Mild, Practical, Scalable, Radical Synthesis of Heteroaryl Amino Acids

R. Adam Aycock, David B. Vogt, Nathan T. Jui*

Department of Chemistry and Winship Cancer Institute, Emory University, Atlanta, GA 30322

Table of Contents

I. General Information	S-2
I-A. General Reagent Information.	S-2
I-B. General Analytical Information	S-2
II. General Procedure	S-3
III. Optimization Details	S-3
III-A. Procedure for In-Text Deviation from Optimal Conditions	S-3
III-B. Optimization Procedure	S-3
III-C. Gas Chromatography Method Conditions	S-4
III-D. Optimization Table.	S-5
IV. Preparation of Starting Materials	S-6
V. Procedure and Characterization Data	S-16
VI. Deprotection Procedure and Characterization Data	S-34
VII. ¹ H and ¹³ C NMR Spectra	S-37
VIII. Chiral HPLC Data	S-107
IX. Stern-Volmer Fluorescence Quenching Experiments	S-109
X. Procedure for α-Deuteration With D ₂ O as Solvent	S-111

I. General Information

I-A. General Reagent Information:

All reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs (LEDwholesalers PAR38 Indoor Outdoor 16-Watt LED Flood Light Bulb, Blue; or PARsource PowerPAR LED Bulb-Blue 15 Watt/440 nm, available at www.eaglelight.com). Flash chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Photoredox catalyst, [Ir(ppy)₂(dtbbpy)]PF₆, was prepared according to a literature procedure¹. Halogenated heteroarenes were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics, Combi-Blocks, or Oakwood Products and were used as received. Dehydroalanines were prepared according to the designated procedures in section IV, Preparation of Dehydroalanine Substrates. Molecular sieves were activated in a commercial microwave oven then cooled under high vacuum. DMSO was purified on a Pure Process Technologies solvent purification system. Reaction solvent was prepared by combining DMSO and tap water (5:1, V:V) which was degassed in a sidearm flask under weak vacuum while subject to sonication. Alcoholic beverages used as solvents for optimization screenings were purchased from a local package store and used as received.

I-B. General Analytical Information:

All yields refer to isolated yields. New compounds were characterized by NMR, IR spectroscopy, HRMS, and melting point. NMR data were recorded on one of six spectrometers: Bruker 600 MHz, INOVA 600 MHz, INOVA 500 MHz, VNMR 400 MHz, INOVA 400 MHz, or Mercury 300 MHz. Chemical shifts (δ) are internally referenced to residual protio solvent (CDCl₃: δ 7.26 ppm for ¹H NMR and 77.23 ppm for ¹³C NMR; C₆D₆: 7.15 ppm for ¹H NMR and 128.4 ppm for ¹³C NMR; CD₃OD: δ 3.31 ppm for ¹H NMR and 49.1 ppm for ¹³C NMR, or D₂O). IR spectra were obtained with a Thermo Scientific Nicolet iS10 Fourier transform infrared spectrophotometer. Mass spectrometry data were obtained from the Emory Mass Spectrometry Center using a Thermo LTQ-FTMS high resolution mass spectrometer. Melting point data was obtained with a Thomas Hoover Unimelt capillary melting point apparatus. Adduct yields for optimization data were obtained via H¹ NMR with an Inova 400 MHz NMR using 1,3,5-trimethoxybenzene as internal standard, with relaxation delay set to 5 seconds. Hydrodehalogenated yields for optimization data were obtained via gas chromatography with an Agilent Technologies 7890B Gas Chromatography system (flame-ionization detection) equipped with an Agilent Technologies 19091J-413 HP-5 column (30 m x 0.320 mm x 0.25 µm, 5% phenyl methyl siloxane) and an Agilent Technologies G4513A autoinjector. Enantioenriched samples were analyzed on a 1100 Series Agilent HPLC on Daicel Chiralcel columns (250 x 4.6 mm ID). Optical rotations were measured at 20 °C using a Perkin Elmer Model 341 Polarimeter at $\lambda = 589$ nm.

¹ Lowry, M. S.; Hudson, W. R.; Pascal, R. A.; Bernhard, S. J. Am. Chem. Soc. 2004, 126, 14129.

II. General Procedure:

A 20-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (1.3 – 1.5 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6(1 \text{ mol}\%)$, dehydroalanine (2 equiv), and halogenated heteroarene (1 equiv). The tube was sealed with PTFE/silicon septum and connected to a Schlenk line. The atmosphere was exchanged by applying vacuum and backfilling with N₂ (this process was conducted a total of three times). Under N₂ atmosphere, the tube was charged with degassed solvent (5:1 DMSO:H₂O, 10 mL/mmol heteroarene) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 16 hours while being cooled with a fan. The reaction was quenched with saturated sodium bicarbonate solution (60 mL) and extracted with ethyl acetate (3 x 40 mL). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

III. Optimization Details

III-A. Procedure for In-Text Deviation from Optimal Conditions:

A 15-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (76 mg, 0.30 mmol, 1.5 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6(1.8 mg, 0.002 mmol, 1 mol%), methyl-$ 2-(di(tert-butoxycarbonyl)amino)but-2-enoate (120 mg, 0.4 mmol, 2 equiv), and 2-bromo-5-hydroxypyridine (34.8 mg, 0.20 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a Schlenk line. The atmosphere was exchanged by applying vacuum and backfilling with N₂ (this process was conducted a total of three times). Under N₂ atmosphere, the tube was charged degassed solvent (2.0 mL) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 16 hours while being cooled with a fan. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (5 x 5 mL). The extracts were combined and passed through a plug of silica which was flushed with additional ethyl acetate, and the solution was transferred to a 20-mL scintillation vial. The contents of the vial were concentrated via rotary evaporation and then subject to high vacuum for 2 hours. 1,3,5-trimethoxybenzene (33.6 mg, 1 equiv) was added, and the contents were thoroughly dissolved in CDCl₃. An aliquot was analyzed by H¹NMR, and the integral values were used to calculate azatyrosine ester yield.

III-B. Optimization Procedure:

A 15-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (76 mg, 0.30 mmol, 1.5 equiv), photoredox catalyst (1 mol%), methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate (120 mg, 0.4 mmol, 2 equiv), and 2-bromopyridine (31.6 mg, 0.20 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a Schlenk line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged degassed solvent (2.0 mL) by syringe. The resulting

suspension was stirred under irradiation with blue LEDs for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (5 x 5 mL). The extracts were combined and passed through a plug of silica which was flushed with additional ethyl acetate, and the solution was transferred to a 20-mL scintillation vial. An internal standard of dodecane (10 μ L, 0.044 mmol) was delivered to the vial, and the contents were thoroughly mixed. A sample was analyzed by gas chromatography, and the integral values were used to calculate hydrodehalogenation product (pyridine) yield. The contents of the vial were concentrated via rotary evaporation and then subject to high vacuum for 2 hours. 1,3,5-trimethoxybenzene (33.6 mg, 1 equiv) was added, and the contents were thoroughly dissolved in CDCl₃. An aliquot was analyzed by H¹NMR, and the integral values were used to calculate pyridylalanine ester yield.

III-C. Gas Chromatography Method Conditions:

The gas chromatography system hardware is reported in section I-B, General Analytical Information. The injection volume for each trial is 0.5 μ L. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. With no hold time, the temperature ramp rate is adjusted to 25 °C/min until reaching the maximum temperature of 325 °C. Maximum temperature is held for one minute before concluding the run.

III-D. Optimization Table:

	R Br	OMe Hantzsch este	tocatalyst		ОМе	
2-	-bromopyridine DH.	A (2.0 equiv) solvent, b	lue LED	(±)-A		В
entry	photocatalyst	solvent	deviation	% yield A	% yield B	selectivity (A:B)
1	Ru(bpy) ₃ Cl ₂	MeCN (0.1 M)	-	0	0	-
2	Ir(ppy) ₃	MeCN (0.1 M)	-	48	2	24:1
3	Ir(dF(CF ₃)ppy) ₂ dtbbpy•P	F ₆ MeCN (0.1 M)	-	50	2	25:1
4	$Ir(ppy)_2dtbbpy\bullet PF_6$	MeCN (0.1 M)	-	52	2	26:1
5	Ru(bpy) ₃ Cl ₂	DMSO (0.1 M)	-	54	2	27:1
6	Ir(ppy) ₃	DMSO (0.1 M)	-	65	2	33:1
7	Ir(dF(CF ₃)ppy) ₂ dtbbpy•P	F ₆ DMSO (0.1 M)	-	81	11	7:1
8	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO (0.1 M)	-	81	11-	7:1
9	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMF/H ₂ O (3:1, 0.1M)	-	34	2	17:1
10	$Ir(ppy)_2dtbbpy\bullet PF_6$	MeCN/H ₂ O (3:1, 0.1M)	-	27	3	9:1
11	$Ir(ppy)_2dtbbpy\bullet PF_6$	MeOH/H ₂ O (3:1, 0.1 M)	-	30	1	30:1
12	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (3:1, 0.1 M)	-	85	3	28:1
13	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (3:1, 0.03 M)	-	98	2	49:1
14	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (5:1, 0.1 M)	-	98	2	49:1
15	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (5:1, 0.1 M)	1.1 equiv DHA	93	7	13:1
16	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (5:1, 0.1 M)	air-exposed	90	5	18:1
17	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (5:1, 0.1 M)	1.1 equiv DHA, air-expose	ed 85	7	12:1
18	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (5:1, 0.1 M)	no Hantzsch ester	0	0	-
19	$Ir(ppy)_2dtbbpy\bullet PF_6$	DMSO/H ₂ O (5:1, 0.1 M)	no light	0	0	-
20	none	DMSO/H ₂ O (5:1, 0.1 M)	-	0	0	-
21	$Ir(ppy)_2dtbbpy\bullet PF_6$	Grey Goose vodka (0.3 M)	-	85	12	7:1
22	$Ir(ppy)_2dtbbpy\bullet PF_6$	Bacardi white rum (0.3 M)	-	86	12	7:1
23	$Ir(ppy)_2dtbbpy\bullet PF_6$	Johnnie Walker Scotch (0.3 M	ſ) -	84	12	7:1
24	$Ir(ppy)_2dtbbpy\bullet PF_6$	Woodford Reserve Bourbon (0.3	M) -	93	4	23:1
25	Ir(ppy) ₂ dtbbpy•PF ₆	Seagram's gin (0.3 M)	-	94	4	24:1
26	$Ir(ppy)_2dtbbpy\bullet PF_6$	Redbull/Grey Goose (1:2, 0.3 I	- (M	42	1	42:1

IV. Preparation of Starting Materials:

methyl (tert-butoxycarbonyl)-L-serinate:

To a stirring solution of L-serine, methyl ester hydrochloride (20.0g, 128 mmol, 1 equiv) in dichloromethane (130 mL) at 0 °C was added triethylamine (40 mL, 282 mmol, 2.2 equiv) and di-*tert*-butyl dicarbonate (37 mL, 135 mmol, 1.1 equiv). After stirring for 30 minutes, the solution was warmed to room temperature, and stirred for an additional 18 hours. The reaction mixture was concentrated by rotary evaporation, diluted with ethyl acetate, and washed with 1M HCl, saturated aqueous NaHCO₃, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The reside was passed through a silica plug (50% ethyl acetate in hexanes) to afford the product as a clear, colorless oil (37.2 g 94% yield). The physical properties and spectral data are consistent with the reported values.²

methyl-2-(di(tert-butoxycarbonyl)amino)but-2-enoate:

To a stirring solution of methyl (*tert*-butoxycarbonyl)-L-serinate (37.2, 120 mmol, 1.0 equiv) in acetonitrile (200 mL) at 0 °C was added di-*tert*-butyl dicarbonate (58.3 mL, 281 mmol, 2.2 equiv) and 4-dimethylaminopyridine (3. 12 g, 25.6 mmol, 0.20 equiv). The resulting solution was warmed to room temperature and stirred for 8 hours. DBU (2.00 g, 12.8 mmol, 0.10 equiv) was added, and the resulting mixture was stirred for an additional 8 hours. The reaction was concentrated by rotary evaporation then diluted in ethyl acetate. The mixture was washed with 1M HCl and saturated aqueous NaHCO₃, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by passing through a short plug of silica (5% – 15% ethyl acetate/hexanes) to afford the product (31.5 g, 89% yield) as a white solid. The physical properties and spectral data are consistent with the reported values.³

² Hiroaki, T. and Hisashi, Y. J. Am. Chem. Soc. 2016, 138, 14218.

³ Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; and Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433.

benzyl (2S,4R)-4-((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate: To a round bottom flask equipped with a stir bar was added S-benzyl-L-cysteine (10 g, 47 mmol, 1 equiv.), NaOH (1.8 g, 45 mmol, 0.95 equiv), and anhydrous MeOH (500 mL). The reaction was stirred at room temperature for 30 minutes or until nearly homogenous. Pivaldehyde (4.9 g, 57 mmol, 1.2 equiv) and activated 3 Å molecular sieves (50 g) were added to the reaction flask, each in one portion. The reaction was placed under nitrogen atmosphere and stirred at room temperature until the starting material had been consumed (determined by ¹H NMR of a filtered and concentrated aliquot of the reaction solution dissolved in D_3COD). The reaction was quickly filtered through celite and concentrated by rotary evaporation. The residue was dried under high vacuum for 4 hours to afford the imine as a white solid. The imine was dissolved in anhydrous DCM (500 mL) and cooled to 0 °C in an oversized, well-insulated ice bath. Benzyl chloroformate (10.1 mL, 71 mmol, 1.5 equiv) was added to the cooled reaction dropwise via syringe. The reaction was stirred at 0 °C for a full 18 hours then warmed to room temperature and stirred for an additional 6 hours. The mixture was washed with 1 M aqueous NaOH (1 x 250 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (5% - 15%) ethyl acetate/hexanes) to afford the product (8.2 g, 42% yield) as a colorless oil.

¹**H NMR** (300 MHz, CDCl₃) δ 7.43 – 7.34 (m, 5H), 7.33 – 7.20 (m, 5H), 5.55 (s, 2H), 5.21 (dd, J = 16.6, 12.1 Hz, 2H), 4.55 (dd, J = 7.8, 6.2 Hz, 1H), 3.78 (q, J = 13.4 Hz, 1H), 2.94 (dd, J = 13.9, 8.0 Hz, 1H), 2.79 (dd, J = 13.9, 6.1 Hz, 1H) 0.93 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 171.1, 155.6, 137.6, 135.0, 128.9, 128.5, 128.4, 128.3, 127.0, 96.1, 68.3, 57.4, 36.7, 36.3, 33.1, 24.7.

FTIR (neat) v_{max} : 33063, 3031, 2970, 1791, 1717, 1481, 1454, 1390, 1344, 1324, 1221, 1196, 1170, 1118, 1036, 1016, 968, 908, 728, and 697 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₃H₂₈O₄NS, 414.1733; found, 414.1731.



benzyl (2*S*,4*R*)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxy-late:

To a round bottom flask equipped with a stir bar was added benzyl (2S,4R)-4-((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (2.4 g, 6 mmol, 1 equiv), *meta*-chloroperoxybenzoic acid (2.5 g, 15 mmol, 2.5 equiv), and DCM (200 mL). The reaction was stirred at room temperature for 18 hours. The reaction mixture was washed with 1 M aqueous sodium hydroxide (3 x 100 mL). The organic layer was dried

over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (5% - 30% ethyl acetate/hexanes) to afford the product (2.5 g, 95% yield) as a white foam.

¹**H** NMR (400 MHz, CDCl₃) δ 7.47 – 7.22 (m, 10H), 5.60 (s, 1H), 5.30 – 5.14 (m, 2H), 5.07 (dd, J = 7.9, 4.0 Hz, 1H), 4.63 (d, J = 14.0 Hz, 1H), 4.40 (d, J = 14.0 Hz, 1H), 3.42 (dd, J = 15.3, 7.9 Hz, 1H), 3.15 (dd, J = 15.3, 4.0 Hz, 1H), 0.87 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) & 170.7, 155.3, 134.9, 129.0, 128.9, 128.7, 128.7, 127.9, 96.8, 68.8, 60.2, 53.5, 52.6, 37.0, 24.5.

FTIR (neat) v_{max} : 3066, 3034, 2972, 2874, 2256, 1791, 1719, 1456, 1392, 1312, 1285, 1119, 1039, 966, 908, 725, and 696 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₄H₂₄O₂N₅S, 446.1645; found, 446.1640.

benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (22):

To a round bottom flask equipped with a stir bar was added (benzyl (2*S*,4*R*)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate) (3.6g, 8 mmol, 1 equiv), and DCM (100 mL). The flask was chilled to 0 °C in an ice bath, and DBU (1.3 mL, 9 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred at 0 °C until the starting material had been consumed (determined by TLC, about 10 minutes). While still at 0 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL), the layers were separated, and the organic phase was washed with saturated aqueous ammonium chloride (3 x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (5% – 15% ethyl acetate/ hexanes) to afford the product (2.0 g, 87% yield) as a colorless oil. The physical properties and spectral data are consistent with the reported values⁴. Chiral HPLC analysis of the alkene (OJ-H, 5% IPA/hexanes, 1.0 mL/min, 254 nm) indicated 97% ee for the major enantiomer (t_R (minor) = 11.800 min, t_R (major) = 13.225 min).

methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-hydroxybutanoate:

To a stirring solution of L-threonine, methyl ester hydrochloride (8.2 g, 49 mmol, 1.0 equiv) in dichloromethane (80 mL) at 0 °C was added triethylamine (21 mL, 150 mmol, 3.0 equiv) and di-*tert*-butyl dicarbonate (12 g, 53 mmol, 1.1 equiv). After stirring 30 minutes, the solution was warmed to room temperature, and stirring was continued for an

⁴ Hargrave, J. D.; Bish, D.; Köhn, G. K.; and Frost, C. G *Org. Biomol. Chem.*, **2010**, *8*, 5120.

additional 18 hours. The reaction mixture was concentrated by rotary evaporation, diluted with ethyl acetate, and washed with 1M HCl, saturated aqueous NaHCO₃, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was passed through a silica plug to afford the product (10.7 g, 95% yield) as a clear, colorless oil. The physical properties and spectral data are consistent with the reported values.²

methyl-2-(di(tert-butoxycarbonyl)amino)but-2-enoate:

To a stirring solution of methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-hydroxybutanoate (10.0 g, 42.9 mmol, 1.0 equiv) in acetonitrile (120 mL) at 0 °C was added di-*tert*-butyl dicarbonate (19.6 g, 90.1 mmol, 2.1 equiv) and DMAP (510 mg, 4.2 mmol, 0.10 equiv). The resulting solution was warmed to room temperature, and after stirring for 8 hours DBU (1.31 g, 8.59 mmol, 0.20 equiv) was added, and the resulting mixture was stirred for 8 hours. The reaction was concentrated by rotary evaporation then diluted in ethyl acetate. The mixture was washed with 1M HCl and saturated aqueous NaHCO₃, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by passing through a short pad of silica (hexane/ethyl acetate = 30%) to afford the product (9.59 g, 71% yield) as a clear, colorless oil.

¹**H NMR** (300 MHz, CDCl₃) δ 6.93 – 6.68 (m, 1H), 3.72 (s, 3H), 1.72 (d, *J* = 7.1 Hz, 2H), 1.41 (d, *J* = 1.0 Hz, 18H).

¹³**C NMR** (75 MHz, CDCl₃) δ 164.3, 150.4, 136.5, 130.1, 82.7, 52.0, 27.8, 13.3. **FTIR** (neat) v_{max}: 2980, 2953, 2935, 1792, 1757, 1727, 1368, 1270, 1250, 1152, 1093, 1044, and 730 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₅H₂₆NO₆, 316.1755; found, 316.1756.



2-amino-3-hydroxy-3-phenylpropanoic acid:

To a stirring solution of NaOH (10 g, 250 mmol, 4.5 equiv) in water (50 mL) was added glycine (5.7 mL, 56 mmol, 1.0 equiv). The solution was stirred 10 minutes, then benzaldehyde (10 g, 151 mmol, 2.9 equiv) was added. The solution was stirred for an additional 30 minutes as an off-white emulsion formed. The precipitant was broken apart in the flask, and concentrated HCl (aq) (130 mL) was added slowly while stirring until consumption of the solid was observed to give a clear yellow solution. After stirring an additional 10 minutes, a beige precipitate formed. The reaction mixture was cooled to 0 °C, and the precipitate was collected by vacuum filtration and washed with ether. The solid

was dried under high vacuum to give the product as an off-white solid (11.6 g, 72% yield). The physical properties and spectral data are consistent with the reported values.⁵

methyl (28)-2-amino-3-hydroxy-3-phenylpropanoate:

To a stirring solution of 3-hydroxyphenylalanine (3.62 g, 20 mmol, 1.0 equiv) in methanol (80 mL) at 0 °C was added thionyl chloride (3.5 g, 30 mmol, 1.5 equiv) dropwise via syringe, and the reaction mixture was stirred for 30 minutes while gradually warming to room temperature. Upon reaching room temperature, a reflux condenser was attached, and the reaction mixture was heated to 65 °C and stirred under reflux for an additional 5 hours. After cooling to room temperature, the reaction mixture was concentrated by rotary evaporation, diluted with chloroform, concentrated by rotary evaporation, washed with ether, and dried under high vacuum for 2 hours to afford the product as a white solid (4.6 g, 99% yield). The physical properties and spectral data are consistent with the reported values.⁶



phenylalanine, *N*-[(1,1-dimethylethoxy)carbonyl]-β-hydroxy-, methyl ester:

To a stirring solution of methyl (2S)-2-amino-3-hydroxy-3-phenylpropanoate hydrochloride (5.8 g, 25 mmol, 1.0 equiv) in dichloromethane (70 mL) at 0 °C was added triethylamine (7.6 mL, 57 mmol, 2.5 equiv) and di-*tert*-butyl dicarbonate (5.5 mL, 25 mmol, 1.0 equiv). After stirring 30 minutes, the solution was warmed to room temperature, and stirred for an additional 18 hours. The reaction mixture was concentrated by rotary evaporation, diluted with ethyl acetate, and washed with 1M HCl, saturated aqueous NaHCO₃, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The reside was passed through a silica plug (50% ethyl acetate/hexanes) to afford the product as a clear, colorless oil (5.10 g 91% yield). The physical properties and spectral data are consistent with the reported values.⁷

methyl 2-(di(tert-butoxycarbonyl)amino)-3-phenylacrylate:

To a stirring solution of phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]- β -hydroxy-, methyl ester (5.01 g, 16.9 mmol, 1.0 equiv) in acetonitrile (22 mL) at 0 °C was added di-

⁵ Shiraiwa, T.; Saijoh, R.; Suzuki, M.; Yoshida, K.; Nishimura, S.; Nagasawa, H. *Chem. Pharm. Bull.* **2003**, *51*, 1363.

⁶ Miyata, O.; Asai, H.; Naito, T. Chem. Pharm. Bull. 2005, 53, 355.

⁷ Bengtsson, C.; Nelander, H.; Almqvist, F. Chem. Eur. J., **2013**, 19, 9916.

tert-butyl dicarbonate (8.10 g, 37.2 mmol, 2.2 equiv) and DMAP (206 mg, 1.69 mmol, 0.10 equiv). The resulting solution was warmed to room temperature, and after stirring for 8 hours DBU (516 mg, 3.4 mmol, 0.2 equiv) was added, and the resulting mixture was allowed to continue stirring for an additional 8 hours. The reaction was concentrated by rotary evaporation then diluted with ethyl acetate. The organic layer was washed with 1M HCl and saturated aqueous NaHCO₃, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (5% – 15% ethyl acetate/hexanes) to afford the product, (5.17 g, 81% yield) as a clear, colorless oil.

¹**H NMR** (300 MHz, CDCl₃) *δ* 7.52 (s, 1H), 7.50 – 7.45 (m, 2H), 7.40 – 7.35 (m, 3H), 3.83 (s, 3H), 1.30 (s, 18H).

¹³C NMR (125 MHz, CDCl₃) δ 165.4, 150.0, 135.7, 133.0, 129.9, 129.6, 128.9, 127.1, 82.9, 52.4, 27.6.

FTIR (neat) v_{max} : 2979, 2952, 2934, 1794, 1752, 1722, 1393, 1317, 1248, 1149, 1113, 1093, 1027, 850, and 780 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₁H₂₄N₂O₂, 378.1925; found, 378.1919.



methyl 2-(phenylamino)but-2-enoate:

To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (6.1 g, 52 mmol, 1.0 equiv), aniline (4.8 g, 52 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (494 mg, 2.6 mmol, 0.05 equiv), and benzene (150 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 50% ethyl acetate/hexanes) to afford the product (6.0 g, 59% yield) as an orange oil.

¹**H NMR** (300 MHz, CDCl₃) δ 7.30 – 7.19 (m, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.78 – 6.43 (m, 3H), 5.64 (s, 1H), 3.79 (s, 3H), 1.73 (d, *J* = 7.3 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 166.3, 144.2, 130.3, 129.0, 119.4, 115.3, 52.2, 14.5.

FTIR (neat) v_{max} : 3375, 3053, 3026, 2971, 2951, 1708, 1647, 1599, 1497, 1434, 1266, 1244, 1175, 747, and 693 cm⁻¹.

HRMS (NSI) m/z: [M+H]+ calcd. for C₁₁H₁₄O₂N, 192.1019; found, 192.1019.



methyl 2-((4-bromophenyl)(methyl)amino)but-2-enoate:

To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 2.0 equiv), 4-bromo-*N*-methylaniline (1.1 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (95 mg, 0.50 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 30% ethyl acetate/hexanes) to afford the product (1.6 g, 83% yield) as a clear, colorless oil.

¹**H NMR** (500 MHz, CDCl₃) δ 7.41 – 7.18 (m, 2H), 6.99 (q, *J* = 7.0 Hz, 1H), 6.49 (d, *J* = 9.0 Hz, 2H), 3.68 (d, *J* = 0.9 Hz, 3H), 3.04 (s, 3H), 1.81 – 1.70 (m, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 165.6, 146.9, 138.2, 136.7, 131.7, 113.9, 109.5, 51.9, 38.0, 13.5.

FTIR (neat) v_{max} : 2972, 2950, 2819, 1732, 1589, 1498, 1434, 1371, 1303, 1239, 1206, 808, and 747 cm⁻¹.

HRMS (NSI) m/z: [M+H]+ calcd. for C₁₂H₁₅O₂NBr, 284.0281; found, 284.0285.



methyl 2-((4-methoxyphenyl)(methyl)amino)but-2-enoate:

To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 2.0 equiv), 4-methoxy-*N*-methylaniline (1.4 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid (95 mg, 0.50 mmol, 0.05equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (1.6 g, 68% yield) as a clear, colorless oil.

¹**H** NMR (500 MHz, CDCl₃) δ 6.91 (q, J = 7.1 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.1 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 3.05 (s, 3H), 1.79 (d, J = 7.1 Hz, 3H). ¹³**C** NMR (125 MHz, CDCl₃) δ 166.2, 151.9, 142.4, 137.6, 136.9, 114.7, 113.3, 55.6, 51.7, 38.3, 13.4. **FTIR** (neat) v_{max} : 2992, 2948, 2906, 2832, 1718, 1647, 1507, 1238, 1201, 1123, 1114, 1036, and 817 cm⁻¹. **HRMS** (NSI) m/z: [M+H]+ calcd. for C₁₃H₁₈O₃N, 236.1281; found, 236.1278.



methyl 4-((1-methoxy-1-oxobut-2-en-2-yl)(methyl)amino)benzoate:

To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 1.0 equiv), methyl 4-(methylamino)benzoate (3.3 g, 20 mmol, 1.0 equiv), *p*-toluenesulfonic acid (190 mg, 1.0 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 50% ethyl acetate/hexanes) to afford the product (4.1 g, 77% yield) as a clear, colorless oil.

¹**H** NMR (500 MHz, CDCl₃) δ 7.87 (d, J = 8.5 Hz, 2H), 7.02 (q, J = 6.8 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 3.81 (s, 4H), 3.66 (s, 3H), 3.08 (s, 3H), 1.72 (d, J = 7.1 Hz, 3H).

¹³**C NMR** (125 MHz, CDCl₃) δ 167.1, 165.2, 151.4, 138.7, 136.2, 131.2, 118.6, 111.2, 52.0, 51.4, 38.0, 13.5.

FTIR (neat) v_{max} : 2990, 2949, 2907, 1705, 1601, 1516, 1433, 1275, 1255, 1177, 1108, 1042, and 768 cm⁻¹.

HRMS (NSI) m/z: [M+H]+ calcd. for C₁₄H₁₈O₄N, 264.1230; found, 264.1227.



methyl 2-(methyl(4-(trifluoromethyl)phenyl)amino)but-2-enoate:

To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 2.0 equiv), 4-trifluoromethyl-*N*-methylaniline (1.8 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (2.3 g, 84% yield) as a clear, colorless oil.

¹**H** NMR (500 MHz, CDCl₃) δ 7.44 (d, *J* = 9.1 Hz, 1H), 7.07 (q, *J* = 7.0 Hz, 0H), 6.65 (d, *J* = 8.9 Hz, 1H), 3.71 (s, 1H), 3.10 (s, 1H), 1.76 (d, *J* = 7.1 Hz, 1H). ¹³**C** NMR (75 MHz, CDCl₃) δ 165.3, 150.2, 139.0, 136.2, 126.5 (q, *J* = 4.2 Hz), 125.0 (q, *J* = 270.0 Hz), 118.7 (q, *J* = 33.1 Hz), 111.5, 52.0, 38.0, 13.4.

¹⁹**F NMR** (282 MHz, CDCl₃) δ -61.01.

FTIR (neat) v_{max} : 2994, 2953, 2912, 2825, 1720, 1650, 1613, 1524, 1321, 1257, 1205, 1193, 1102, 1067, 1043, 849, and 576 cm⁻¹.

HRMS (NSI) m/z: [M+H]+ calcd. for C₁₃H₁₅O₂NF₃, 274.1049; found, 274.1050.



6-oxocyclohex-1-en-1-yl trifluoromethanesulfonate:

To a stirring solution of 1,2-cyclohexanedione (5.0 g, 45 mmol, 1.0 equiv) in dichlormethane (100 mL) at -78 °C was added triethylamine (5.5 g, 54 mmol, 1.2 equiv) and trifluoromethanesulfonic anhydride (12.7 g, 45 mmol, 1.0 equiv). The resulting solution was warmed to room temperature and stirred for an additional 3 hours. The reaction was concentrated by rotary evaporation then diluted with ethyl acetate. The organic layer was washed with 1M HCl and saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (10% - 30% ethyl acetate/hexanes) to afford the product (6.2 g, 57% yield) as a white crystalline, low-melting solid.

¹**H** NMR (600 MHz, CDCl₃) δ 6.93 (t, J = 4.4 Hz, 1H), 2.84 – 2.34 (m, 4H), 2.07 (p, J = 7.4, 6.9, 5.6, 5.6 Hz, 2H).

¹³**C NMR** (150 MHz, CDCl₃) δ 189.8, 144.5, 139.5, 118.5 (q, J = 320.1 Hz), 37.6, 24.9, 21.8.

¹⁹**F NMR** (282 MHz, CDCl₃) *δ* -73.99.

FTIR (neat) v_{max} : 2953, 1702, 1419, 1349, 1202, 1137, 1070, 914, and 809 cm⁻¹. **HRMS** (NSI) m/z: [M+H]⁺ calcd. for C₇H₈O₄S, 245.0090; found, 245.0087.



ŃНВос

tert-butyl (6-oxocyclohex-1-en-1-yl)carbamate:

A three-neck round-bottom flask equipped with a stir bar was charged with 6-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (4.0 g, 16.3 mmol, 1.0 equiv), tert-butyl carbamate (2.2 g, 19.6 mmol, 1.2 equiv, $Pd_2(dba)_3$ (372 mg, 0.41 mmol, 0.025 equiv), 2-di-tertbutylphosphino-2',4',6'-triisopropylbiphenyl (691 mg, 1.6 mmol, 0.10 equiv), and K₂CO₃ (5.5 g, 40.8 mmol, 2.5 equiv). A reflux condenser was connected, and each inlet was sealed with a rubber septum. The atmosphere was exchanged by applying vacuum and backfilling with N₂ (this process was conducted a total of three times). Under N₂ atmosphere, the tube was charged with degassed toluene (40 mL). The reaction mixture was heated to 80 °C and stirred under N₂ for 12 hours. After cooling to room temperature, the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (10% – 70% ethyl acetate/hexanes) to afford the product (2.8 g, 80% yield) as a pale yellow oil.

¹**H NMR** (400 MHz, CDCl₃) δ 7.29 (t, J = 4.7 Hz, 1H), 7.05 (s, 1H), 2.56 – 2.28 (m, 4H), 2.00 – 1.76 (m, 2H), 1.39 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) 193.7, 152.8, 132.4, 127.2, 80.1, 37.0, 28.1, 24.5, 22.4.

FTIR (neat) v_{max} : 3402, 2977, 2933, 2871, 2832, 1784, 1721, 1672, 1638, 1507, 1355, 1227, 1151, 1042, 1020, 877, and 867 cm⁻¹. **HRMS** (NSI) m/z: [M+H]+ calcd. for C₁₁H₁₈O₃N, 212.1281; found, 212.1279.

2-(methyl(phenyl)amino)cyclohex-2-en-1-one:

To a round-bottom flask equipped with stir bar was added cyclohexane-1,2-dione (2.2 g, 20 mmol, 2.0 equiv), *N*-methylaniline (1.1 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid (95 mg, 0.5 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was diluted with ethyl acetate, washed with water (2 x 50 mL), dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (5% – 30% ethyl acetate/hexanes) to afford the product (1.5 g, 80% yield) as a yellow oil.

¹**H NMR** (300 MHz, CDCl₃) δ 7.19 (dd, J = 8.7, 7.2 Hz, 2H), 6.83 – 6.76 (m, 2H), 6.75 – 6.68 (m, 2H), 3.07 (s, 3H), 2.54 (qd, J = 6.3, 3.8 Hz, 4H), 2.09 (p, J = 6.2 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 196.4, 149.0, 144.6, 143.1, 128.8, 118.4, 114.7, 39.5, 39.3, 26.0, 22.9.

FTIR (neat) v_{max} : 3058, 3024, 2942, 2874, 2813, 1680, 1596, 1497, 1323, 1128, 747, and 691 cm⁻¹.

HRMS (NSI) m/z: [M+H]+ calcd. for C₁₃H₁₆ON, 202.1226; found, 202.1225.

4-(methyl(phenyl)amino)hex-4-en-3-one:

To a round-bottom flask equipped with stir bar was added hexane-3,4-dione (5.5 g, 50 mmol, 5.0 equiv), *N*-methylaniline (1.1 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid (95 mg, 0.5 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 18 hours. The reaction mixture was diluted with ethyl acetate, washed with water (2 x 50 mL), dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (5% – 30% ethyl acetate/hexanes) to afford the product (1.8 g, 91% yield) as a yellow oil.

¹**H NMR** (300 MHz, CDCl₃) δ 7.28 – 7.16 (m, 2H), 6.88 – 6.80 (m, 1H), 6.75 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.60 (dd, *J* = 7.7, 1.1 Hz, 2H), 3.13 (s, 3H), 2.44 (q, *J* = 7.1 Hz, 2H), 1.75 (d, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 201.5, 147.5, 145.0, 135.0, 129.3, 117.3, 111.9, 38.1, 31.8, 13.6, 7.9.

FTIR (neat) v_{max} : 3060, 2972, 2935, 2917, 1713, 1593, 1503, 1360, 746, and 691 cm⁻¹. **HRMS** (NSI) m/z: [M+H]+ calcd. for C₁₃H₁₈ON, 204.1383; found, 204.1381.



1-(methoxycarbonyl)piperidine-4-carboxylic acid:

To a round bottom flask equipped with a stir bar was added piperidine-4-carboxylic acid (5.0 g, 39 mmol, 1 equiv), THF (100 mL), and saturated aqueous sodium bicarbonate (100 mL). Methyl chloroformate (6.0 mL, 77.0 mmol, 2 equiv) was then added dropwise via syringe. The reaction was allowed to stir at room temperature overnight. The reaction mixture was filtered over celite then concentrated to remove THF. The remaining solution was acidified to pH = 2 using 1 M HCl then extracted with ethyl acetate (3 x 100 mL). The combined extracts were dried over sodium sulfate, filtered, then concentrated by rotary evaporation. The residue was purified by flash chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (5.65 g, 78% yield) as a white solid.

¹**H NMR** (500 MHz, CDCl₃) δ 11.46 (s, 1H), 4.01 (m, 2H), 3.65 (s, 3H), 2.89 (t, *J* = 11.5 Hz, 2H), 2.46 (tt, *J* = 10.8, 4.0 Hz, 1H), 1.88 (d, *J* = 11.5 Hz, 2H), 1.61 (qd, *J* = 11.2, 4.0 Hz, 2H).

¹³C NMR (125 MHz, CDCl₃) δ 179.6, 156.0, 52.8, 43.1, 40.6, 27.6.

FTIR (neat) v_{max} : 3003, 2956, 2863, 1674, 1479, 1449, 1411, 1275, 1209, 1182, 1126, 1080, 1033, 930, 758, and 730 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₈H₁₄O₄N, 188.0917; found, 188.0916.



4-(1,3-dioxoisoindolin-2-yl) 1-methyl piperidine-1,4-dicarboxylate:

To a round bottom flask equipped with a stir bar was added 1-(methoxycarbonyl)piperidine-4-carboxylic acid (5.7 g, 30 mmol, 1 equiv), *N*hydroxyphthalamide (4.9 g, 30 mmol, 1 equiv), DMAP (369 mg, 3 mmol, 0.1 equiv), and DCM (300 mL). DIC (4.7 mL, 30 mmol, 1 equiv) was then added dropwise via syringe. The reaction was allowed to stir at this temperature until the starting material had been consumed (determined by TLC). The reaction mixture was filtered over celite and rinsed with an additional 50 mL of DCM. The filtrate was concentrated by rotary evaporation and the residue was purified by flash chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (7.52 g, 75% yield) as a white solid. ¹**H NMR** ¹**H** NMR (400 MHz, CDCl₃) δ 7.85 (dd, J = 5.6, 3.0 Hz, 1H), 7.77 (dd, J = 5.6, 3.0 Hz, 1H), 4.13 – 3.90 (m, 1H), 3.68 (d, J = 1.4 Hz, 2H), 3.05 (t, J = 11.0 Hz, 2H), 2.91 (tt, J = 10.2, 4.0 Hz, 1H), 2.10 – 2.00 (m, 3H), 1.84 (ddt, J = 13.3, 10.2, 5.3 Hz, 3H). ¹³**C NMR** (101 MHz, CDCl₃) δ 170.5, 161.9, 155.8, 134.9, 128.8, 124.0, 52.7, 42.7, 38.3, 27.7.

FTIR (neat) v_{max} : 2956, 2863, 1813, 1785, 1754, 1694, 1468, 1448, 1411, 1373, 1316, 1276, 1233, 1186, 1128, 1076, 1000, 968, 913, 877, 786, 767, 729, 695 cm⁻¹. **HRMS** (NSI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{17}O_6N_2$, 333.1081; found, 333.1081.

V. Procedure and Characterization Data:

methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-hydroxypyridin-2-yl)propanoate (1): Following the general procedure, the reaction of 6-bromopyridin-3-ol (174 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (608 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.4 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (361 mg, 91% yield) as an off-white solid after purification by flash column chromatography (50% – 75% ethyl acetate/hexanes).

Mp: 163 °C (decomp.)

¹**H** NMR (400 MHz, CDCl₃) δ 10.58 (s, 1H), 8.13 (d, J = 2.9 Hz, 1H), 7.15 (dd, J = 8.5, 2.8 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.29 (dd, J = 10.2, 4.8 Hz, 1H), 3.69 (s, 3H), 3.51 (dd, J = 14.1, 4.9 Hz, 1H), 3.26 (dd, J = 14.2, 10.2 Hz, 1H), 1.34 (s, 18H).

¹³C NMR (100 MHz, CDCl₃) *δ* 170.5, 153.3, 151.5, 147.6, 136.5, 125.2, 125.0, 83.2, 58.4, 52.3, 36.8, 27.7.

FTIR (neat) v_{max} : 3002, 2980, 2950, 2933, 2612, 1744, 1729, 1697, 1573, 1364, 1280, 1232, 1253, 1142, and 1115 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₃₁O₆N₂, 397.1969; found, 397.1967.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoate (2):

1 mmol scale:

Following the general procedure, the reaction of 2-iodopyridine (207 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.9 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (344 mg, 1.36 mmol, 1.3 equiv) provided the product (371 mg, 97% yield) as a clear, colorless crystalline solid after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

25-mmol scale:

A 250-mL Schlenk flask equipped with a stir bar was charged with Hantzsch ester (6.33 g, 25 mmol, 1.0 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (22.9 mg, 0.025 mmol, 0.001 equiv), methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate (9.03, 30 mmol, 1.2 equiv), 2-bromopyridine (3.95 g, 25 mmol, 1.0 equiv), and degassed DMSO/H₂O (5/1, V/V; 230 mL). The tube was connected to a N₂ line, and N₂ was streamed over the headspace of the reaction for 10 minutes before sealing with a rubber septum. The suspension was stirred under irradiation with blue LEDs for 18 hours while being cooled with a fan. The reaction was quenched with saturated sodium bicarbonate solution (1200 mL) and extracted with ethyl acetate (3 x 250 mL). The extracts were combined, passed through a silica plug, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (5 – 60% ethyl acetate/hexanes) to afford the title compound (8.0 g, 84% yield) as a white crystalline solid.

Mp: 49 – 51 °C

¹**H NMR** (300 MHz, CDCl₃) δ 8.45 (d, J = 4.8 Hz, 1H), 7.50 (td, J = 7.7, 1.9 Hz, 1H), 7.09 – 7.00 (m, 2H), 5.45 (dd, J = 9.3, 5.2 Hz, 1H), 3.65 (s, 3H), 3.57 (dd, J = 14.2, 5.1 Hz, 1H), 3.25 (dd, J = 14.2, 9.4 Hz, 1H), 1.34 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) *δ* 170.8, 157.9, 151.5, 149.3, 136.1, 123.8, 121.4, 82.8, 58.1, 52.2, 38.7, 27.8.

FTIR (neat) v_{max} : 3002, 2977, 2950, 2936, 1742, 1724, 1689, 1378, 1365, 12533, 1234, 1163, 1121, 1010, and 776 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₂₉O₆N₂, 381.2020; found, 381.2018.

methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(3-methylpyridin-2-yl)propanoate (3): Following the general procedure, the reaction of 2-bromo-3-methylpyridine (175 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (604 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.9 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (344 mg, 1.36 mmol, 1.3 equiv) provided the product (376 mg, 94% yield) as a pale yellow oil after purification by flash column chromatography (2% – 6% tetrahydrofuran/dichloromethane).

¹**H** NMR (300 MHz, CDCl₃) δ 8.33 – 8.29 (m, 1H), 7.38 – 7.28 (m, 1H), 6.97 (dd, J = 7.6, 4.8 Hz, 1H), 5.64 (dd, J = 8.9, 5.1 Hz, 1H), 3.69 (s, 3H), 3.58 (dd, J = 14.8, 5.1 Hz, 1H), 3.34 (dd, J = 14.8, 8.9 Hz, 1H), 2.27 (s, 3H), 1.38 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 171.1, 156.4, 151.6, 146.6, 137.4, 131.6, 121.3, 82.8, 57.9, 52.2, 35.3, 27.8, 18.7.

FTIR (neat) v_{max} : 2979, 2952, 2935, 1793, 1743, 1698, 1575, 1451, 1436, 1366, 1227, 1167, 1141, 1116, and 778 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₃₁O₆N₂, 395.2177; found, 395.2174.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(4-methylpyridin-2-yl)propanoate (4): Following the general procedure, the reaction of 2-bromo-4-methylpyridine (173 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.6 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (331 mg, 1.31 mmol, 1.3 equiv) provided the product (377 mg, 96% yield) as a pale yellow oil after purification by flash column chromatography (2% – 6% tetrahydrofuran/dichloromethane).

¹**H NMR** (300 MHz, CDCl₃) δ 8.33 (d, J = 5.8 Hz, 1H), 6.89 (s, 2H), 5.46 (dd, J = 9.3, 5.1 Hz, 1H), 3.68 (s, 3H), 3.55 (dd, J = 14.2, 5.1 Hz, 1H), 3.22 (dd, J = 14.2, 9.4 Hz, 1H), 2.24 (s, 3H), 1.37 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 170.9, 157.7, 151.5, 149.1, 147.1, 124.7, 122.4, 82.8, 58.2, 52.2, 38.6, 27.8, 20.8.

FTIR (neat) v_{max} : 2978, 2952, 2935, 1794, 1740, 1606, 1366, 1270, 1251, 1227, 1166, 1138, 852, and 778 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₃₁O₆N₂, 395.2177; found, 395.2175.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-methylpyridin-2-yl)propanoate (5): Following the general procedure, the reaction of 2-bromo-5-methylpyridine (175 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (604 mg, 2.01 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided the product (373 mg, 93% yield) as a pale yellow oil after purification by flash column chromatography (3% – 8% tetrahydrofuran/dichloromethane).

¹**H NMR** (300 MHz, CDCl₃) δ 8.38 – 8.24 (m, 1H), 7.45 – 7.31 (m, 1H), 6.98 (dd, J = 7.8, 0.8 Hz, 1H), 5.44 (dd, J = 9.4, 5.2 Hz, 1H), 3.69 (s, 3H), 3.56 (dd, J = 14.1, 5.2 Hz, 1H), 3.25 (dd, J = 14.1, 9.4 Hz, 1H), 2.24 (s, 3H), 1.38 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 170.8, 154.9, 151.5, 149.7, 136.7, 130.6, 123.3, 82.8, 58.3, 52.2, 38.3, 27.8, 17.9.

FTIR (neat) v_{max} : 2978, 2952, 2935, 1793, 174, 1710, 1366, 1270, 1167, 1137, and 808 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₃₀O₆N₂, 395.2177; found, 395.2173.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(6-methylpyridin-2-yl)propanoate (6): Following the general procedure, the reaction of 2-bromo-6-methylpyridine (175 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (606 mg, 2.01 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (10.1 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (334 mg, 1.30 mmol, 1.3 equiv) provided the product (388 mg, 97% yield) as a pale yellow oil after purification by flash column chromatography (3% – 8% tetrahydrofuran/dichloromethane).

¹**H** NMR (400 MHz, CDCl₃) δ 7.42 (t, J = 7.6 Hz, 1H), 6.90 (dd, J = 17.4, 7.6 Hz, 2H), 5.44 (dd, J = 9.7, 5.1 Hz, 1H), 3.69 (s, 3H), 3.53 (dd, J = 14.0, 5.1 Hz, 1H), 3.26 (dd, J = 13.9, 9.7 Hz, 1H), 2.46 (s, 3H), 1.37 (d, J = 0.9 Hz, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 170.8, 157.8, 157.1, 136.4, 120.9, 120.8, 82.8, 58.3, 52.2, 38.6, 27.8, 24.4.

FTIR (neat) v_{max} : 3000, 2980, 2957, 2933, 1743, 172, 1689, 1579, 1456, 1430, 1377, 1364, 1278, 1246, 1231, 1166, 1011, and 788 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₃₁O₆N₂, 395.2177; found, 395.2170.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-(trifluoromethyl)pyridin-2-yl)propanoate (7):

Following the general procedure, the reaction of 2-bromo-5-(trifluoromethyl)pyridine (225 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (605 mg, 2.01 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.6 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided the product (420 mg, 94% yield) as a pale yellow oil after purification by flash column chromatography (3% – 12% tetrahydrofuran/hexanes).

¹**H NMR** (300 MHz, CDCl₃) δ 8.76 – 8.68 (m, 1H), 7.76 (dd, J = 8.1, 2.2 Hz, 1H), 7.28 – 7.16 (m, 1H), 5.50 (dd, J = 8.7, 5.8 Hz, 1H), 3.71 – 3.59 (m, 4H), 3.34 (dd, J = 14.3, 8.8 Hz, 1H), 1.37 (s, 18H).

¹³**C NMR** (75MHz, CDCl₃) *δ* 177.5, 170.7, 151.9, 149.9, 147.1, 140.0, 128.8, 121.7, 83.3, 57.7, 52.3, 39.3, 32.4, 27.8, 27.4.

¹⁹**F NMR** (282 MHz, CDCl₃) δ -62.45.

FTIR (neat) v_{max} : 2981, 2954, 2936, 1793, 1745, 1700, 1608, 1367, 1381, 1271, 1161, 1127, 1017, and 756 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₂₈O₆N₂F₃, 449.1894; found, 449.1891.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-iodopyridin-2-yl)propanoate (8):

Following the general procedure, the reaction of 2,5-diiodopyridine (333 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (601 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.1 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (321 mg, 1.27 mmol, 1.3 equiv) provided the product (378 mg, 74% yield) as white solid after purification by flash column chromatography (0% – 30% tetrahydrofuran/hexanes).

Mp: 59 – 62 °C

¹**H** NMR (300 MHz, CDCl₃) δ 7.74 8.66 (dd, J = 2.2, 0.7 Hz, 1H), 7.81 (dd, J = 8.1, 2.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 5.41 (dd, J = 9.0, 5.6 Hz, 1H), 3.66 (s, 3H), 3.51 (dd, J = 14.2, 5.6 Hz, 1H), 3.20 (dd, J = 14.2, 9.0 Hz, 1H), 1.37 (s, 18H).

¹³C NMR (75MHz, CDCl₃) δ 170.6, 156.9, 155.2, 151.5, 144.3, 125.7, 90.7, 83.0, 57.8, 52.3, 38.1, 27.8.

FTIR (neat) v_{max} : 3005, 2980, 2968, 2945, 1746, 1728, 1697, 1363, 1273, 1163, 1128, and 760 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₂₈O₆N₂I, 507.0987; found, 507.0976.



methyl 3-(5-aminopyridin-2-yl)-2-(di(*tert*-butoxycarbonyl)amino)propanoate (9): Following the general procedure, the reaction of 6-iodopyridin-3-amine (220 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (603 mg, 2.00 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.2 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (280 mg, 71% yield) as an off-white solid after purification by flash column chromatography (50% – 100% ethyl acetate/hexanes).

Mp: 80 – 82 °C

¹**H NMR** (500 MHz, CDCl₃) δ 7.95 (s, 1H), 6.82 (s, 2H), 5.33 (dd, J = 9.6, 5.1 Hz, 1H), 3.72 (s, 2H), 3.66 (s, 4H), 3.44 (dd, J = 14.2, 5.1 Hz, 1H), 3.14 (dd, J = 14.2, 9.6 Hz, 1H), 1.36 (s, 18H).

¹³C NMR (125 MHz, CDCl₃) *δ* 171.0, 151.5, 147.1, 141.0, 136.9, 123.8, 121.9, 82.8, 58.5, 52.1, 37.7, 27.8.

FTIR (neat) v_{max} : 3452, 3367, 2983, 2970, 2943, 1730, 1718, 1488, 1366, 1218, 1141, and 1115 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₃₀O₆N₃, 396.2129; found, 396.2113.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-3-yl)propanoate (10):

Following the general procedure, the reaction of 3-iodopyridine (205 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (609 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.2 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (279 mg, 73% yield) as a clear, colorless crystalline solid after purification by flash column chromatography (20% – 50% ethyl acetate/hexanes).

Mp: 76 – 78 °C

¹**H** NMR (400 MHz, CDCl₃) δ 8.36 (dd, J = 8.4, 3.5 Hz, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 7.8, 4.8 Hz, 1H), 5.06 (dd, J = 10.3, 5.2 Hz, 1H), 3.66 (s, 3H), 3.34 (dd, J = 14.2, 5.2 Hz, 1H), 3.15 (dd, J = 14.3, 10.3 Hz, 1H), 1.30 (s, 18H).

¹³**C NMR** (100 MHz, CDCl₃) δ 170.3, 151.5, 150.7, 147.9, 136.9, 132.9, 123.1, 83.2, 58.6, 52.3, 33.3, 27.7.

FTIR (neat) v_{max} : 2975, 2951, 1793, 1739, 1392, 1368, 1138, 1112 1103, and 718 cm⁻¹. **HRMS** (NSI) m/z: [M+H]+ calcd. for C₁₉H₂₉O₆N₂, 381.2020; found, 381.2015.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-hydroxypyridin-3-yl)propanoate (11): Following the general procedure, the reaction of 5-iodopyridin-3-ol (220 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (371 mg, 1.47 mmol, 1.5 equiv) provided the product (265 mg, 67% yield) as an off-white solid oil after purification by flash column chromatography (50% – 100% ethyl acetate/hexanes).

Mp: 112 – 116 °C

¹**H NMR** (300 MHz, CDCl₃) δ 8.10 (d, J = 2.6 Hz, 1H), 7.94 (d, J = 1.7 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 5.14 (dd, J = 10.2, 5.0 Hz, 1H), 3.74 (s, 3H), 3.41 (dd, J = 14.2, 5.0 Hz, 1H), 3.16 (dd, J = 14.2, 10.2 Hz, 1H), 1.38 (s, 18H).

¹³C NMR (75MHz, CDCl₃) δ 170.3, 154.8, 151.6, 140.2, 135.3, 134.9, 125.4, 83.6, 58.8, 52.4, 33.2, 27.7.

FTIR (neat) v_{max} : 2980, 2581, 1744, 1696, 1437, 1366, 1269, 1222, and 1166 cm⁻¹. **HRMS** (NSI) m/z: [M+H]⁺ calcd. for C₁₉H₂₉O₇N₂, 397.1969; found, 397.1962.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-pivalamidopyridin-3-yl)propanoate (12): Following the general procedure, the reaction of N-(3-iodopyridin-2-yl)pivalamide (302 mg, 0.99 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (609 mg, 2.02 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.9 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (380 mg, 1.50 mmol, 1.5 equiv) provided the product (347 mg, 73% yield) as a white solid after purification by flash column chromatography (20% – 100% ethyl acetate/hexanes).

Mp: 104 − 107 °C

¹**H** NMR (300 MHz, CDCl₃) δ 8.56 (s, 1H), 8.30 (dd, J = 4.8, 1.8 Hz, 1H), 7.49 (dd, J = 7.6, 1.9 Hz, 1H), 7.05 (dd, J = 7.6, 4.8 Hz, 1H), 5.21 (dd, J = 8.5, 6.0 Hz, 1H), 3.66 (s, 3H), 3.46 (dd, J = 14.5, 6.0 Hz, 1H), 3.01 (dd, J = 14.5, 8.6 Hz, 1H), 1.34 (s, 18H), 1.29 (s, 9H). ¹³C NMR (75MHz, CDCl₃) δ 177.5, 170.7, 151.9, 149.9, 147.1, 140.0, 128.8, 121.7, 83.3, 57.7, 52.3, 39.3, 32.4, 27.8, 27.4.

FTIR (neat) v_{max} : 3160, 2970, 1749, 1738, 1697, 1437, 1365, and 1140 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₄H₃₈O₇N₃, 480.2704; found, 480.2694.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(6-chloropyridin-3-yl)propanoate (13): Following the general procedure, the reaction of 2-chloro-5-iodopyridine (240 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.7 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (318 mg, 77% yield) as a clear, colorless crystalline solid after purification by flash column chromatography (3% – 25% tetrahydrofuran/hexanes).

Mp: 87 – 90 °C

¹**H NMR** (300 MHz, CDCl₃) δ 8.18 (d, J = 1.9 Hz, 1H), 7.49 (dd, J = 8.2, 2.5 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 5.09 (dd, J = 10.0, 5.4 Hz, 1H), 3.73 (s, 3H), 3.38 (dd, J = 14.3, 5.4 Hz, 1H), 3.20 (dd, J = 14.2, 10.0 Hz, 1H), 1.39 (s, 18H).

¹³C NMR (75MHz, CDCl₃) δ 170.2, 151.7, 150.5, 149.8, 139.9, 132.0, 123.8, 83.5, 58.4, 52.4, 32.6, 27.8.

FTIR (neat) v_{max} : 3007, 1970, 1954, 2937, 2916, 2848, 1743, 1729, 1690, 1340, 1274, 1201, 1161, 1019, and 758 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₂₈O₆N₂Cl, 415.1644; found, 415.1638.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-chloropyridin-3-yl)propanoate (14):

Following the general procedure, the reaction of 2-chloro-3-iodopyridine (239 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (611 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (10.2 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (383 mg, 1.51 mmol, 1.5 equiv) provided the product (306 mg, 74% yield) as a white crystalline solid after purification by flash column chromatography (10% – 30% ethyl acetate/hexanes).

Mp: 71 − 74 °C

¹**H** NMR (300 MHz, CDCl₃) δ 8.23 – 8.18 (m, 1H), 7.45 (dd, J = 7.5, 1.9 Hz, 1H), 7.12 (dd, J = 7.5, 4.8 Hz, 1H), 5.24 (dd, J = 10.8, 4.3 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, J = 14.2, 4.3 Hz, 1H), 3.26 (dd, J = 14.2, 10.8 Hz, 1H), 1.33 (s, 18H).

¹³C NMR (75MHz, CDCl₃) δ 170.2, 151.7, 151.2, 148.0, 140.4, 132.1, 122.5, 83.3, 56.9, 52.4, 33.7, 27.7.

FTIR (neat) v_{max} : 2980, 2952, 2936, 1794, 1745, 1696, 1367, 1137, 1126, and 748 cm⁻¹. **HRMS** (NSI) *m/z*: [M+H]⁺ calcd. for C₁₉H₂₈O₆N₂Cl, 415.1630; found, 415.1623.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-(methylthio)pyrimidin-4-yl) propanoate (15):

Following the general procedure, the reaction of 4-iodo-2-(methylthio)pyrimidine (249 mg, 0.99 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (370 mg, 1.46 mmol, 1.5 equiv) provided the product (338 mg, 80% yield) as a white crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

Mp: 71 − 75 °C

¹**H NMR** (400 MHz, CDCl₃) δ 8.32 (d, J = 5.0 Hz, 1H), 6.78 (d, J = 5.0 Hz, 1H), 5.46 (dd, J = 9.2, 5.4 Hz, 1H), 3.68 (s, 3H), 3.45 (dd, J = 14.2, 5.5 Hz, 1H), 3.19 (dd, J = 14.2, 9.2 Hz, 1H), 2.47 (s, 3H), 1.38 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 172.3, 170.4, 166.8, 156.9, 151.5, 116.2, 83.2, 57.0, 52.3, 37.9, 27.8, 13.9.

FTIR (neat) v_{max} : 2983, 2940, 1948, 1703, 1565, 1550, 1451, 1296, 1162, 1136, and 778 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₇H₂₈O₆N₃S, 428.1850; found, 428.1841.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-4-yl)propanoate (16):

Following the general procedure, the reaction of 4-iodopyridine (205 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (609 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.2 mg, 0.012 mmol, 0.01 equiv) and Hantzsch ester (376 mg, 1.50 mmol, 1.5 equiv) provided the product (129 mg, 34% yield) as a white crystalline solid after purification by flash column chromatography (10% – 80% ethyl acetate/hexanes).

Mp: 97 – 100 °C

¹**H NMR** (500 MHz, CDCl3) δ 8.49 – 8.41 (m, 2H), 7.10 (d, J = 5.7 Hz, 2H), 5.15 (dd, J = 10.1, 5.3 Hz, 1H), 3.72 (s, 3H), 3.40 (dd, J = 14.0, 5.3 Hz, 1H), 3.19 (dd, J = 14.0, 10.2 Hz, 1H), 1.37 (s, 18H).

¹³C NMR (125 MHz, CDCl₃) δ 170.3, 151.6, 149.6, 146.7, 124.8, 83.3, 58.2, 52.4, 35.6, 27.8.

FTIR (neat) v_{max} : 3005, 2970, 2948, 1748, 1736, 1690, 1366, 1228, 1217, and 1140 cm⁻¹. **HRMS** (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₂₉O₆N₂, 381.2020; found, 381.2017.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-methoxypyridin-3-yl)propanoate (17): Following the general procedure, the reaction of 4-bromo-2-methoxypyridine (195 mg, 1.04 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (604 mg, 2.01 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (385 mg, 1.52 mmol, 1.5 equiv) provided the product (280 mg, 66% yield) as a white crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

Mp: 69 − 72 °C

¹**H** NMR (300 MHz, CDCl₃) δ 8.00 (dd, J = 5.3, 0.7 Hz, 1H), 6.67 (dd, J = 5.3, 1.5 Hz, 1H), 6.52 (dd, J = 1.5, 0.7 Hz, 1H), 5.12 (dd, J = 10.2, 5.1 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.32 (dd, J = 13.9, 5.1 Hz, 1H), 3.12 (dd, J = 13.9, 10.2 Hz, 1H), 1.36 (s, 18H).

¹³C NMR (75MHz, CDCl₃) *δ* 170.3, 164.3, 151.6, 149.3, 146.6, 118.1, 111.5, 83.2, 58.2, 53.2, 52.3, 35.4, 27.7.

FTIR (neat) v_{max} : 2979, 2950, 1745, 1697, 1613, 1561, 1380, 1270, 1244, 1136, 1112, and 774 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₃₁O₇N₂, 411.2126; found, 411.2118.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-chloropyridin-4-yl)propanoate (18):

Following the general procedure, the reaction of 2-chloro-4-iodopyridine (244 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbyy)]PF₆ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (390 mg, 1.54 mmol, 1.5 equiv) provided the product (352 mg, 83% yield) as a white crystalline solid after purification by flash column chromatography (10% – 30% ethyl acetate/hexanes).

Mp: 104 − 108 °C

¹**H** NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 5.1 Hz, 1H), 7.13 (s, 1H), 7.04 (dd, J = 5.1, 1.5 Hz, 1H), 5.12 (dd, J = 10.0, 5.4 Hz, 1H), 3.71 (s, 3H), 3.38 (dd, J = 14.0, 5.4 Hz, 1H), 3.18 (dd, J = 14.0, 10.0 Hz, 1H), 1.38 (s, 18H).

¹³C NMR (75MHz, CDCl₃) δ 170.0, 151.7, 151.4, 150.1, 149.4, 125.2, 123.6, 83.5, 57.9, 52.5, 35.3, 27.8.

FTIR (neat) v_{max} : 3054, 3001, 2982, 2972, 1743, 1727, 1692, 1596, 1375, 1275, 1139, 1128, and 1010 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₂₈O₆N₂Cl, 415.1630; found, 415.1626.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-chloro-3-methylpyridin-4-yl) propanoate (19):

Following the general procedure, the reaction of 2-chloro-4-iodo-3-methylpyridine (250 mg, 0.99 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (600 mg, 1.99 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (381 mg, 1.51 mmol, 1.5 equiv) provided the product (330 mg, 78% yield) as a white crystalline solid after purification by flash column chromatography (0% – 30% tetrahydrofuran/hexanes).

Mp: 83 – 86 °C

¹**H NMR** (300 MHz, CDCl₃) δ 8.05 (dd, J = 4.9, 0.7 Hz, 1H), 6.93 (d, J = 4.9 Hz, 1H), 5.10 (dd, J = 10.7, 4.7 Hz, 1H), 3.71 (s, 3H), 3.43 (dd, J = 14.1, 4.7 Hz, 1H), 3.28 (dd, J = 14.1, 10.7 Hz, 1H), 2.33 (s, 3H), 1.33 (s, 18H).

¹³C NMR (75MHz, CDCl₃) δ 170.0, 152.3, 151.6, 147.9, 146.1, 131.6, 124.7, 83.4, 57.4, 52.5, 33.7, 27.7, 15.6.

FTIR (neat) v_{max} : 2996, 2980, 2955, 2936, 1752, 1741, 1706, 1365, 1249, 1136, 1113, and 1015 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₃₀O₆N₂Cl, 429.1787; found, 429.1779.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(isoquinolin-1-yl)propanoate (20):

Following the general procedure, the reaction of 1-iodoisoquinoline (260 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (371 mg, 1.47 mmol, 1.5 equiv) provided the product (381 mg, 87% yield) as a colorless oil after purification by flash column chromatography (1% – 10% tetrahydrofuran/dichloromethane).

¹**H** NMR (300 MHz, CDCl₃) δ 8.43 (d, J = 5.7 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.57 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.51 (d, J = 5.7 Hz, 1H), 5.77 (dd, J = 9.1, 4.7 Hz, 1H), 4.15 (dd, J = 15.1, 4.7 Hz, 1H), 3.93 (dd, J = 15.1, 9.1 Hz, 1H), 3.76 (s, 3H), 1.34 (s, 18H).

¹³**C NMR** (75MHz, CDCl₃) *δ* 171.0, 158.1, 151.7, 141.9, 136.1, 129.8, 127.5, 127.2, 127.1, 124.9, 119.4, 82.8, 58.2, 52.3, 35.1, 27.8.

FTIR (neat) v_{max} : 2978, 1793, 1741, 1696, 1366, 1381, 1273, 1251, 1226, 1135, 1109, and 764 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₃H₃₁O₆N₂, 431.2177; found, 431.2168.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-yl) propanoate (21):

Following the general procedure, the reaction of 4-bromo-7H-pyrrolo[2,3-d]pyrimidine (199 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (611 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (9.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (381 mg, 1.51 mmol, 1.5 equiv) provided the product (401 mg, 95% yield) as an off-white crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

Mp: 112 – 114 °C

¹**H NMR** (300 MHz, CDCl₃) δ 11.84 (s, 1H), 8.82 (s, 1H), 7.35 (dd, J = 3.6, 2.2 Hz, 1H), 6.56 (dd, J = 3.6, 1.8 Hz, 1H), 5.72 (dd, J = 9.0, 5.1 Hz, 1H), 3.88 (dd, J = 14.4, 5.2 Hz, 1H), 3.72 (s, 3H), 3.67 (dd, J = 14.4, 9.0 Hz, 1H), 1.35 (s, 18H).

¹³C NMR (75MHz, CDCl₃) δ 170.7, 159.1, 151.6, 151.4, 150.7, 125.5, 118.4, 99.5, 83.1, 57.5, 52.4, 36.0, 27.8.

FTIR (neat) v_{max}: 3127, 3002, 2974, 2852, 1745, 1691, 1583, 1379, 1346, 1142, 1119, 971, and 748 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₂₉O₆N₄, 421.2082; found, 421.2073.



methyl 2-(di(tert-butoxycarbonyl)amino)-3-(pyridin-2-yl)butanoate (22):

Following the general procedure, the reaction of 2-bromopyridine (161 mg, 1.02 mmol, 1 equiv), methyl-2-(di(tert-butoxycarbonyl)amino)but-2-enoate (638 mg, 2.02 mmol, 2 equiv), [Ir(ppy)₂(dtbbyy)]PF₆ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided an inseparable 3:1 mixture of diastereomers (261 mg, 66% yield) as a white crystalline solid after purification by flash column chromatography (10% - 60% ethyl acetate/hexanes).

For the mixture of diastereomers:

Mp: 84 − 88 °C

¹**H** NMR (600 MHz, CDCl₃) δ 8.56 – 8.49 (m, 1H_{dr1} + 1H_{dr2}), 7.60 (td, *J* = 7.6, 1.9 Hz, 1H_{dr1}), 7.55 (td, *J* = 7.6, 1.9 Hz, 1H_{dr2}), 7.25 (d, *J* = 7.9 Hz, 1H_{dr1}), 7.12 (d, *J* = 7.8 Hz, 1H_{dr2}), 7.09 (m, 1H_{dr1}+1H_{dr2}), 5.95 (d, *J* = 9.8 Hz, 1H_{dr1}), 5.17 (d, *J* = 9.7 Hz, 1H_{dr2}), 3.87 (dq, *J* = 9.7, 6.7 Hz, 1H_{dr2}), 3.76 (m, 1H_{dr1}+3H_{dr2}), 3.58 (s, 3H_{dr1}), 1.58 (d, *J* = 7.2, 1H_{dr2}) 1.56 (s, 18H_{dr1}), 1.42 (s, 18H_{dr2}), 1.18 (d, *J* = 7.2 Hz, 3H_{dr1}).

¹³C NMR (150 MHz, CDCl₃) δ 171.0, 171.0, 164.2, 162.6, 152.3, 151.7, 149.3, 149.0, 136.1, 135.9, 123.2, 123.1, 121.3, 121.1, 83.1, 82.6, 62.1, 61.1, 52.1, 42.7, 28.0, 27.9, 20.2, 18.5

FTIR (neat) v_{max}: 2979, 2936, 1793, 1745, 1699, 1523, 1365, 1143, 1122, 1104, 845, 758, and 749 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₀H₃₁O₆N₂, 395.2177; found, 395.2170.



methyl 2-(di(tert-butoxycarbonyl)amino)-3-phenyl-3-(pyridin-2-yl)propanoate (23): Following the general procedure, the reaction of 2-bromopyridine (158 mg, 1.00 mmol, 1 equiv), methyl 2-(di(tert-butoxycarbonyl)amino)-3-phenylacrylate (750 mg, 2.00 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (10.0 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (340 mg, 1.34 mmol, 1.3 equiv) provided an inseparable 4:1 mixture of diastereomers (246 mg, 54% yield) as a colorless oil after purification by flash column chromatography (10% – 60% ethyl acetate/hexanes).

For the mixture of diastereomers:

¹**H** NMR (600 MHz, C₆D₆) δ 8.44 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H_{dr1}), 8.40 (ddd, J = 4.8, 1.9, 0.9 Hz, 1H_{dr2}), 7.88 – 7.82 (m, 2H_{dr2}), 7.60 (d, J = 6.9 Hz, 2H_{dr1}), 7.27 (d, J = 10.2 Hz, 1H_{dr1}), 7.13 (t, J = 7.7 Hz, 2H_{dr2}), 7.10 (d, J = 7.9 Hz, 1H_{dr2}), 7.07 (t, J = 7.7 Hz, 2H_{dr1}), 7.01 (d, J = 8.1, 1H_{dr1}), 6.99 – 6.93 (m, 2H_{dr1} + 2H_{dr2}), 6.54 (ddd, J = 7.3, 4.9, 1.3 Hz, 1H_{dr1}), 6.50 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H_{dr2}), 6.42 (d, J = 10.2 Hz, 1H_{dr2}), 5.46 (d, J = 10.3 Hz, 1

 $1H_{dr2}$), 5.35 (d, J = 10.2 Hz, $1H_{dr1}$), 3.19 (s, $3H_{dr1}$), 3.17 (s, $3H_{dr2}$), 1.38 (s, $18H_{dr2}$), 1.34 (s, $18H_{dr1}$).

¹³C NMR (150 MHz, C₆D₆) δ 170.4, 170.1, 161.9, 161.2, 152.4, 152.1, 149.0, 148.5, 142.3, 140.5, 135.8, 135.5, 129.3, 129.0, 128.2, 128.0, 126.6, 126.5, 124.2, 123.7, 120.9, 120.8, 81.7, 81.7, 61.7, 60.1, 54.8, 53.7, 51.2, 27.6, 27.6.

FTIR (neat) v_{max} : 2970, 2941, 1753, 1736, 1719, 1367, 1227, 1139, 1108, 770, and 755 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₅H₃₃O₆N₂, 457.2333; found, 457.2325.

methyl 2-(phenylamino)-3-(pyridin-2-yl)butanoate (24):

Following the general procedure, the reaction of 2-bromopyridine (158 mg, 1.00 mmol, 1.0 equiv), methyl 2-(phenylamino)but-2-enoate (380 mg, 2.00 mmol, 2.0 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.0 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (325 mg, 1.28 mmol, 1.30 equiv) provided an inseparable 5:4 mixture of diastereomers (186 mg, 69% yield) as a yellow crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

For the mixture of diastereomers:

Mp: 62 − 64 °C

¹**H NMR** (500 MHz, CDCl₃) δ 8.64 – 8.54 (m, 1H_{dr1} + 1H_{dr2}), 7.65 – 7.52 (m, 1H_{dr1} + 1H_{dr2}), 7.23 – 7.07 (m, 4H_{dr1} + 4H_{dr2}), 6.70 (m, 1H_{dr1} + 1H_{dr2}), 6.63 (d, *J* = 7.6 Hz, 2H_{dr1}), 6.58 – 6.51 (d, *J* = 8.0 Hz, 2H_{dr2}), 4.97 (d, *J* = 8.9 Hz, 1H_{dr1}), 4.61 (d, *J* = 8.3 Hz, 1H_{dr2}), 4.42 (m, 1H_{dr1} + 1H_{dr2}), 3.62 (s, 3H_{dr1}), 3.59 (s, 3H_{dr2}), 3.53 – 3.40 (m, 1H_{dr1} + 1H_{dr2}), 1.49 (d, *J* = 7.1 Hz, 3H_{dr2}), 1.44 (d, *J* = 7.0 Hz, 3H_{dr1}).

¹³C NMR (125 MHz, CDCl₃) *δ* 173.8, 173.5, 161.7, 161.6, 149.2, 149.1, 147.2, 147.1, 136.5, 136.5, 129.2, 129.1, 122.4, 122.3, 121.9, 118.2, 117.8, 113.6, 113.2, 61.9, 61.7, 51.9, 51.8, 44.3, 43.7, 17.4, 15.4.

FTIR (neat) v_{max} : 3373, 3053, 2969, 2950, 1732, 1601, 1590, 1507, 1149, 908, 729, and 691 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₆H₁₉O₂N₂, 271.1441; found, 271.1439



methyl 2-((4-bromophenyl)(methyl)amino)-3-(pyridin-2-yl)butanoate (25):

Following the general procedure, the reaction of 2-bromopyridine (160 mg, 1.01 mmol, 1 equiv), methyl 2-((4-bromophenyl)(methyl)amino)but-2-enoate (570 mg, 2.01 mmol, 2 equiv), [Ir(ppy)₂(dtbbyy)]PF₆ (9.1 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (325 mg, 1.28 mmol, 1.3 equiv) provided an inseparable 4:3 mixture of diastereomers (311 mg, 86% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

For the mixture of diastereomers:

¹**H** NMR (500 MHz, CDCl₃) 8.56 – 8.52 (m, 1H_{dr1}), 8.44 (m, 1H_{dr2}), 7.60 (td, J = 7.7, 1.8 Hz, 1H_{dr1}), 7.49 (td, J = 7.6, 1.8 Hz, 1H_{dr2}), 7.40 – 7.29 (m, 2H_{dr1}), 7.23 (d, J = 7.8 Hz, 1H_{dr1}), 7.18 (d, J = 9.0 Hz, 2H_{dr2}), 7.12 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H_{dr1}), 7.06 (d, J = 7.8 Hz, 1H_{dr2}), 7.03 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H_{dr2}), 6.85 (d, J = 9.1 Hz, 2H_{dr1}), 6.59 (d, J = 9.0 Hz, 2H_{dr2}), 4.98 (d, J = 10.8 Hz, 1H_{dr1}), 4.78 (d, J = 11.0 Hz, 1H_{dr2}), 3.72 (s, 3H_{dr2}), 3.67 – 3.57 (m, 1H_{dr1} + 1H_{dr2}), 3.46 (s, 3H_{dr1}), 2.93 (s, 3H_{dr1}), 2.72 (s, 3H_{dr2}), 1.32 (d, J = 6.7 Hz, 3H_{dr2}), 1.21 (d, J = 7.0 Hz, 3H_{dr1}).

¹³C NMR (125 MHz, CDCl₃) *δ* 171.4, 171.4, 162.7, 161.9, 149.3, 149.2, 148.8, 136.4, 136.2, 131.8, 131.4, 123.4, 122.4, 121.7, 121.6, 115.4, 115.0, 109.6, 109.5, 66.7, 65.5, 51.7, 51.5, 41.7, 41.6, 33.1, 32.7, 18.5, 18.2.

FTIR (neat) v_{max} : 2990, 2948, 2904, 2817, 1718, 1648, 1490, 1434, 1252, 1202, 1120, 1108, 1042, 811, 776, and 766 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{20}O_2N_2Br$, 363.0703; found, 363.0707.



methyl 2-((4-methoxyphenyl)(methyl)amino)-3-(pyridin-2-yl)butanoate 26):

Following the general procedure, the reaction of 2-bromopyridine (159 mg, 1.00 mmol, 1 equiv), methyl 2-((4-methoxyphenyl)(methyl)amino)but-2-enoate (477 mg, 2.03 mmol, 2 equiv), [Ir(ppy)₂(dtbbyy)]PF₆ (10.1 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (335 mg, 1.32 mmol, 1.3 equiv) provided an inseparable 3:1 mixture of diastereomers (182mg, 58% yield) as a colorless oil after purification by flash column chromatography (5% – 40% ethyl acetate/hexanes).

For the mixture of diastereomers:

¹**H** NMR (600 MHz, CDCl₃) δ 8.53 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H_{dr2}), 8.49 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H_{dr1}), 7.59 (td, J = 7.7, 1.9 Hz, 1H_{dr2}), 7.50 (td, J = 7.6, 1.8 Hz, 1H_{dr1}), 7.22 (dt, J = 7.8, 1.1 Hz, 1H_{dr2}), 7.13 – 7.07 (m, 1H_{dr1} + 1H_{dr2}), 7.04 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H_{dr1}), 6.98 – 6.92 (m, 2H_{dr2}), 6.87 – 6.83 (m, 2H_{dr2}), 6.75 – 6.65 (m, 4H_{dr1}), 4.85 (d, J = 11.0 Hz, 1H_{dr2}), 4.68 (d, J = 11.1 Hz, 1H_{dr1}), 3.77 (s, 3H_{dr2}), 3.64 – 3.55 (m, 1H_{dr1} + 1H_{dr2}), 3.43 (s, 3H_{dr2}), 2.91 (s, 3H_{dr2}), 2.71 (s, 3H_{dr1}), 1.31 (d, J = 6.7 Hz, 3H_{dr1}), 1.27 (d, J = 7.0 Hz, 3H_{dr2}).

¹³C NMR (150 MHz, CDCl₃) δ 174.2, 174.1, 171.7, 163.1, 162.5, 152.4, 152.2, 149.2, 149.1, 144.9, 144.6, 136.3, 136.1, 123.4, 122.6, 121.5, 121.5, 116.2, 115.5, 114.6, 114.1, 83.3, 82.7, 68.5, 67.0, 55.6, 55.5, 52.9, 52.8, 51.4, 51.2, 41.6, 41.6, 33.3, 33.1, 25.7, 25.6, 18.4, 18.3, 8.0, 7.8.

FTIR (neat) v_{max} : 3043, 2949, 2832, 1730, 1589, 1509, 1242, 1165, 1034, 991, 817, 786, and 749 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₈H₂₃O₃N₂, 315.1703; found, 315.1703.



methyl 4-((1-methoxy-1-oxo-3-(pyridin-2-yl)butan-2-yl)(methyl)amino)benzoate (27):

Following the general procedure, the reaction of 2-bromopyridine (158mg, 1.00 mmol, 1 equiv), methyl 4-((1-methoxy-1-oxobut-2-en-2-yl)(methyl)amino)benzoate (530 mg, 2.02 mmol, 2 equiv), $[Ir(pp)_2(dtbbpy)]PF_6$ (9.1 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (340 mg, 1.34 mmol, 1.3 equiv) provided an inseparable 5:2 mixture of diastereomers (267 mg, 78% yield) as a low-melting white solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

For the mixture of diastereomers:

¹**H** NMR (600 MHz, CDCl₃) δ 8.56 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H_{dr1}), 8.40 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H_{dr2}), 7.99 – 7.91 (m, 2H_{dr1}), 7.82 – 7.77 (m, 1H_{dr2}), 7.62 (td, J = 7.6, 1.8 Hz, 1H_{dr1}), 7.47 (td, J = 7.7, 1.8 Hz, 1H_{dr2}), 7.25 (d, J = 7.5 Hz, 1H_{dr1}), 7.14 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H_{dr1}), 7.05 (dd, J = 7.7, 1.1 Hz, 1H_{dr1}), 7.00 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H_{dr2}), 6.96 (d, J = 9.0 Hz, 2H_{dr1}), 6.69 (d, J = 9.0 Hz, 2H_{dr2}), 5.20 (d, J = 10.7 Hz, 1H_{dr1}), 4.96 (d, J = 10.9 Hz, 1H_{dr2}), 3.87 (s, 3H_{dr1}), 3.83 (s, 3H_{dr2}), 3.75 (s, 3H_{dr2}), 3.71 – 3.61 (m, 1H_{dr1} + 1H_{dr2}), 3.49 (s, 3H_{dr1}), 3.04 (s, 3H_{dr1}), 2.83 (s, 3H_{dr2}), 1.36 (d, J = 6.7 Hz, 3H_{dr2}), 1.19 (s, 3H_{dr1}).

¹³**C** NMR (150 MHz, CDCl₃) δ 171.3, 171.2, 167.2, 162.5, 161.5, 153.4, 152.9, 149.3, 149.2, 136.5, 136.3, 131.3, 130.9, 123.4, 122.3, 121.8, 121.7, 118.5, 118.4, 112.0, 111.9, 65.6, 64.7, 51.9, 51.7, 51.5, 51.5, 41.9, 41.7, 33.2, 32.9, 18.5, 18.1.

FTIR (neat) v_{max} : 2949, 2839, 1735, 1705, 1602, 1518, 1433, 1276, 1186, 1110, 769, and 747 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₂₃O₄N₂, 343.1652; found, 343.1651.



methyl 2-(methyl(4-(trifluoromethyl)phenyl)amino)-3-(pyridin-2-yl)butanoate (28): Following the general procedure, the reaction of 2-bromopyridine (158 mg, 1.00 mmol, 1 equiv), methyl 2-(methyl(4-(trifluoromethyl)phenyl)amino)but-2-enoate (551 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided an inseparable 5:2 mixture of diastereomers (274 mg, 78% yield) as a colorless oil after purification by flash column chromatography (0% – 25% ethyl acetate/hexanes).

For the mixture of diastereomers:

¹**H** NMR (600 MHz, CDCl₃) 8.55 (dd, J = 5.0, 1.7 Hz, 1H_{dr1}), 8.41 (dd, J = 4.9, 1.7 Hz, 1H_{dr2}), 7.62 (td, J = 7.6, 1.8 Hz, 1H_{dr1}), 7.50 (d, J = 8.6 Hz, 2H_{dr1} + 1H_{dr2}), 7.34 (d, J = 8.6 Hz, 2H_{dr2}), 7.27 - 7.22 (m, 1H_{dr1}), 7.16 - 7.12 (m, 1H_{dr2}), 7.01 (m, 2H_{dr1} + 1H_{dr2}), 6.74 (d, J = 8.6 Hz, 2H_{dr2}), 5.15 (d, J = 10.8 Hz, 1H_{dr1}), 4.92 (d, J = 11.0 Hz, 1H_{dr2}), 3.75 (s, 3H_{dr2}), 3.64 (dq, J = 10.5, 7.2 Hz, 1H_{dr1} + 1H_{dr2}), 3.49 (s, 3H_{dr1}), 3.02 (s, 3H_{dr1}), 2.80 (s, 3H_{dr2}), 1.35 (d, J = 6.7 Hz, 3H_{dr2}), 1.20 (d, J = 7.0 Hz, 3H_{dr1}).

¹³**C** NMR (150 MHz, CDCl₃) δ 171.3, 171.3, 162.5, 161.6, 152.3, 151.9, 149.3, 136.5, 136.3, 126.5 (q, *J* = 3.7 Hz), 126.0 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 268.6), 124.9 (q, *J* = 268.7), 123.4, 122.4, 121.8, 118.9 (q, *J* = 32), 118.8 (q, *J* = 33), 112.5, 112.3, 65.9, 64.9, 51.9, 51.7, 41.8, 33.2, 32.8, 18.5, 18.2.

¹⁹F NMR (282 MHz, CDCl3) δ -61.01.

FTIR (neat) v_{max} : 2971, 2953, 2830, 1735, 1614, 1526, 1454, 1326, 1296, 1163, 1104, 1069, and 819 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₈H₂₀O₂N₂F₃, 353.1471; found, 353.1480.



tert-butyl (2-oxo-6-(pyridin-2-yl)cyclohexyl)carbamate (29): Following the general procedure, 2-bromopyridine (160 mg, 1.01 mmol, 1 equiv) was reacted with tert-butyl (6-oxocyclohex-1-en-1-yl)carbamate (421 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (331 mg, 1.31 mmol, 1.3 equiv). Analysis of the crude ¹H NMR spectrum indicated a mixture of stereoisomers (cis:trans = 2:9), and purification by flash column chromatography (5% – 100% ethyl acetate/hexanes) provided the title compounds (trans, 170 mg, 59% yield; cis, 52 mg, 18% yield).

Major isomer (trans):

 $\mathbf{R}_{\mathbf{f}}$: 0.3 (50% ethyl acetate/hexanes)

Mp: 181 – 185 °C

¹**H NMR** (300 MHz, CDCl₃) δ 8.67 – 8.31 (m, 1H), 7.59 (td, *J* = 7.7, 1.8 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.12 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 5.00 (s, 1H), 4.69 – 4.51 (m, 1H), 2.97 – 2.83 (m, 1H), 2.63 – 2.43 (m, 2H), 2.32 – 1.89 (m, 3H), 1.74 (dddd, *J* = 16.9, 9.9, 8.6, 4.1 Hz, 1H), 1.21 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 207.1, 160.2, 155.1, 149.2, 136.3, 122.3, 121.9, 79.3, 62.5, 54.6, 41.0, 31.5, 28.0, 26.1.

FTIR (neat) v_{max} : 3206, 3025, 2978, 2935, 2864, 1737, 1714, 1686, 1555, 169, 1014, 785, and 735 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₁₆H₂₃O₃N₂, 291.1703; found, 291.1699.

Minor isomer (cis):

 $R_f: 0.7 (50\% \text{ ethyl acetate/hexanes})$

Mp: 92 – 95 °C

¹**H** NMR (300 MHz, CDCl₃) δ 8.52 – 8.22 (m, 1H), 7.58 (td, J = 7.7, 1.9 Hz, 1H), 7.09 (dtd, J = 7.5, 5.2, 1.1 Hz, 2H), 5.48 (d, J = 7.3 Hz, 1H), 4.44 (ddd, J = 7.2, 5.7, 1.2 Hz, 1H), 3.98 (dt, J = 5.9, 3.9 Hz, 1H), 2.74 – 2.50 (m, 1H), 2.46 – 2.12 (m, 2H), 2.09 – 1.88 (m, 1H), 1.73 (dq, J = 11.2, 3.3 Hz, 2H), 1.34 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 206.0, 160.80, 155.7, 148.2, 136.5, 123.3, 121.5, 79.3, 60.0, 48.7, 40.2, 30.7, 28.2, 20.8.

FTIR (neat) v_{max} : 3448, 3005, 2969, 2944, 1737, 1719, 1694, 1494, 1365, 1352, 1229, and 770 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₆H₂₃O₃N₂, 291.1703; found, 291.1698.



2-(methyl(phenyl)amino)-3-(pyridin-2-yl)cyclohexan-1-one (30): Following the general procedure, the reaction of 2-bromopyridine (160 mg, 1.01 mmol, 1 equiv), 2-(methyl(phenyl)amino)cyclohex-2-en-1-one (401 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.5 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (330 mg, 1.30 mmol, 1.3 equiv) provided the product (196 mg, 70% yield) as a white solid after purification by flash column chromatography (10% – 80% ethyl acetate/hexanes).

Mp: 111 – 115 °C

¹**H NMR** (300 MHz, CDCl₃) δ 8.52 – 8.37 (m, 1H), 7.48 (tdd, J = 7.7, 1.9, 1.0 Hz, 1H), 7.13 – 6.90 (m, 4H), 6.59 (td, J = 7.3, 1.0 Hz, 1H), 6.57 – 6.53 (m, 2H), 4.97 (d, J = 11.6 Hz, 1H), 3.60 – 3.27 (m, 1H), 2.77 (d, J = 1.0 Hz, 3H), 2.63 – 2.47 (m, 2H), 2.26 – 2.09 (m, 3H), 1.86 – 1.72 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 196.4, 149.0, 144.6, 143.1, 128.8, 118.4, 114.7, 39.5, 39.3, 26.0, 22.9. **FTIR** (neat) v_{max}: 2950, 2933, 2866, 1710, 1596, 1505, 745, and 690 cm⁻¹. **HRMS** (NSI) *m/z*: [M+H]⁺ calcd. for C₁₈H₂₁ON₂, 281.1648; found, 281.1647.



4-(methyl(phenyl)amino)-5-(pyridin-2-yl)hexan-3-one (31):

Following the general procedure, the reaction of 2-bromopyridine (159 mg, 1.00 mmol, 1 equiv), 4-(methyl(phenyl)amino)hex-4-en-3-one (406 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (325 mg, 1.28 mmol, 1.3 equiv) provided the product (180 mg, 64% yield) as a yellow oil after purification by flash column chromatography (0% – 30% ethyl acetate/hexanes).

¹**H NMR** (400 MHz, CDCl₃) δ 8.46 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.57 (td, J = 7.8, 1.8 Hz, 1H), 7.36 – 7.26 (m, 2H), 7.24 (dd, J = 7.7, 1.1 Hz, 1H), 7.06 (ddd, J = 7.6, 4.9, 1.3 Hz, 1H), 7.00 (d, J = 8.2 Hz, 2H), 6.84 – 6.70 (m, 1H), 5.24 (d, J = 10.6 Hz, 1H), 3.62 (dq, J = 10.6, 7.1 Hz, 1H), 2.81 (s, 3H), 2.37 (dq, J = 17.7, 7.3 Hz, 1H), 2.21 (dq, J = 17.7, 7.3 Hz, 1H), 1.14 (d, J = 7.1 Hz, 3H), 0.96 – 0.70 (m, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 208.4, 163.8, 149.8, 136.3, 129.4, 123.7, 121.2, 117.3, 112.7, 68.8, 39.6, 34.4, 32.6, 18.5, 7.4.

FTIR (neat) v_{max} : 3061, 3027, 2976, 2937, 2906, 2816, 1682, 1625, 1597, 1499, 1355, 1339, 1310, 1221, 1184, 1164, 1109, 747, and 692 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₉H₂₃ON₂, 283.1805; found, 283.1804.



benzyl (2*S*,4*S*)-2-(*tert*-butyl)-4-((5-hydroxypyridin-2-yl)methyl)-5-oxooxazolidine-3-carboxylate (33):

Following the general procedure, the reaction of 6-bromopyridin-3-ol (43 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (55 mg, 57% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

¹**H** NMR (500 MHz, CDCl₃) δ 8.06 (s, 1H), 7.36 – 7.27 (m, 3H), 7.24 – 7.20 (m, 2H), 7.12 (q, J = 8.5 Hz, 2H), 5.57 (s, 1H), 5.06 (d, J = 12.0 Hz, 1H), 4.91 (t, J = 12.0 Hz, 1H), 4.75 (t, J = 6.9 Hz, 1H), 3.32 (ddd, J = 56.7, 14.1, 7.1 Hz, 2H), 1.02 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 171.8, 156.0, 153.2, 146.9, 136.0, 135.2, 128.7, 128.7, 128.5, 125.5, 125.3, 96.6, 68.5, 58.0, 39.5, 37.2, 25.1.

FTIR (neat) v_{max} : 3066, 3033, 2960, 2925, 2872, 1790, 1717, 1575, 1481, 1392, 1346, 1335, 1272, 1228, 1198, 1172, 1121, 1037, 976, 908, 839, 720, and 668cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₃H₂₅O₅N₂, 385.1758; found, 385.17753.



benzyl (2*S*,4*S*)-2-(*tert*-butyl)-4-((2-chloropyridin-4-yl)methyl)-5-oxooxazolidine-3-carboxylate (34):

Following the general procedure, the reaction of 2-chloro-4-iodopyridine (60 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (75 mg, 75% yield) as a colorless oil after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).

¹**H NMR** (500 MHz, CDCl₃) δ 8.20 (d, J = 5.0 Hz, 1H), 7.41 – 7.38 (m, 3H), 7.27 (dd, J = 6.6, 2.8 Hz, 2H), 7.20 (s, 1H), 7.08 – 7.02 (m, 1H), 5.58 (s, 1H), 5.07 (dd, J = 70.4, 11.7 Hz, 2H), 4.43 (dd, J = 7.6, 5.4 Hz, 1H), 3.19 – 3.02 (m, 2H), 1.00 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 171.4, 155.7, 151.8, 149.7, 149.1, 134.8, 129.1, 129.0, 128.8, 125.1, 123.5, 96.6, 68.9, 58.1, 38.4, 37.3, 25.0.

FTIR (neat) v_{max} : 3063, 3033, 2970, 2873, 1790, 1720, 1594, 1549, 1481, 1388, 1341, 1305, 1230, 1200, 1173, 1122, 1087, 1036, 980, 899, 878, 839, 746, and 698 cm⁻¹. **HRMS** (NSI) m/z: [M+H]⁺ calcd. for C₂₁H₂₄O₄N₂Cl, 403.1419; found, 403.1414.



benzyl (2*S*,4*S*)-4-((7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)methyl)-2-(*tert*-butyl)-5oxooxazolidine-3-carboxylate (35):

Following the general procedure, the reaction of 4-bromo-5*H*-pyrrolo[3,2-*d*]pyrimidine (50 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (82 mg, 80% yield) as a pale yellow oil after purification by flash column chromatography (20% – 70% ethyl acetate/hexanes).

¹**H** NMR (500 MHz, CDCl₃) δ 11.04 (s, 1H), 8.78 (s, 1H), 7.31 (dd, J = 3.4, 2.3 Hz, 1H), 7.25 (d, J = 2.9 Hz, 3H), 7.12 (s, 2H), 6.57 (s, 1H), 5.63 (s, 1H), 5.19 (t, J = 6.8 Hz, 1H), 5.02 (d, J = 12.1 Hz, 1H), 4.76 (d, J = 11.0 Hz, 1H), 3.70 – 3.51 (m, 2H), 1.07 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 171.8, 157.8, 155.8, 151.5, 150.9, 135.0, 128.6, 128.5, 128.3, 125.5, 117.9, 99.5, 96.7, 68.2, 56.7, 39.0, 37.3, 25.1.

FTIR (neat) v_{max} : 3202, 3133, 2969, 1792, 1721, 1585, 1393, 1349, 1307, 1230, 1194, 1119, 1043, 976, 903, 733, and 698cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₂H₂₅O₄N₄, 409.1870; found, 409.1866.



benzyl (2*S*,4*S*)-2-(*tert*-butyl)-5-oxo-4-(pyridin-2-ylmethyl)oxazolidine-3-carboxylate (36):

Following the general procedure, the reaction of 2-bromopyridine (39 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (63 mg, 68% yield) as a colorless oil after purification by flash column chromatography (10% – 40% ethyl acetate/hexanes).

¹**H** NMR (500 MHz, CDCl₃) δ 8.49 (d, J = 4.2 Hz, 1H), 7.53 (td, J = 7.7, 1.8 Hz, 1H), 7.32 (td, J = 4.8, 1.8 Hz, 3H), 7.24 (dd, J = 6.9, 2.6 Hz, 2H), 7.16 (d, J = 7.7 Hz, 1H), 7.08 (dd, J = 7.1, 5.3 Hz, 1H), 5.59 (s, 1H), 5.08 (d, J = 12.2 Hz, 1H), 4.97 (t, J = 6.9 Hz, 1H), 4.85 (d, J = 11.9 Hz, 1H), 3.38 (dd, J = 14.0, 6.9 Hz, 1H), 3.30 (dd, J = 14.0, 6.9 Hz, 1H) 1.03 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 172.0, 156.7, 155.9, 149.4, 136.2, 135.3, 128.6, 128.4, 128.3, 123.7, 121.9, 96.4, 68.1, 57.5, 41.4, 37.2, 25.0.

FTIR (neat) v_{max} : 3064, 3034, 3010, 2970, 2873, 1791, 1716, 1593, 1475, 1438, 1391, 1347, 1305, 1231, 1173, 1190, 1121, 1036, 977, 932, 825, 731, and 697 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₁H₂₅O₄N₂, 369.1809; found, 369.1804.



benzyl (2*S*,4*S*)-2-(*tert*-butyl)-4-((1-(methoxycarbonyl)piperidin-4-yl)methyl)-5oxooxazolidine-3-carboxylate (38):

Following the general procedure, the reaction of 4-(1,3-dioxoisoindolin-2-yl) 1-methyl piperidine-1,4-dicarboxylate (83 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.5 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (93 mg, 86% yield) as a white solid after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).
¹**H NMR** (500 MHz, CDCl₃) δ 7.39 – 7.34 (m, 5H), 5.59 – 5.39 (m, 3H), 4.66 (d, *J* = 11.0 Hz, 1H), 4.06 – 3.52 (m, 7H), 2.52 – 2.20 (m, 2H), 1.82 (dd, *J* = 14.1, 7.6 Hz, 1H), 1.65 – 1.35 (m, 3H), 1.06 (s, 9H), 0.93 – 0.66 (m, 1H).

¹³C NMR (125 MHz, cdcl₃) δ 168.5, 156.0, 153.9, 134.6, 129.7, 129.1, 128.8, 95.6, 71.7, 68.1, 52.5, 44.1, 43.6, 38.8, 37.1, 31.5, 26.9.

FTIR (neat) v_{max} : 2959, 2852, 1792, 1724, 1701, 1472, 1448, 1396, 1309, 1258, 1193, 1125, 1043, 966, 916, 757, 731, and 699cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₃H₃₃O₆N₂, 433.2333; found, 433.2333.



benzyl (2*S***,4***S***)-4-(but-3-en-1-yl)-2-(***tert***-butyl)-5-oxooxazolidine-3-carboxylate (39): Following the general procedure, the reaction of 3-bromoprop-1-ene (22 \muL, 0.25 mmol, 1 equiv), 32** (145 mg, 0.50 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (35 mg, 42% yield) as a colorless oil after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).

¹**H** NMR (500 MHz, CDCl₃) δ 7.41 – 7.34 (m, 5H), 5.76 (td, J = 16.7, 6.7 Hz, 1H), 5.55 (s, 1H), 5.22 – 5.12 (td J = 16.9, 11.9 Hz, 2H), 5.06 (d, J = 17.1 Hz, 1H), 4.98 (d, J = 11.2 Hz, 1H), 4.30 (dd, J = 7.8, 6.7 Hz, 1H), 2.34 (m, 2H), 2.06 – 1.98 (m, 1H), 1.90 (m, 1H), 0.96 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 172.7, 156.1, 137.0, 135.3, 128.8, 128.8, 128.6, 115.9, 96.4, 68.5, 56.5, 37.1, 32.5, 30.3, 25.0.

FTIR (neat) v_{max} : 3068, 3034, 2960, 2873, 1790, 1716, 1641, 1391, 1324, 1282, 1195, 1117, 1041, 979, 914, and 968 cm⁻¹.

HRMS (NSI) m/z: [M+H]+ calcd. for C₁₉H₂₆O₄N, 332.1856; found, 332.1859.



benzyl (2*S*,4*S*)-2-(*tert*-butyl)-5-oxo-4-(2,2,2-trifluoroethyl)oxazolidine-3-carboxylate (40):

A 20-mL screw-top test tube equipped with a stir bar was charged with **32** (289 mg, 1.0 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (5 mg, 0.005 mmol, 0.01 equiv) and Hantzsch ester (164 mg, 0.65 mmol. 1.3 equiv). The tube was sealed PTFE/silicon septum and connected to a Schlenk line. The atmosphere was exchanged by applying vacuum and backfilling with N₂ (this process was conducted a total of three times). The reaction vial was disconnected from the nitrogen line and massed.

The trifluoromethyl iodide lecture bottle outlet was fitted with a rubber septum, and a cannula needle (cooled to -78 °C) was used to condense trifluoromethyl iodide into the reaction tube. The reaction tube and contents were massed once more to measure the loading of trifluoromethyl iodide (861 mg, 4.4 mmol, 4.4 equiv). The reaction was then stirred for 18 hours under irradiation by blue LEDs. The reaction was quenched with aqueous sodium bicarbonate then extracted with ethyl acetate (5 x 25 mL). The combined extracts were dried over sodium sulfate then concentrated by rotary evaporation to provide the product (222 mg, 93% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

¹**H** NMR (500 MHz, DMSO- d_6 , 80 °C) δ 7.44 – 7.34 (m, 7H), 5.43 – 5.34 (m, 2H), 4.92 (s, 1H), 3.58 (s, 1H), 3.43 (dq, J = 15.5, 10.2 Hz, 1H), 3.17 (s, 1H), 0.94 (s, 9H). ¹³C NMR (126 MHz, DMSO- d_6 , 80 °C) δ 165.3, 152.5, 133.8, 128.4, 128.3, 128.1, 124.3 (q, J = 278.6 Hz), 95.9, 68.0, 66.7, 37.6, 33.8 (q, J = 28.5), 26.0. ¹⁹F NMR (282 MHz, cdcl₃) δ -59.92. FTIR (neat) v_{max} : 3035, 2965, 1799, 1732, 1483, 1394, 1333, 1290, 1230, 1200, 1138,

FTR (neat) v_{max} : 3035, 2965, 1799, 1732, 1483, 1394, 1333, 1290, 1230, 1200, 11 1117, 1044, 1018, 976, 916, 819, 798, 767, 755, and 696 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₇H₂₁O₄NF₃, 360.1417; found, 360.1421.



benzyl (2*S*,4*S*)-2-(*tert*-butyl)-4-(2-(diethoxyphosphoryl)-2,2-difluoroethyl)-5oxooxazolidine-3-carboxylate (41):

Following the general procedure, the reaction of 2-bromo-2,2-diethyl (bromodifluoromethyl)phosphonate (89 μ L, 0.5 mmol, 1 equiv), **32** (289 mg, 1.0 mmol, 2 equiv), [Ir(ppy)₂(dtbbpy)]PF₆ (5 mg, 0.005 mmol, 0.01 equiv) and Hantzsch ester (164 mg, 0.65 mmol, 1.3 equiv) provided the product (222 mg, 93% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

¹**H NMR** (500 MHz, CDCl₃) δ 7.37 – 7.29 (m, 5H), 5.59 (s, 1H), 5.24 – 5.11 (m, 2H), 4.84 (t, *J* = 5.9 Hz, 1H), 4.24 (tddd, *J* = 12.4, 6.8, 5.2, 2.7 Hz, 4H), 2.77 – 2.48 (m, 2H), 1.35 (td, *J* = 7.0, 1.0 Hz, 6H), 0.95 (s, 9H).

¹³**C NMR** (150 MHz, CDCl₃) δ 171.1, 155.6, 135.1, 128.6, 128.5, 121.0, 119.6, 119.3, 117.9, 117.6, 116.1, 96.8, 68.5, 64.9, 64.8, 64.8, 64.8, 51.1, 51.1, 51.0, 51.0, 37.3, 37.1, 37.0, 36.9, 24.8, 16.4, 16.3.

¹⁹**F NMR** (282 MHz, CDCl₃) δ -113.20 (dddd, J = 299.8, 103.3, 32.6, 7.5 Hz).

³¹**P** NMR (243 MHz, CDCl₃) δ 5.81 (tt, *J* = 104.4, 7.6 Hz).

FTIR (neat) v_{max} : 2976, 2875, 1796, 1720, 1482, 1392, 1291, 1270, 1236, 1197, 1177, 1105, 1010, 977, 791, 732, and 698 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₂₁H₃₁O₇NF₂P, 478.1801; found, 478.1802.



benzyl (2*S*,4*S*)-4-(3-amino-2,2-difluoro-3-oxopropyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (42):

Following the general procedure, the reaction of 2-bromo-2,2-difluoroacetamide (43 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (58 mg, 60% yield) as a colorless oil after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).

¹**H NMR** (500 MHz, CDCl₃) δ 7.40 – 7.31 (m, 5H), 6.40 (s, 1H), 6.13 (s, 1H), 5.58 (s, 1H), 5.26 – 5.08 (m, 2H), 4.70 (dd, J = 7.5, 5.9 Hz, 1H), 2.82 – 2.60 (m, 2H), 0.96 (s, 9H).

¹³**C** NMR (125 MHz, CDCl₃) δ 171.0, 165.4 (t, *J* = 29.0 Hz), 155.9, 135.1, 128.8, 128.8, 128.7, 116.0 (t, *J* = 254.8 Hz), 97.1, 68.8, 52.3, 37.0, 36.7 (t, *J* = 24.6 Hz), 24.9.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -101.11 – -104.68 (m).

FTIR (neat) v_{max} : 3446, 3354, 3198, 2964, 2875, 1793, 1719, 1607, 1394, 1319, 1196, 1037, 1014, 909. 731, and 698 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₁₈H₂₃O₅N₂F₂, 385.1570; found, 385.1570.

VI. Deprotection Procedures and Characterization Data



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoic acid (2A):

To a stirring solution of methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2yl)propanoate (2) (190 mg, 0.5 mmol, 1 equiv) in THF/H₂O (3:2, 5 mL) was added LiOH (24 mg, 1.0 mmol, 2.0 equiv). The resultant solution was stirred until consumption of starting material was observed by thin layer chromatography. The reaction mixture was extracted once with ethyl acetate, and the organic extract was discarded. The aqueous phase was gently acidified with 0.1 M HCl to pH 4 and extracted with ethyl acetate (5 x 5 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated to provide the product (172 mg, 94% yield) as a clear, colorless crystalline solid.

Mp: 164 °C (decomp.)

¹**H NMR** (300 MHz, CDCl₃) δ 8.53 (dt, J = 5.0, 1.4 Hz, 1H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.41 – 7.12 (m, 2H), 5.21 (dd, J = 7.9, 4.7 Hz, 1H), 3.93 (dd, J = 15.3, 7.9 Hz, 1H), 3.17 (dd, J = 15.3, 4.7 Hz, 1H), 1.45 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 171.6, 158.0, 152.0, 147.1, 138.6, 124.4, 122.4, 83.2, 58.2, 39.2, 27.9.

FTIR (neat) v_{max} : 3456, 3068, 2970, 2930, 2853, 1748, 1708, 1366, 1108, 1062, and 778 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{18}H_{27}O_6N_2$, 367.1864; found, 367.1859.



2-(2-ammonio-3-methoxy-3-oxopropyl)pyridin-1-ium ditrifluoroacetate (2B):

To a stirring solution of of methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoate (2) (190 mg, 0.5 mmol, 1 equiv) in dichloromethane (2 mL) was added trifluoroacetic acid (1.5 mL) dropwise. The resultant solution was allowed to continue stirring, and after 10 minutes consumption of starting material was observed by thin layer chromatography. The reaction mixture was concentrated directly by rotary evaporation. The solution was re-dissolved in dichloromethane and concentrated once more to quantitatively provide the product as a pale, yellow low-melting solid (203 mg, >99% yield).

¹**H NMR** (300 MHz, D₃COD) δ 8.78 (dd, J = 5.7, 1.6 Hz, 1H), 8.44 (td, J = 7.9, 1.7 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.89 (td, J = 5.9, 2.8 Hz, 1H), 5.73 (s, 4H), 4.65 (t, J = 7.1 Hz, 1H), 3.77 (s, 3H), 3.69 (t, J = 7.2 Hz, 2H).

¹³**C NMR** (75 MHz, D₃COD) δ 167.8, 159.8 (q, *J* = 37.9 Hz), 151.4, 144.9, 143.1, 127.4, 125.3, 117.6 (q, *J* = 289.1 Hz), 52.6, 51.5, 33.6, 26.2.

¹⁹**F NMR** (282 MHz, D₃COD) δ -77.45.

FTIR (neat) v_{max} : 2964, 2563, 2111, 1746, 1666, 1651, 1172, 1157, 1127, 836, 798, and 720 cm⁻¹.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C₉H₁₃O₂N₂, 181.0972; found, 181.0967.

2-amino-3-(pyridin-2-yl)propanoic acid dihydrochloride (2C):

A 20-mL scintillation vial equipped with stir bar was charged with methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoate (2) (190 mg, 0.5 mmol, 1 equiv), EtOH (5 mL) and 3N NaOH (5 mL), and the resultant solution was stirred until consumption of starting material was observed (\sim 1 hour). The reaction mixture was acidified with 1M HCl and concentrated by rotary evaporation. The residue was reconstituted in EtOH, and precipitated NaCl was removed by vacuum filtration. The filtrate was concentrated under reduced pressure. Concentrated HCl (3 mL) was added dropwise to the residue and stirred 10 minutes. The mixture was concentrated directly to provide the product (119 mg, 96% yield) as a white crystalline solid.

¹**H NMR** (300 MHz, D₂O) δ 8.49 (d, J = 6.0 Hz, 1H), 8.32 (td, J = 8.0, 1.7 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.75 (dd, J = 7.7, 6.1 Hz, 1H), 4.34 (t, J = 7.4 Hz, 1H), 3.47 (d, J = 7.4 Hz, 2H).

¹³C NMR (75 MHz, D₂O) δ 169.6, 149.6, 147.2, 141.4, 128.2, 126.1, 51.6, 33.2.

FTIR (neat) v_{max} : 3399, 2780, 2934, 1702, 1567, 1477, 1403, 1367, 1243, 1139, 1102, 1101, 921, and 750 cm⁻¹. **HRMS** (NSI) m/z: $[M+H]^+$ calcd. for C₈H₁₁O₂N₂, 167.0815; found, 167.0811.

(S)-2-amino-3-(pyridin-2-yl)propanoic acid dihydrochloride (37):

To a round bottom flask equipped with a stir bar was added **23** (20.2 mg), and concentrated aqueous HCl (2 mL). The reaction was stirred at 80 °C for 30 minutes then concentrated by rotary evaporation to afford the product (12.8, 98%) as a white solid. The physical properties and spectral data are consistent with the values of the racemate (**2C**) reported herein, with the exception of optical rotation.

[α]_D²⁰ +31.7 (*c* 0.1, 1 M HCl) (lit.,⁸ +46.0 (*c* 0.1, 1 M HCl))



methyl (S)-2-(((benzyloxy)carbonyl)amino)-3-(pyridin-2-yl)propanoate (37A):

To a round bottom flask equipped with a stir bar was added **24**, Et₂O (5 mL), and MeOH (5 mL). The reaction was placed under nitrogen atmosphere then cooled to 0 °C. (Trimethylsilyl)diazomethane solution (2.0 M in ether, 80 μ L, 0.16 mmol, 2.0 equiv) was added dropwise via syringe and the reaction was warmed to room temperature and stirred for 30 minutes. The reaction was quenched with AcOH (2 mL) then concentrated by rotary evaporation. The residue was dissolved in saturated aqueous sodium bicarbonate (1 mL) and THF (1 mL). The solution was set to stir and chilled to 0 °C. Benzyl chloroformate (12.5 μ L, 0.09 mmol, 1.1 equiv) was added dropwise via syringe, and the reaction was warmed to room temperature and stirred until HPLC indicated the starting material had been consumed. The reaction was concentrated to remove THF then diluted with water (1 mL). The aqueous solution was extracted with EtOAc (3 x 2 mL), and the combined extracts were concentrated by rotary evaporation. The residue was purified by preparative HPLC to afford the product as a colorless oil. Chiral HPLC analysis (OD-H, 15% IPA/hexanes, 1.0 mL/min, 254 nm) indicated 97% ee for the major enantiomer (*t*_R (major) = 14.949 min, *t*_R (minor) = 21.299 min).

¹**H** NMR (500 MHz, CDCl₃) δ 8.47 (d, J = 4.7 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.39 – 7.27 (m, 5H), 7.15 – 7.09 (m, 2H), 6.30 (d, J = 8.2 Hz, 1H), 5.15 – 5.05 (m, 2H), 4.76 (dt, J = 8.4, 5.3 Hz, 1H), 3.68 (s, 3H), 3.36 (dd, J = 14.9, 5.7 Hz 1H), 3.28 (dd, J = 14.9, 4.7 Hz 1H).

⁸ Anaïs F. M. Noisier, Craig S. Harris, and Margaret A. Brimble *Chem. Commun.*, **2013**, *49*, 7744.

¹³C NMR (125 MHz, CDCl₃) δ 172.1, 157.1, 156.1, 149.3, 136.7, 136.5, 128.5, 128.2, 128.2, 123.8, 121.9, 67.0, 53.4, 52.4, 39.0.

FTIR (neat) v_{max} : 3333, 3032, 2951, 1716, 1593, 1507, 1436, 1340, 1210, 1050, 911, 752, and 670 cm⁻¹.

HRMS (NSI) m/z: [M+H]⁺ calcd. for C₁₇H₁₉O₄N₂, 315.1339; found, 315.1335.

VII. ¹H and ¹³C NMR Spectra




































































































raa_5-55_ketoneb_1h



































VIII. Chiral HPLC Data:





This is a result compounds table. Use the footer button in the table format dialog box to define the summations in the last table line.

#	Compound Name	Amount	Resp.	Resp.%	Exp.RT	Meas.RT
1 2		0.000 0.000	326.194 2.099e4	1.530 98.470	0.000 0.000	11.800 13.225
Totals:		0.000				





This is a result compounds table. Use the footer button in the table format dialog box to define the summations in the last table line.

#	Compound Name	Amount	Resp.	Resp.%	Exp.RT	Meas.RT
1 2		0.000	8.375e3 130.034	98.471 1.529	0.000 0.000	14.949 21.299
Totals:		0.000				
IX. Stern-Volmer Fluorescence Quenching Experiments:

All fluorescence measurements were recorded using a Horiba Scientific Dual-FL Fluorometer. Quenching studies were conducted in DMSO:H₂O (5:1) at 20 ±0.5 °C (Peltier temperature controller) with an [Ir(ppy)₂(dtbbpy)]PF₆ concentration of 5 μ M. Raw fluorescence intensity was measured at $\lambda = 591$ nm after excitation at $\lambda = 450$ nm in a quartz cuvette with a path length of 1 cm. Measurements using Hantzsch ester, dehydroalanine, or 2-bromopyridine as quenchers were taken in triplicate at concentrations of 0, 50, 100, 250, and 500 μ M. At quencher concentration of 0 μ M, additional duplicate measurements were collected prior to successive quenchers to maintain accuracy. Stern-Volmer plots were generated using Igor Pro 7; data points were fit with a linear trend line.



Stern-Volmer Plots



Measured Fluorescence	Intensities at $\lambda =$	591 nm	(counts)
------------------------------	----------------------------	--------	----------

[HEH] (µM)	1	2	3	avg	stdev	I _o /I	error
0	5966.1219	5849.4855	-	5907.8037	82.4743	1.0000	0.0140
50	5819.8148	5929.6318	5902.7293	5884.0586	57.2398	1.0040	0.0098
100	5841.5493	5819.6902	5813.9702	5825.0699	14.5553	1.0142	0.0025
250	5374.5285	5468.2221	5461.4238	5434.7248	52.2422	1.0870	0.0104
500	5200.5652	5253.6675	5331.9516	5262.0614	66.0942	1.1227	0.0141
	1						
[DHA] (µM)	1	2	3	avg	stdev	I _o /I	error
[DHA] (µM) 0	1 5839.3979	2 5914.3043	3 5903.3400	avg 5885.6807	stdev 40.4553	I_o/I 1.0519	error 0.0072
[DHA] (µM) 0 50	1 5839.3979 6095.6538	2 5914.3043 6197.9486	3 5903.3400 6307.0152	avg 5885.6807 6200.2059	stdev 40.4553 105.6987	I₀/I 1.0519 0.9985	error 0.0072 0.0170
[DHA] (μM) 0 50 100	1 5839.3979 6095.6538 6173.1678	2 5914.3043 6197.9486 6181.4130	3 5903.3400 6307.0152 6138.4126	avg 5885.6807 6200.2059 6164.3311	stdev 40.4553 105.6987 22.8216	I ₀ / I 1.0519 0.9985 1.0043	error 0.0072 0.0170 0.0037
[DHA] (μM) 0 50 100 250	1 5839.3979 6095.6538 6173.1678 6057.7748	2 5914.3043 6197.9486 6181.4130 6100.8092	3 5903.3400 6307.0152 6138.4126 5884.9329	avg 5885.6807 6200.2059 6164.3311 6014.5056	stdev 40.4553 105.6987 22.8216 114.2576	I₀/I 1.0519 0.9985 1.0043 1.0294	error 0.0072 0.0170 0.0037 0.0196

[2-BrPy] (µM)	1	2	3	avg	stdv	I _o /I	error
0	6151.0503	6231.0219	-	6191.0361	56.5485	0.9507	0.0087
50	5805.9303	5890.0415	5918.6204	5871.5308	58.5812	1.0024	0.0100
100	5951.2881	5923.7698	5915.9019	5930.3199	18.5802	0.9925	0.0031
250	5829.0025	5848.4549	6057.4723	5911.6432	126.6656	0.9956	0.0213
500	5840.9751	5825.5125	5946.4111	5870.9662	65.7930	1.0025	0.0112

X. α-Deuteration With D₂O as Solvent:

Following the general procedure, the reaction of 2-bromopyridine (32 mg, 0.20 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (120 mg, 0.40 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2.1 mg, 0.0021 mmol, 0.01 equiv) and Hantzsch ester (76 mg, 0.30 mmol, 1.3 equiv) provided the product (72 mg, 94% yield) as white solid after purification by flash column chromatography (5% – 40% ethyl acetate/hexanes). Integration of the alpha proton ¹H NMR signal was used to determine the percent of deuterium incorporation (94% D).



