), 1.88-1.53 (m, 4H), 1.49-1.05 (m, 6H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ

167.1, 139.0, 135.2, 133.0, 131.7, 129.5, 129.0, 128.6, 128.2, 126.9, 126.8, 65.7, 42.2, 29.4 (2C), 26.3, 26.2, 26.1.



Ph N'-(Cyclohexyl(4-(dimethylamino)phenyl)methyl)benzohydrazide
 (7h): Using General Procedure A, from hydrazone 6h (0.0464 g, 0.174
 mmol, 1.00 eq), MgCl₂ (0.0360 g, 0.378 mmol, 2.17 eq), diisopropyl-ammonium bis(catecholato)cyclohexylsilicate (0.2318 g, 0.540 mmol,

3.10 eq), and 4CzIPN (0.0224 g, 0.284 mmol, 0.163 eq) was obtained the title compound (0.0195 g, 32% yield) as a yellow solid. mp 123-125°C; HRMS(ESI) *m/z* calcd for C₂₂H₃₀N₃O 352.2389 ([M+H]⁺), found 352.2397; ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.52 (m, 2H), 7.49-7.41 (m, 1H), 7.39-7.31 (m, 2H), 7.25-7.14 (m, 3H), 6.75-6.68 (m, 2H), 5.43 (br s, 1H), 3.72 (d, *J* = 7.7 Hz, 1H), 2.96 (s, 6H), 2.09-1.99 (m, 1H), 1.85-1.75 (m, 1H), 1.70-1.40 (m, 4H), 1.35-0.79 (m, 5H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 166.7, 150.0, 133.3, 131.7, 129.3, 128.7 (2C), 126.9, 112.4, 70.1, 42.5, 40.8, 30.3, 29.5, 26.5, 26.3 (2C).

N'-(5-Methyl-1-phenylhexan-3-yl)benzohydrazide (9): Using General HN^{_ŃH} Procedure A, from hydrazone 6b (0.0517 g, 0.205 mmol, 1.00 eg), MgCl₂ Ph (0.0433 g, 0.455 mmol, 2.22 eq), diisopropylammonium

bis(catecholato)isobutylsilicate (0.1403 g, 0.348 mmol, 1.70 eq), and 4CzIPN (0.0101 g, 0.0128 mmol, 0.0624 eq) was obtained the title compound (0.0296 g, 47% yield) as a yellow oil. HRMS(ESI) *m/z* calcd for C₂₀H₂₇N₂O 311.2123 ([M+H]⁺), found 311.2121; ¹H NMR (300 MHz, CDCl₃) δ 7.74-7.69 (m, 2H), 7.56-7.40 (m, 4H), 7.32-7.25 (m, 2H), 7.25-7.14 (m, 3H), 4.98 (br s, 1H), 3.09-3.02 (m, 1H), 2.84-2.66 (m, 2H), 1.90-1.71 (m, 3H), 1.49-1.29 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 167.5, 142.6, 133.1, 132.0, 128.9, 128.5 (2C), 126.9, 125.9, 58.2, 42.3, 35.0, 31.9, 25.2, 23.3, 22.9.



ammonium bis(catecholato)(3-methoxypropyl)silicate (0.1661 g, 0.396 mmol, 1.56 eq), and 4CzIPN (0.0123 g, 0.0156 mmol, 0.0614 eq) was obtained the title compound (0.0508 g, 61% yield) as a colorless oil. HRMS(ESI) *m/z* calcd for $C_{20}H_{27}N_2O_2$ 327.2073 ([M+H]+), found 327.2073; ¹H NMR (300 MHz, CDCl₃) δ 7.77-7.70 (m, 3H), 7.56-7.40 (m, 3H), 7.32-7.15 (m, 5H), 5.02 (br s, 1H), 3.48-3.40 (m, 2H), 3.34 (s, 3H), 3.07-2.98 (m, 1H), 2.76 (m, apparent t, *J* = 8.0 Hz, 2H), 1.89-1.52 (m, 6H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 167.2, 142.4, 133.1, 131.9, 128.8, 128.5 (2C), 127.0, 126.0, 73.0, 59.7, 58.8, 34.4, 32.1, 28.7, 25.3.

 O
 Ph

 HN
 HN

 Ph
 Procedure A, from hydrazone 6a (0.0589 g, 0.263 mmol, 1.00 eq), MgCl₂

 Ph
 OAc

(0.570 g, 0.599 mmol, 2.28 eq), diisopropylammonium bis(catecholato)(3-acetoxypropyl)silicate (0.1900 g, 0.424 mmol, 1.61 eq), and 4CzIPN (0.0123 g, 0.0156 mmol, 0.0593 eq) was obtained the title compound (0.0638 g, 74% yield) as an amorphous solid. mp 94-97°C; HRMS(ESI) *m/z* calcd for C₁₉H₂₂N₂O₃Na 349.1528 ([M+Na]⁺), found 349.1525; ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.57 (m, 2H), 7.51-7.44 (m, 2H), 7.41 -7.26 (m, 7H), 5.16 (br s, 1H), 4.09 (dd, *J* = 8.2, 6.7 Hz, 1H), 4.02 (m, apparent t, *J* = 6.4 Hz, 2H), 2.01 (s, 3H), 1.98-1.85 (m, 1H), 1.82-1.43 (m, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 171.2, 167.3, 141.3, 132.8, 131.9, 128.7 (3C), 127.9, 126.8, 64.9, 64.2, 31.5, 25.1, 21.0.

O Ph N'-HN^{NH} Pro

N'-(1-(2-Fluorophenyl)-3-methylbutyl)benzohydrazide (12): Using General
Procedure A, from 2-fluorobenzaldehyde N-benzoylhydrazone (0.0506 g,
0.209 mmol, 1.00 eq), MgCl₂ (0.0424 g, 0.445 mmol, 2.13 eq),

diisopropylammonium bis(catecholato)isobutylsilicate (0.1436 g, 0.356 mmol, 1.70 eq), and 4CzIPN (0.0099 g, 0.0125 mmol, 0.0598 eq) was obtained the title compound (0.0485 g, 77% yield) as a yellow oil. mp 67-70°C; HRMS(ESI) *m/z* calcd for C₁₈H₂₂N₂OF 301.1716 ([M+H]⁺), found 301.1720; ¹H NMR (300 MHz, CDCl₃) δ 7.63-7.55 (m, 2H), 7.55-7.44 (m, 3H), 7.42-7.33 (m, 3H), 7.29-7.13 (m, 2H), 7.07-6.99 (m, 1H), 5.23 (br s, 1H), 4.55 (m, apparent t, *J* = 7.3 Hz, 1H), 1.76-1.58 (m, 3H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 6H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 167.4, 160.0, 133.1, 131.9, 128.9, 128.8 (2C), 127.0 (2C), 124.5, 115.8 (d, *J*_{CF} = 22.8 Hz), 56.7, 43.6, 25.3, 23.1, 22.8.



N'-(1-(2-Bromophenyl)-3-methylbutyl)benzohydrazide (13): Using General
Procedure A, from 2-bromobenzaldehyde *N*-benzoylhydrazone (0.0828 g,
0.273 mmol, 1.00 eq), MgCl₂ (0.0576 g, 0.605 mmol, 2.22 eq),

diisopropylammonium bis(catecholato)isobutylsilicate (0.1728 g, 0.428 mmol, 1.57 eq), and 4CzIPN (0.0151 g, 0.0191 mmol, 0.07 eq) was obtained the title compound (0.0800 g, 81% yield) as an amorphous solid. mp 106-107°C; HRMS(ESI) *m/z* calcd for C₁₈H₂₂N₂O⁸¹Br 363.08941([M+H]⁺), found 363.0894; ¹H NMR (300 MHz, CDCl₃) δ 7.65-7.57 (m, 3H), 7.56-7.51 (m, 1H), 7.50-7.43 (m, 1H), 7.40-7.31 (m, 4H), 7.15-7.09 (m, 1H), 5.28 (br s, 1H), 4.73 (t, *J* = 7.0 Hz, 1H), 1.81-1.51 (m, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 167.4, 141.8, 133.0, 131.8, 128.9, 128.7 (2C), 127.9, 127.0 (2C), 125.1, 61.7, 44.2, 25.4, 23.4, 22.6.

Reductive Cleavage of N-N Bond

 $Ph \rightarrow Cy$ **Cyclohexyl(phenyl)methanamine (14)**: To a solution of **7a** (0.0895 g, 0.290 mmol, $Ph \rightarrow Cy$ 1.00 eq) in 1:1 THF:MeOH (1 mL) under Ar was added a solution of Sml₂ in THF dropwise via syringe until the reaction mixture sustained a blue color. At this time, opening the reaction to air caused the mixture to quickly turn yellow, and it was promptly filtered through a pad of Celite using EtOAc. Concentration and gradient flash chromatography (hexanes and EtOAc, with 1% Et₃N to buffer silica) furnished the title compound (0.0363 g, 66% yield) as an orange oil. Product identity was confirmed by comparison of ¹H NMR to literature reports.⁵

Formal Synthesis of Racemic Repaglinide



2-(Piperidin-1-yl)benzaldehyde (15): To a mixture of K₂CO₃ (2.7298 g, 19.8 mmol, 2.08 eq) and 2-fluorobenzaldehyde (1.00 mL, 9.51 mmol, 1.00 eq) in DMF (10 mL) was added piperidine (0.95 mL, 9.62 mmol, 1.01 eq). The reaction mixture was heated at reflux for 20.5 h, and then cooled to room temperature. Filtration, rinsing the solid fraction with EtOAc, and concentration afforded an orange oil. Gradient flash chromatography (50:1 hexanes:EtOAc to 10:1) furnished the title compound (1.5462 g, 86% yield) as a viscous yellow oil. Product identity was confirmed by comparison of ¹H NMR to literature reports.⁶

found 308.1762; ¹H NMR (300 MHz, DMSO) δ 11.87 (s, 1H), 8.71 (s, 1H), 7.96-7.81 (m, 3H), 7.64-7.47 (m, 3H), 7.42-7.32 (m, 1H), 7.16-7.06 (m, 2H), 2.90-2.79 (m, 4H), 1.77-1.66 (m, 4H), 1.60-1.48 (m, 2H); ¹³C NMR {¹H} δ 163.3, 153.5, 145.6, 133.7, 131.6, 131.4, 130.7, 128.4, 127.7, 126.3, 122.8, 119.3, 54.3, 53.0, 25.8, 25.0, 23.6.

N'-(3-methyl-1-(2-(piperidin-1-yl)phenyl)butyl)benzohydrazide (17): A Βz ΗŇ NH mixture of 16 (0.0537 g, 0.175 mmol, 1.00 eg) and MgCl₂ (0.0491 g, 0.516 mmol, 2.95 eq) in DMSO (2.7 mL) was stirred under Ar. After 1 h, diisopropylammonium bis(catecholato)isobutylsilicate (0.960 g, 0.238 mmol, 1.36 eq) and 4CzIPN (0.0233 g, 0.0295 mmol, 0.169 eq) were added. The reaction mixture was irradiated with 470 nm LED light under Ar at ca. 30 °C. At 6 h and 15 h, additional portions of silicate (0.0641 g, 0.0571 g, and 0.0516 g) were added as solutions in DMSO (0.2 mL) and radiation was resumed. A total of 3.80 equivalents of silicate were added in 4 portions. After 44 h of irradiation, workup and purification as in General Procedure A furnished the title compound (0.0321 g, 50% yield) as a yellow oil. HRMS(ESI) *m/z* calcd for C₂₃H₃₂N₃O 366.2545 ([M+H]⁺), found 366.2546; ¹H NMR (300 MHz, CDCl₃) δ 7.61-7.51 (m, 3H), 7.49-7.32 (m, 4H), 7.24-7.20 (m, 1H), 7.17-7.08 (m, 2H), 5.26 (br s, 1H), 4.87 (t, J = 7.2 Hz, 1H), 2.97-2.62 (m, 4H), 1.78-1.36 (m, 9H), 1.01 (t, J = 6.4 Hz, 1H), 0.99 (t, J = 6.1 Hz, 1H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 167.1, 154.0, 138.6, 133.3, 131.7, 128.7, 127.9, 127.7, 126.8, 124.4, 120.8, 56.2, 55.0, 45.1, 26.6 (2C), 25.3, 24.3, 23.5, 22.8.



Spectral Data for New Compounds













S26





















S36





rrent Data Parameters























































S64



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