Electronic Supplementary Material (ESI) for ChemComm.

Visible-Light-Induced Chemoselective Reductive Decarboxylative Alkynylation under Biomolecule-Compatible Conditions

Jie Yang, Jing Zhang, Li Qi, and Yiyun Chen*

Supplementary Information

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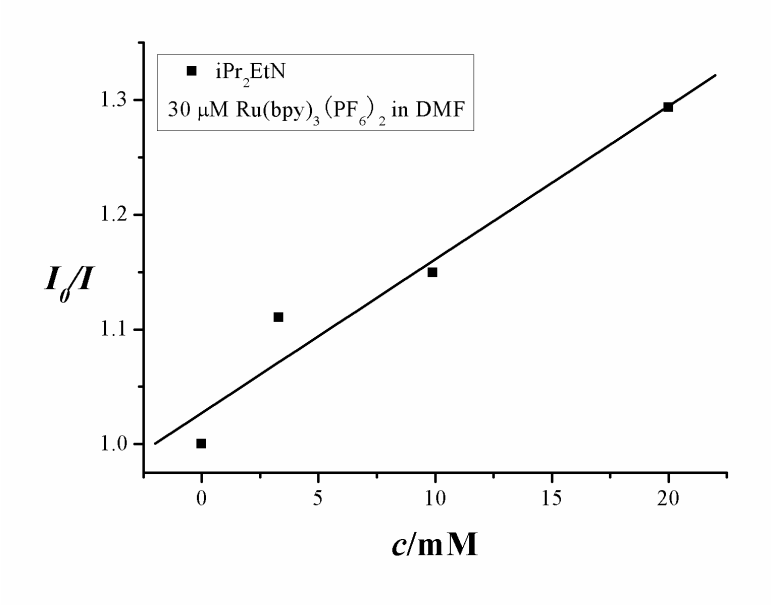
I. General Procedures

Unless otherwise noted, all reactions of substrates preparation were conducted in flame-dried glassware under a nitrogen atmosphere using anhydrous solvent passed through an activated alumina column (Innovative Technology). Commercially available reagents were used without further purification. Hantzsch ester (HE) was recrystallized from ethanol. Thin layer chromatography (TLC) was performed using Jiangyou TLC silica gel plates HSG F_{254} and visualized using UV light, anisaldehyde or potassium permanganate. Flash chromatography was performed on Lisure science EZ purification system using the Santai technologies silica gel cartridges. Photochemical reactions were carried with 4 W blue LED (468 nm peak wavelength, 25 nm spectral half-wave width, composed of 65 LED units each with 60 mW, 3 V, 20 mA) obtained from Qiding Photo Electric (analyzed by Everfine PMS-50). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, acetone-d_6 or DMSO-d_6, unless otherwise noted, on a Bruker AV-400 MHz or an Agilent 500 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of residual $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), acetone-d_6 (2.05 ppm), or DMSO-d_6 (2.50 ppm). Data for ^{1}H NMR were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in Hertz (Hz) and integration. Data for ^{13}C NMR spectra were reported in terms of chemical shift in ppm from the central peak of $CDCl_3$ (77.16 ppm), acetone-d_6 (29.84 ppm), or DMSO-d_6 (39.52 ppm). IR spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. MS experiments were performed on a Bruker maXis 4G instrument for HRMS-ESI, and a Waters Micromass GCT Premier instrument for HRMS-EI. HPLC experiments were performed on a ThermoFisher scientific/Dionex Ultimate 3000 HPLC system using C18 column (250x4.6mm internal diameter, particle size 5 μm). Fluorescence spectrometry was recorded on a Microplate Accessory 5JO-0139 spectrometer. UV/Vis spectrometry was measured on a Thermo Nanodrop 2000c UV/Vis spectrometer.

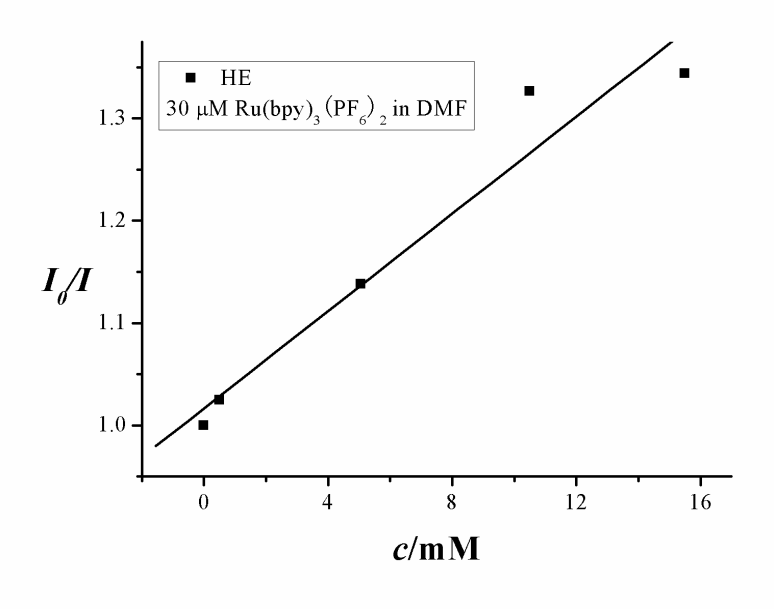
II. Mechanistic Studies

The Luminescence Quenching Experiment

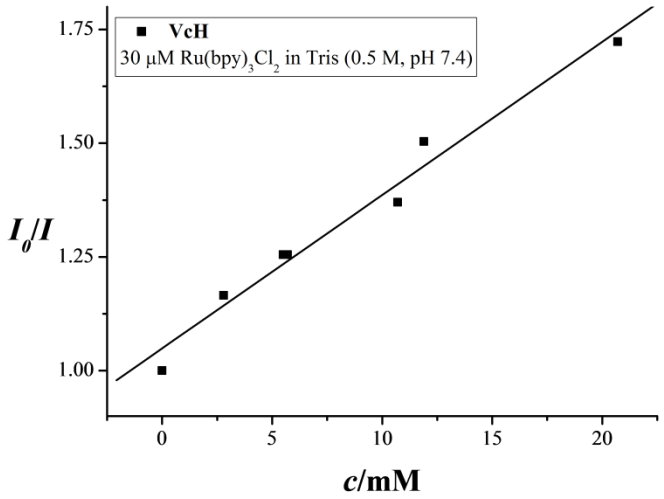
Emission intensities were recorded using Microplate Accessory 5JO-0139 spectrometer for all experiments. All $Ru(bpy)_3(PF_6)_2$ or $Ru(bpy)_3Cl_2$ solutions were excited at 460 nm and the emission intensity at 600 nm was observed. In a typical experiment, the DMF solution of $Ru(bpy)_3(PF_6)_2$ (30 μM), or the tris(hydroxymethyl)aminomethane chloride (Tris-Cl) aqueous buffer (0.5 M, pH 7.4) of $Ru(bpy)_3Cl_2$ (30 μM), was added the appropriate amount of quencher in a screw-top 1.0 cm quartz cuvette. After degassing with nitrogen for 10 min, the emission spectra of the samples were collected. The results showed that *N*,*N*-diisopropylethylamine (DIPEA), hanztsch ester (HE), and ascorbates quenched the photoexcited Ru(II)* effectively, while *N*-acyloxyphthalimide **1** and alkynyl sulfone **27** had no effect.



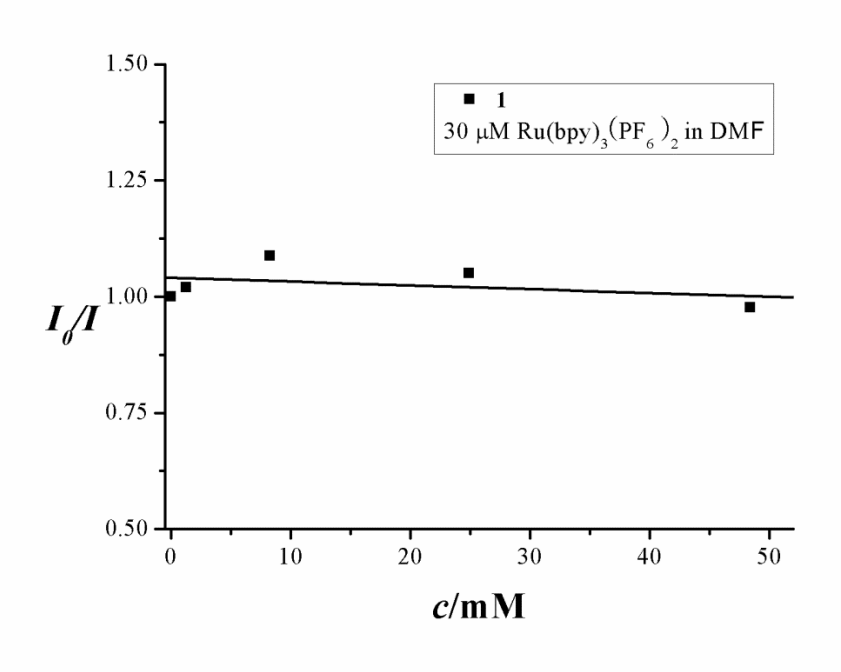
Scheme S1. $Ru(bpy)_3(PF_6)_2$ Emission Quenching by *N*,*N*-diisopropylethylamine (DIPEA).



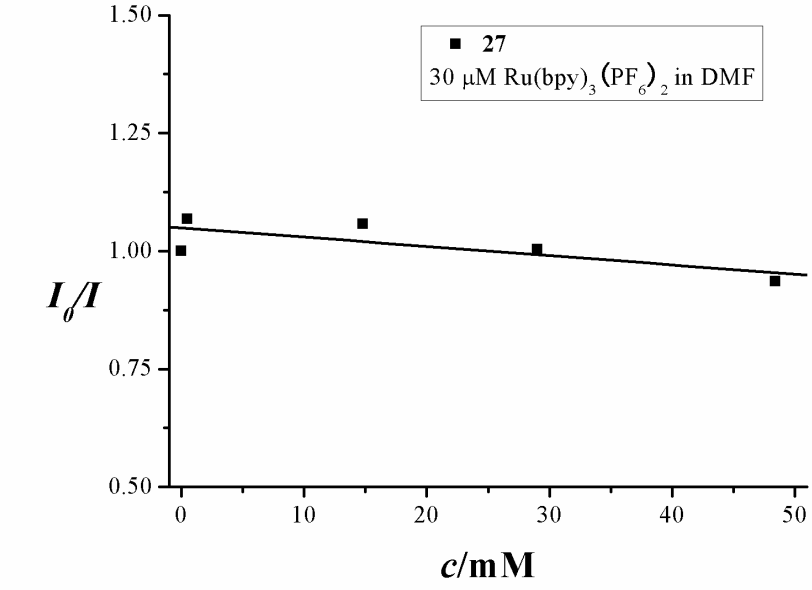
Scheme S2. $Ru(bpy)_3(PF_6)_2$ Emission Quenching by Hanztsch Ester (HE).



Scheme S3. $Ru(bpy)_3Cl_2$ Emission Quenching by Ascorbates.



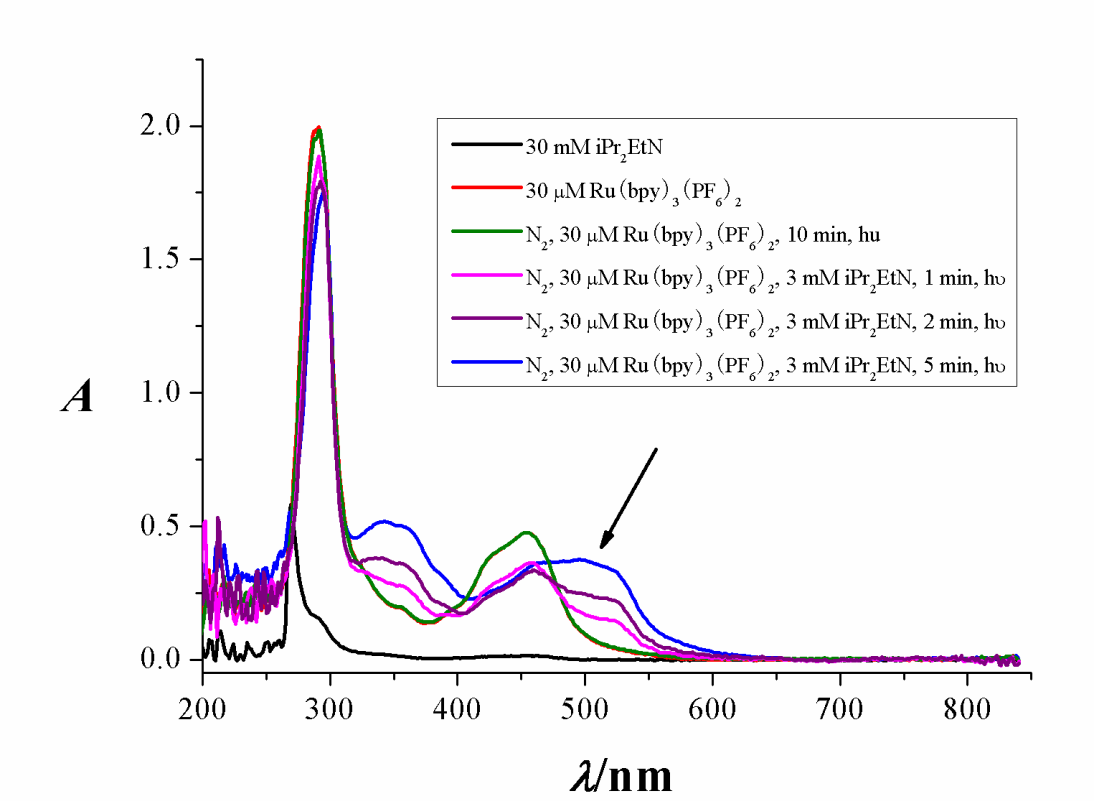
Scheme S4. $Ru(bpy)_3(PF_6)_2$ Emission Quenching by *N*-acyloxyphthalimide 1.



Scheme S5. $Ru(bpy)_3(PF_6)_2$ Emission Quenching by Alkynyl Sulfone 27.

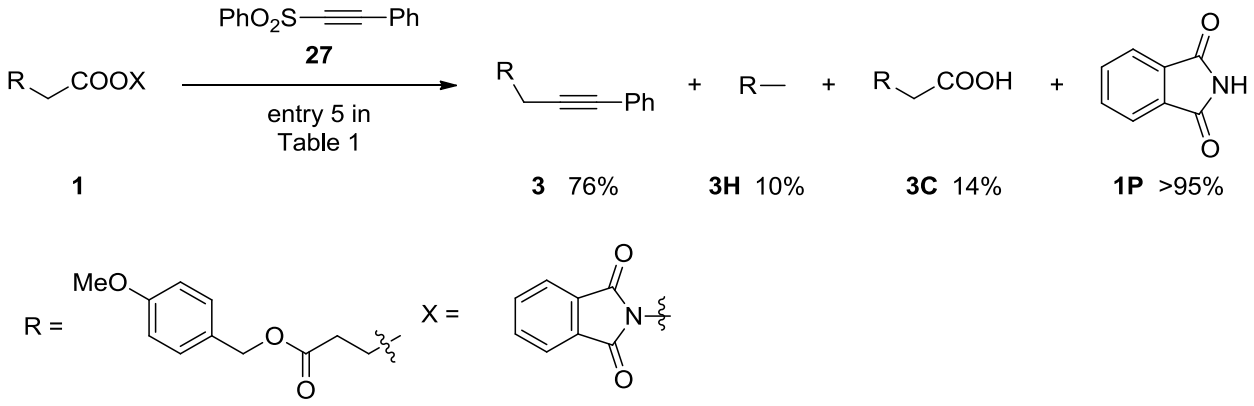
The Observation of the Ru(I) Intermediate

The Ru(I) intermediate ($Ru(bpy)_3^+$) was reported[1] showing a signature absorption band at ~510 nm. Spectrometry of $Ru(bpy)_3(PF_6)_2$ (30 μM) in the presence of DIPEA (3 mM) in 0.5 mL DMF were recorded on a Thermo Nanodrop 2000c UV/Vis spectrometer. The data were collected at different time points under a nitrogen atmosphere with 468 nm LED irradiation at 25 °C.



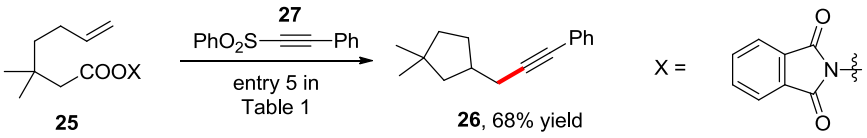
Scheme S6. The $Ru(bpy)_3(PF_6)_2$ Showed the Signature Absorption Band of Ru(I) at ~510 nm in the Presence of DIPEA under 468 nm LED irradiation.

The Characterization of the Reaction Mixture



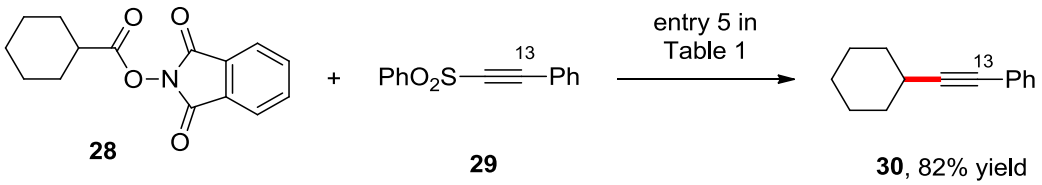
The reaction mixture of **1** and **27** under the standard reaction conditions was carefully characterized: Besides the decarboxylative alkynylation adduct **3**, the decarboxylative hydrogenation adduct **3H**, and carboxylic acid **3C** (the DIPEA salt) were also observed. From ^{1}H NMR analysis using HE as the internal standard, the yields were determined as 76%, 10%, and 14%, respectively. The hydrogens on Ar-CH_2-O were measured: 5.08 ppm (**1**), 5.06 ppm (**3**), 5.03 ppm (**3H**), and 5.00 ppm (**3C**). From the reaction mixture, phthalimide **1P** was isolated in >95% yield while no *N*-hydroxyphthalimides, which suggested that **3C** was originated from the carboxyl radical before decarboxylation rather than the hydrolysis of the *N*-acyloxyphthalimide **1**.

The Radical Probe Experiment

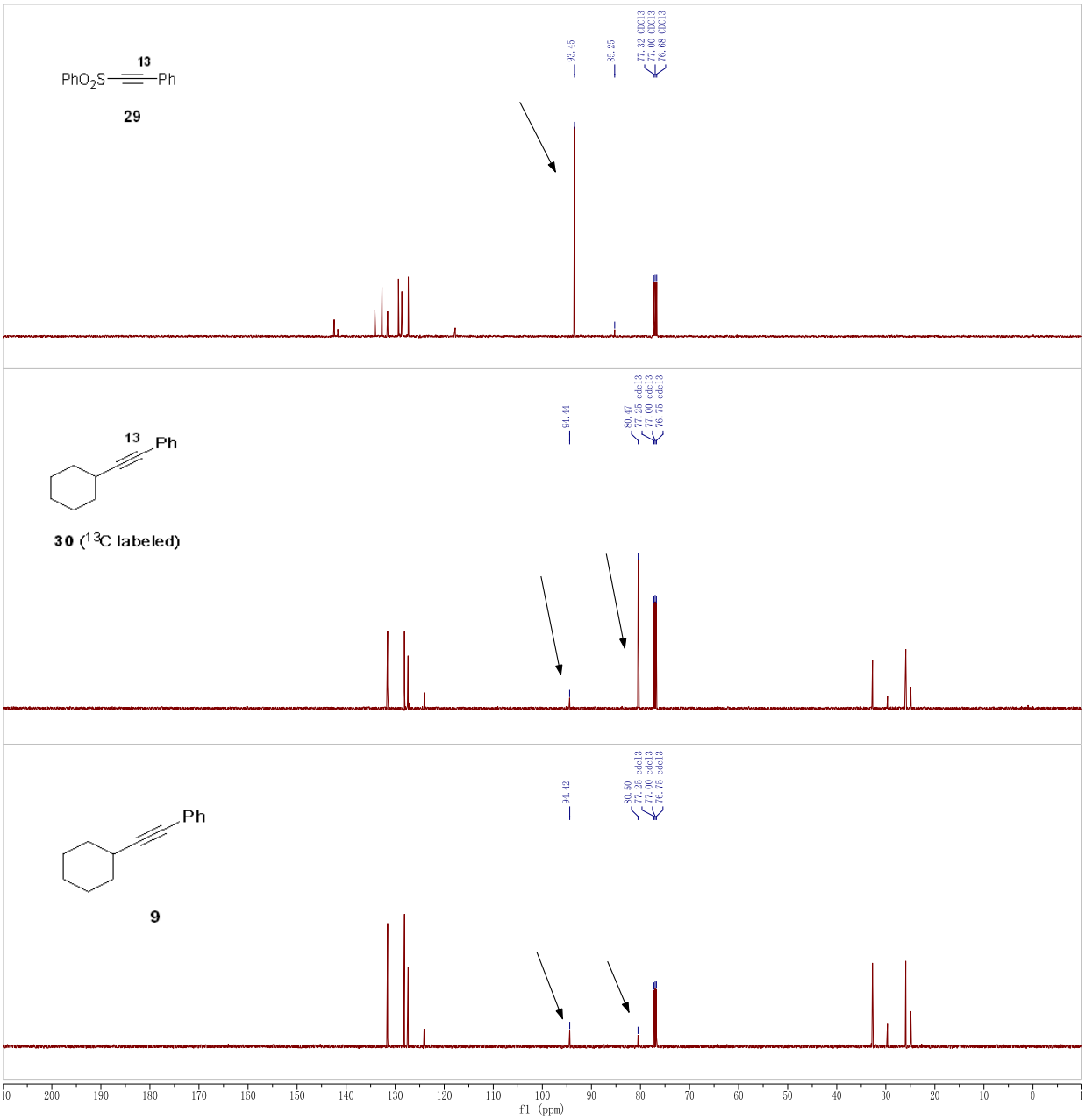


1-(3-(3,3-dimethylcyclopentyl)prop-1-ynyl)benzene 26. Following the standard procedure, the reaction of **25** (30.8 mg, 0.1 mmol) with **27** (36.6 mg, 0.15 mmol) for 30 min afforded **26** as a colorless oil (14.8 mg, 68% yield) after flash chromatography: TLC R_f = 0.7 (100%, Hexanes); IR (KBr, thin film) 3301, 2926, 2852, 2359, 2015, 1894, 1736, 1166, 1093, 669, 650, 582 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ 7.40-7.38 (m, 2H), 7.29-7.25 (m, 3H), 2.42 (d, J = 6.5 Hz, 2H), 2.34-2.27 (m, 1H), 1.95-1.89 (m, 1H), 1.70-1.65 (m, 1H), 1.52-1.39 (m, 3H), 1.24-1.20 (m, 2H), 1.05 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 131.5, 128.1, 127.4, 124.1, 89.8, 80.7, 47.2, 40.7, 39.2, 38.5, 31.3, 30.2, 29.4, 25.7; HRMS-EI (m/z) calculated for $C_{12}H_{20}$ $[M]^+$: 212.1565, found 212.1566.

The C13-Isotopic-Labeling Experiment

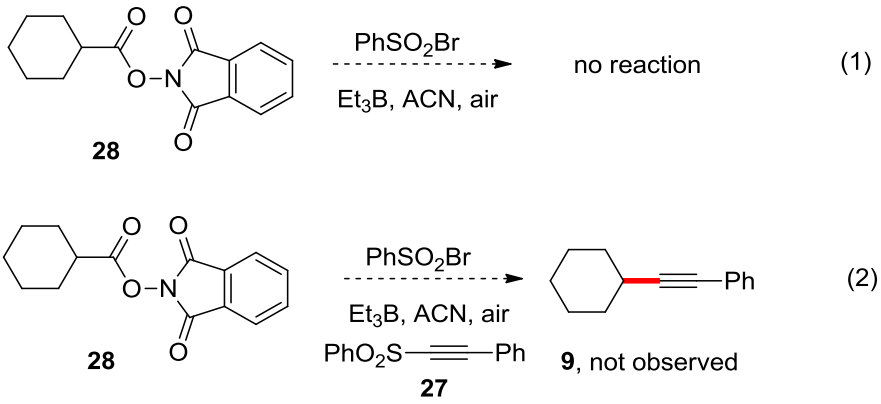


Labeled 1-(2-cyclohexylethynyl)benzene 30. Following the standard procedure, the reaction of **28** (27.9 mg, 0.1 mmol) and the C13-labeled alkynyl sulfone **29** which was prepared according to literatures[2][3] (35.6 mg, 0.15 mmol) for 0.5 h afforded alkyne **30** as a colorless oil (15.5 mg, 82% yield) after flash chromatography: TLC R_f = 0.74 (Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$), δ7.41-7.38 (m, 2H), 7.29-7.24 (m, 3H), 2.61-2.56 (m, 1H), 1.89-1.86 (m, 2H), 1.79-1.73 (m, 2H), 1.57-1.50 (m, 3H), 1.37-1.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ131.7, 128.3, 127.5, 124.3, 94.6, 80.6 (labeled 20x more intensive), 32.9, 29.8, 26.1, 25.1. When compared with the ^{13}C NMR of an unlabeled sample, 20% ^{13}C incorporation showed at the indicated position only.

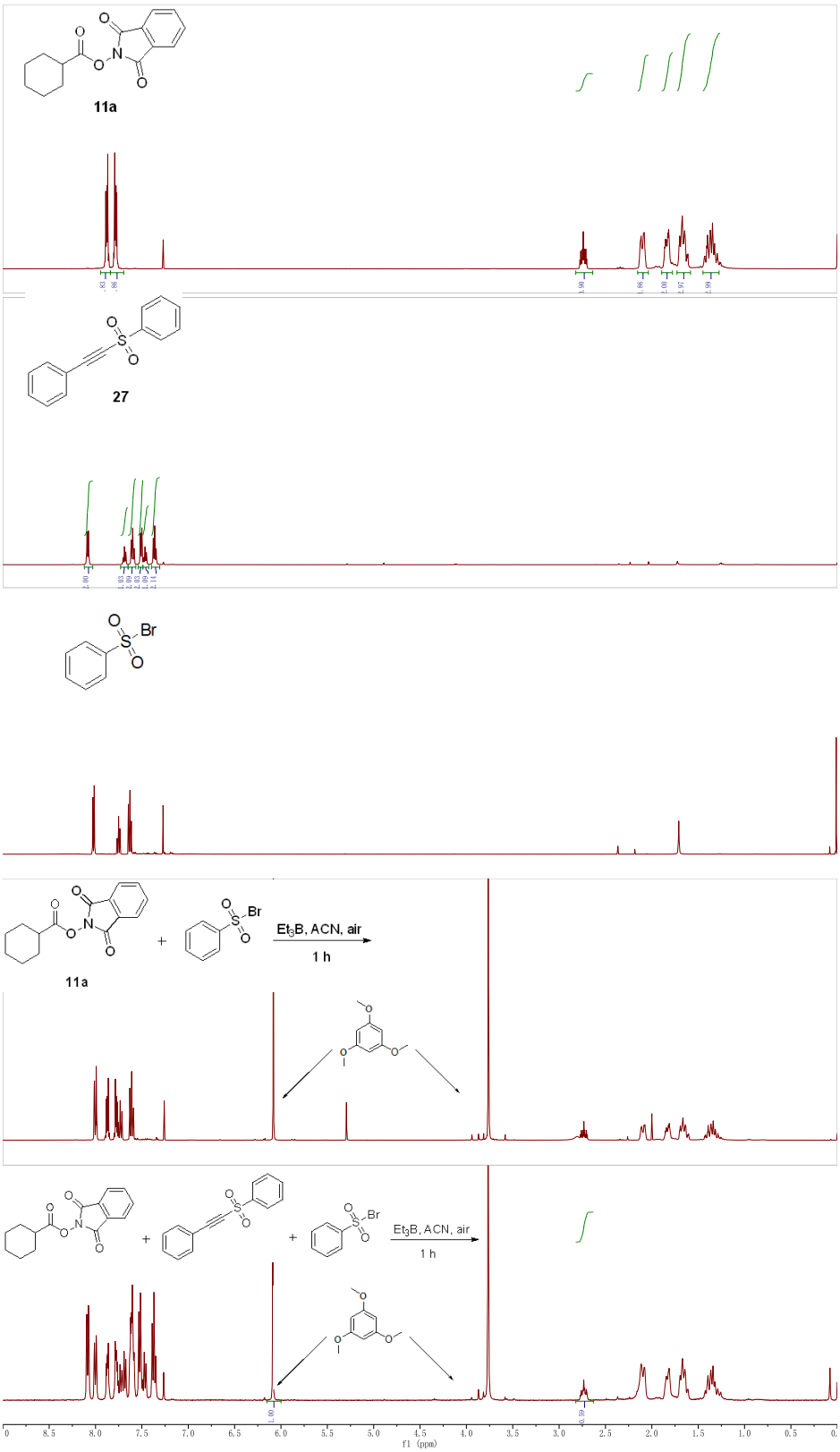


Scheme S7. The C13-Isotopic-Labeling Experiment. (NMR Traces)

The Sulfonyl Radical Experiments



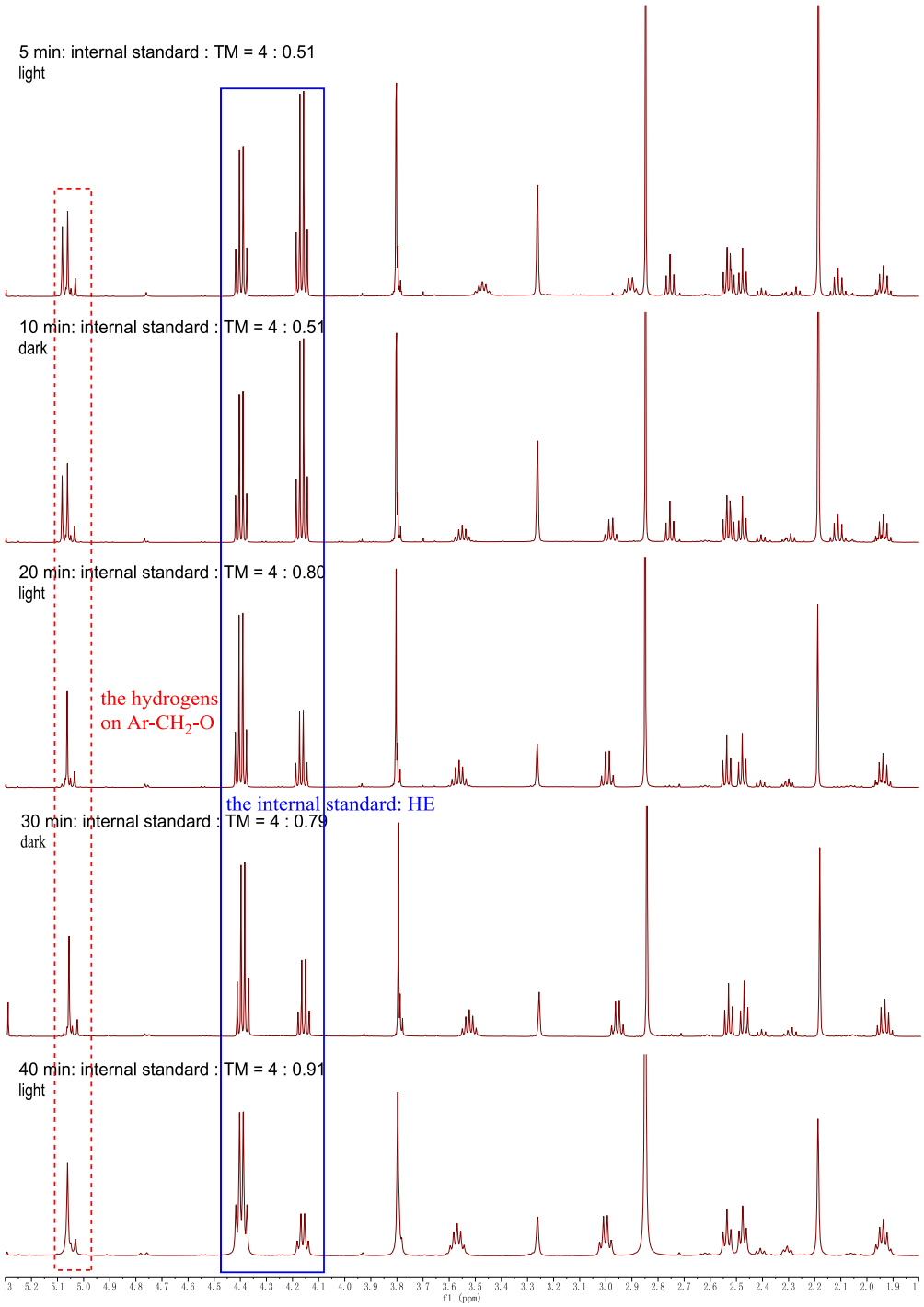
Following the literature procedure[4][5], to a vigorously stirred and open to air solution of **28** (0.1 mmol, 0.1 M, 1.0 equiv.), benzenesulfonyl bromide (25.8 mg, 1.2 equiv.) (equation 1), w/o **27** (38.5 mg, 0.15 mmol, 1.5 equiv.) (equation 2), in CH_3CN was added Et_3B (30 μL, 0.3 equiv., 1M in THF) at room temperature and stirred for additional 1 h. The resulting reaction mixture was concentrated in vacuo and no alkynylation adduct was observed from ^1H NMR analysis.



Scheme S8. The Benzenesulfonyl Radical Experiments.

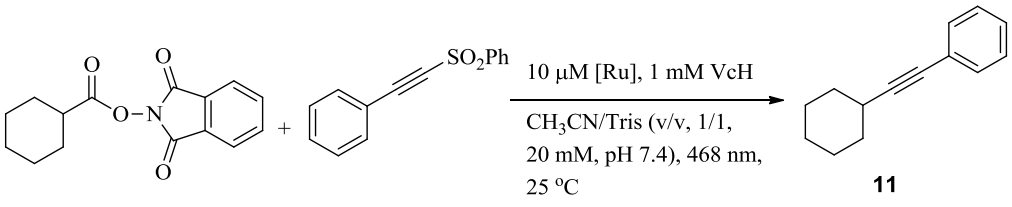
The On-Off-Light Experiments

Following the standard procedure, to a solution of **1** (79.9 mg, 0.2 mmol), **27** (74.1 mg, 0.3 mmol), $Ru(bpy)_3(PF_6)_2$ (1.8 mg, 0.002 mmol), and HE (76 mg, 0.3 mmol) in DCM (2 mL) was added DIPEA (70 μL, 0.4 mmol). The reaction mixture was stirred at 25 ^{o}C at a distance of 10 cm from a 4 W blue LED with on-off-light. 400 μL of the reaction mixture aliquot was collected at different points and concentrated in vacuo. The ^{1}H NMR analysis was calculated using HE as the internal standard.



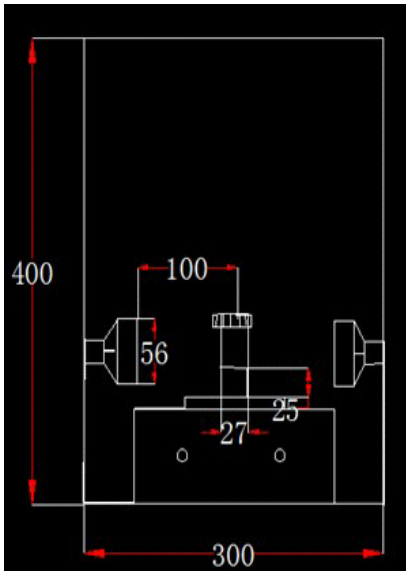
Scheme S9. The On-off-light Experiments. (NMR Traces)

Quantum Yield Determination



28, 100 μM **27**, 1 mM **11**

Time	Yield / %	Φ / %
40 s	41.9	25.9
80 s	81.2	25.1



$$\Phi = \frac{N_{\text{prod}}}{N_{abs,\text{photon}}} = N_A hc \frac{N_{\text{prod}}}{P_{abs}\,\Delta t\,\lambda_{LED}}$$

$N_A = 6.02 \times 10^{23}\ \text{mol}^{-1}$

$h = 6.63 \times 10^{-34}\ \text{J} \bullet \text{s}$

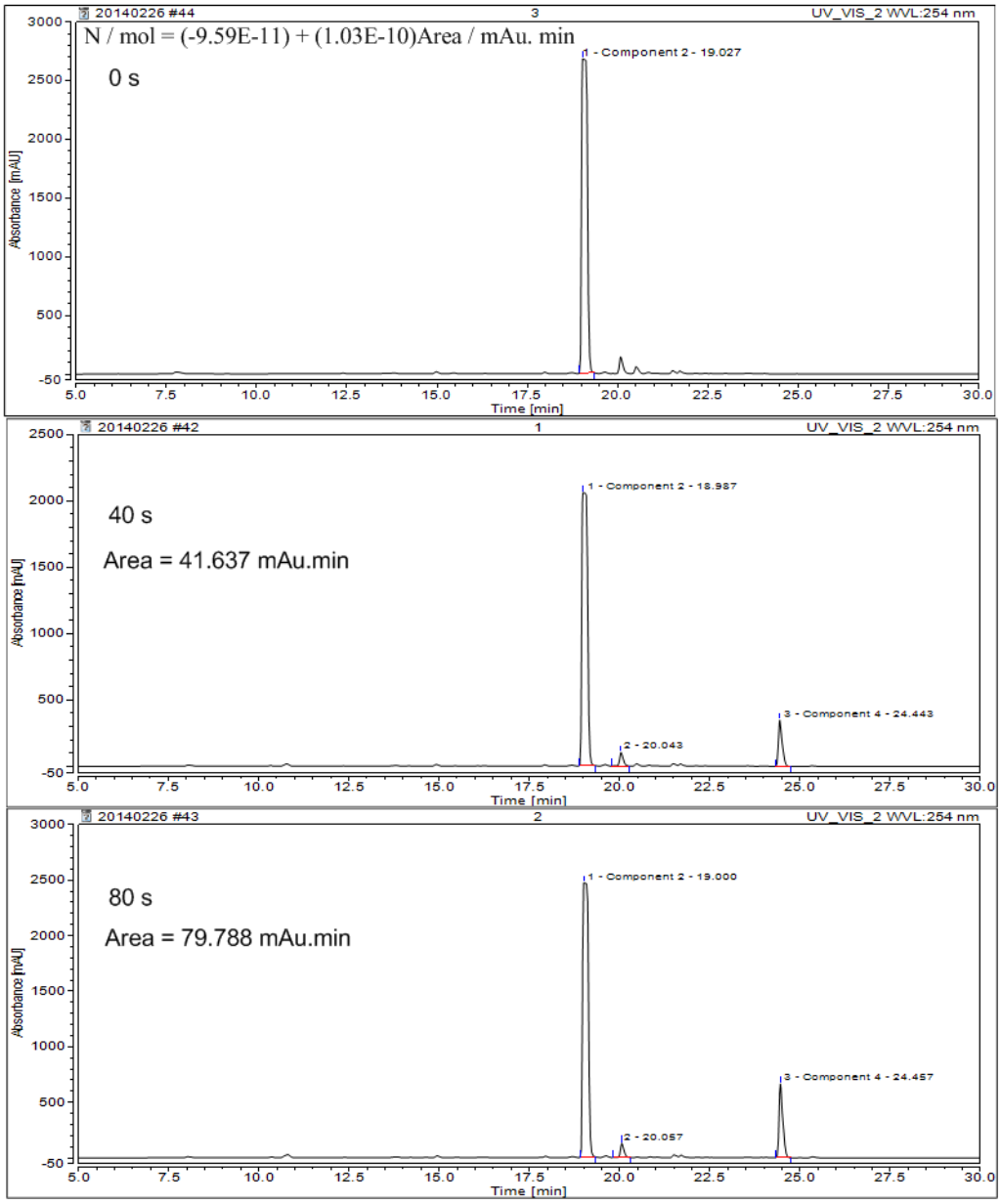
$c = 3 \times 10^{8}\ \text{m/s}$

$\lambda_{LED} = 468 \times 10^{-9}\ \text{m}$

$P_{abs} = 10.3\ \text{mW}$

Tris-HCl (20 mM, pH = 7.4, 5 mL, bubbled with N_2 for 10 min) and acetonitrile (5 mL) were mixed in 20 mL clear glass vial equipped with a magnetic bar. To the mixture were added successively 10 μL of 1 M ascorbic acid (dissolved in water), 10 μL of 1 M **27** (dissolved in acetonitrile), 10 μL of 100 mM **28** (dissolved in acetonitrile) and 1 μL of 100 mM $Ru(bpy)_3Cl_2$ (dissolved in water). Under N_2 atmosphere and vigorous stirring the reaction mixture was irradiated under 468 nm at 25 °C at a distance of 10 cm from two 4 W LEDs. The absorbed optical power was measured to P_{abs} = 10.3 mW (power density: 1.5 mW/cm^2). Aliquots of 100 μL reaction solution from the sample were withdrawn at 0 second, 40 second, 80 second and directly subjected to HPLC analysis. The relative amounts of **11** in the reaction mixture were monitored by UV absorbance at 254 nm (Scheme S10) and quantified according to the standard curve (N / mol = (-9.59E-11) + (1.03E-10)Area / mAu. Min). The yield of **11** after 40 s

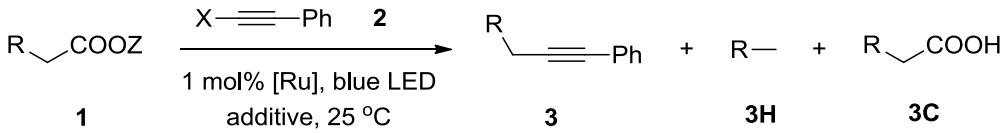
irradiation was determined as 41.9%, which corresponds to a quantum yield(Q.Y.) of 25.9% in correlation to the absorbed optical power (**International Light Technologies**, **ILT1400 *Radiometer Photometer***). After 80 s irradiation, the yield was 81.2%, which corresponds to a Q.Y. of 25.1%.



Scheme S10. HPLC Traces of Quantum Yield Determination.

III. Detailed Reaction Optimizations

Table S1. Screen of Alkynes and Solvents



1 3 3H 3C

entry	Condition	Time	Conversion	3[a]	3H	3C[c]
1	Z = phth, X = Br	30 min	>95%	28%	47%	13%
2	Z = phth, X = BI	30 min	>95%	16%	17%	22%
3	Z = phth, X = SO_2CF_3	30 min	60%	29%	8%	5%
4	Z = phth, X = SO_2CH_3	30 min	>95%	57%	7%	10%
5	Z = phth, X = SO_2Ph	30 min	>95%	76%(74%)	10%	14%
6	Z = oxime, X = SO_2Ph	30 min	< 5%	0%	0%	0%
7	entry 5, in CH_3CN	30 min	>95%	53%	5%	14%
8	entry 5, in DMF	30 min	>95%	35%	5%	N/A[d]
9	entry 5, in THF	30 min	>95%	64%	16%	8%
10	entry 5, in MeOH	30 min	>95%	0%	55%	20%
11	entry 5, in Toluene	30 min	< 5%	0%	0%	0%

[a] Reaction conditions: **1** (0.10 mmol, 1.0 equiv), **2** (0.15 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (0.001 mmol, 0.01 equiv), iPr_2NEt (0.20 mmol, 2.0 equiv.), and hantzsch ester (HE, 0.15 mmol, 1.5 equiv.) in 1.0 mL CH_2Cl_2 under nitrogen with 468 nm LED irradiation for 30 min. [b] Conversions and yields were determined by ^1H NMR analysis, isolated yields were in parentheses. [c] ^1H NMR spectra was obtained from the salt adduct, confirmed by the addition of iPr_2EtN (2.0 equiv.) to the carboxylic acid. [d] The salt adduct was not detected as the reaction mixture was treated by water wash.

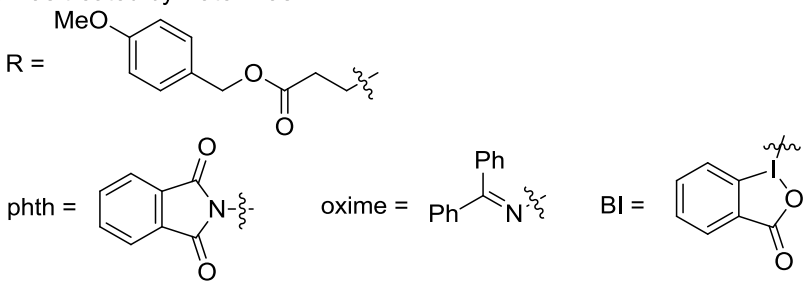
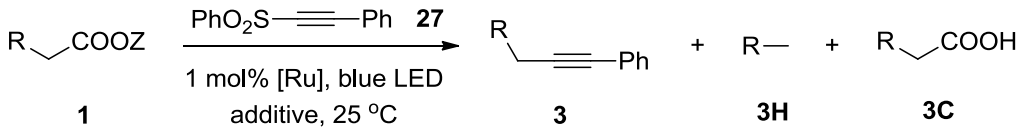


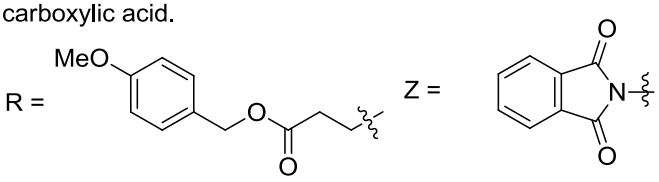
Table S2. Control Experiments



1 **3** **3H** **3C**

entry	Condition	Time	Conversion	**3**[a]	**3H**[c]	**3C**
1	entry 5, no blue LED	12 h	< 5%	0%	0%	0%
2	entry 5, no [Ru]	12 h	< 5%	0%	0%	0%
3	entry 5, no iPr_2NEt/HE	12 h	< 5%	0%	0%	0%
4	entry 5, no iPr_2EtN	30 min	>95%	37%	47%	0%
5	entry 5, no HE	30 min	40%	28%	0%	5%
6	entry 5, no **2**	30 min	>95%	0%	76%(71%)	9%
7	entry 5, air	30 min	>95%	71%	8%	14%
8	entry 5, in CH_2Cl_2/H_2O	30 min	92%	69%	5%	5%

[a] Reaction conditions: **1** (0.10 mmol, 1.0 equiv), **27** (0.15 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (0.001 mmol, 0.01 equiv), iPr_2NEt (0.20 mmol, 2.0 equiv.), and hantzsch ester (HE, 0.15 mmol, 1.5 equiv.) in 1.0 mL different solvents under nitrogen with 468 nm LED irradiation for 30 min. [b] Conversions and yields were determined by ^1H NMR analysis, isolated yields were in parentheses. [c]^1H NMR spectra was obtained from the salt adduct, confirmed by the addition of iPr_2EtN (2.0 equiv.) to the carboxylic acid.

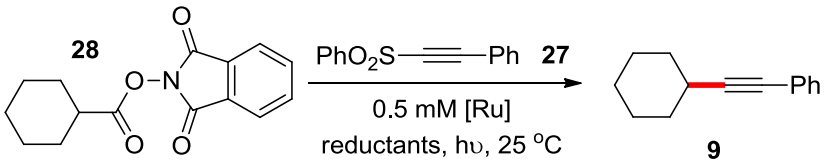


IV. Biomolecule Compatibility Studies

Decarboxylative Alkynylation in the Presence of Biomolecules and Bio-Relevant Molecules

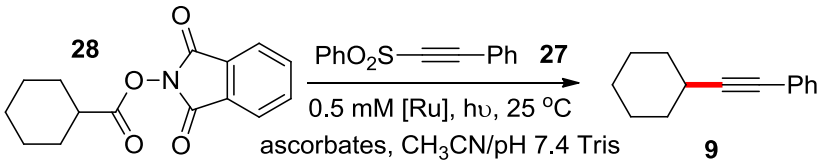
To a solution of *N*-acyloxyphthalimide **28** (0.1 mmol, 1.0 equiv., 10 mM), alkynyl sulfones **27** (0.15 mmol, 1.5 equiv., 15 mM) and $Ru(bpy)_3Cl_2$ (0.005 mmol, 0.05 equiv., 0.5 mM) in 10 mL CH_3CN/aqueous buffer (v/v, 1/1, 300 mM, Tris or phosphate buffer) was added ascorbic acid (0.23 mmol, 2.3 equiv., 23 mM) under nitrogen, and stirred under blue LED at room temperature for 30 min. Conversions and yields were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard, isolated yields were in parentheses.

Table S3. Reductive Decarboxylative Alkynylation in Neutral and Different pH Aqueous Conditions



entry	conditions	conversion	yield
1	entry 5 in Table S1, CH_2Cl_2/H_2O	92%	69%
2	entry 5 in Table S1, CH_3CN/H_2O	92%	36%
3	entry 5 in Table S1, CH_3CN/H_2O NADH to replace HE	>95%	24%
4	ascorbates, CH_3CN/pH 7.4 Tris	>95%	76%(76%)
5	entry 4, CH_3CN/pH 6.0 phosphates	>95%	71%
6	entry 4, CH_3CN/pH 5.0 phosphates	>95%	74%
7	entry 6, CH_3CN/pH 4.2 phosphates	>95%	88%

Table S4. Reductive Decarboxylative Alkynylation in the Presence of Biomolecules and Bio-Relevant Molecules



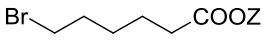
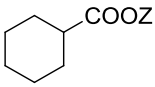
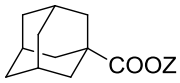
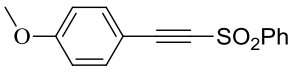
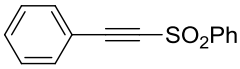
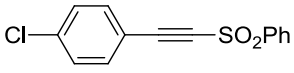
entry	additive	conversion	yield
1	3.0 equiv. 2-phenylethanamine	>95%	83%
2	1.0 equiv. 2-phenylethanamine	>95%	(79%)
3	1.0 equiv. aniline	>95%	(75%)
4	1.0 equiv. L-cystine	>95%	73%
5	1.0 equiv. guanosine	>95%	80%
6	1.0 equiv. naringin	>95%	75%
7	2.9 mg/mL ss DNA	>95%	84%
8	10 mg/mL bovine serum albumin	>95%	73%
9	2 mg/mL bacterial cell lysates	>95%	78%

[a] Conditions: entry 4 in Table S3; [b] The single stranded DNA sequence was CGGGATCCATGGAGAAAAGTTTCGTGATAAC.

The Stability of Substrates under Aqueous Conditions in the Presence of Biomolecules and Bio-Relevant Molecules

We next texted the stability of different *N*-acyloxyphthalimides and alkynyl sulfones. Substrates (100 μM) were incubated with biomolecules or bio-relevant molecules including 2-phenylethanamine, L-lysine, L-cysteine (1 mM) in pH 7.4 aqueous buffers for 10 h. The reaction mixture was subjected to HPLC analysis monitored at 220 nm, 254 nm and 280 nm. The tertiary *N*-acyloxyphthalimides and alkynyl sulfones bearing different electronic groups were stable after 10 h incubation.

Table S5. The Retention of *N*-acyloxyphthalimides and Alkynyl Sulfones After 10 h Incubation.

	no additives	w/ 10 equiv. 2-phenylethanamine
 **19a**	48%	< 5%
 **28**	84%	38%
 **35**	>95%	>95%
 **12b**	>95%	>95%
 **27**	>95%	>95%
 **13b**	>95%	>95%

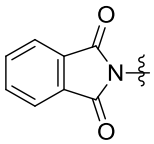
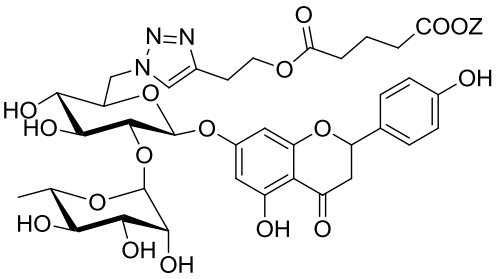
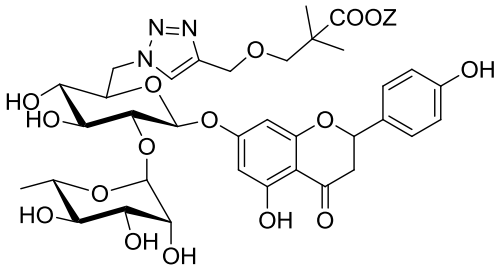
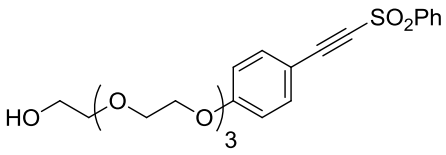
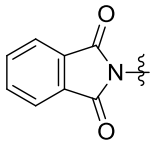
Z = 

Table S6. The Retention of Oligosaccharide-Conjugated *N*-acyloxyphthalimides and Alkynyl Sulfones After 10 h Incubation.

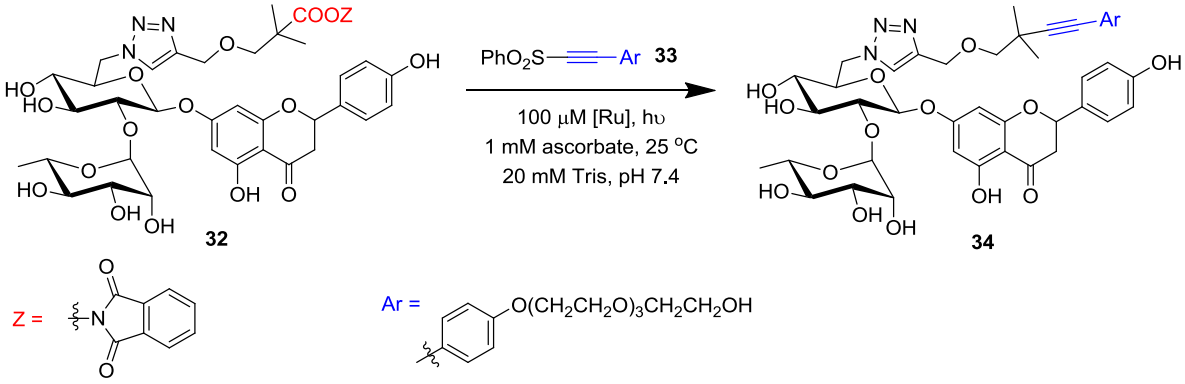
	no additives	w/ 10 equiv. L-lysine	w/ 10 equiv. L-cysteine
 **32'**	56%	< 5%	34%
 **32**	>95%	94%	89%
 **33**	>95%	>95%	>95%

Z = 

Oligosaccharides Alkynylation

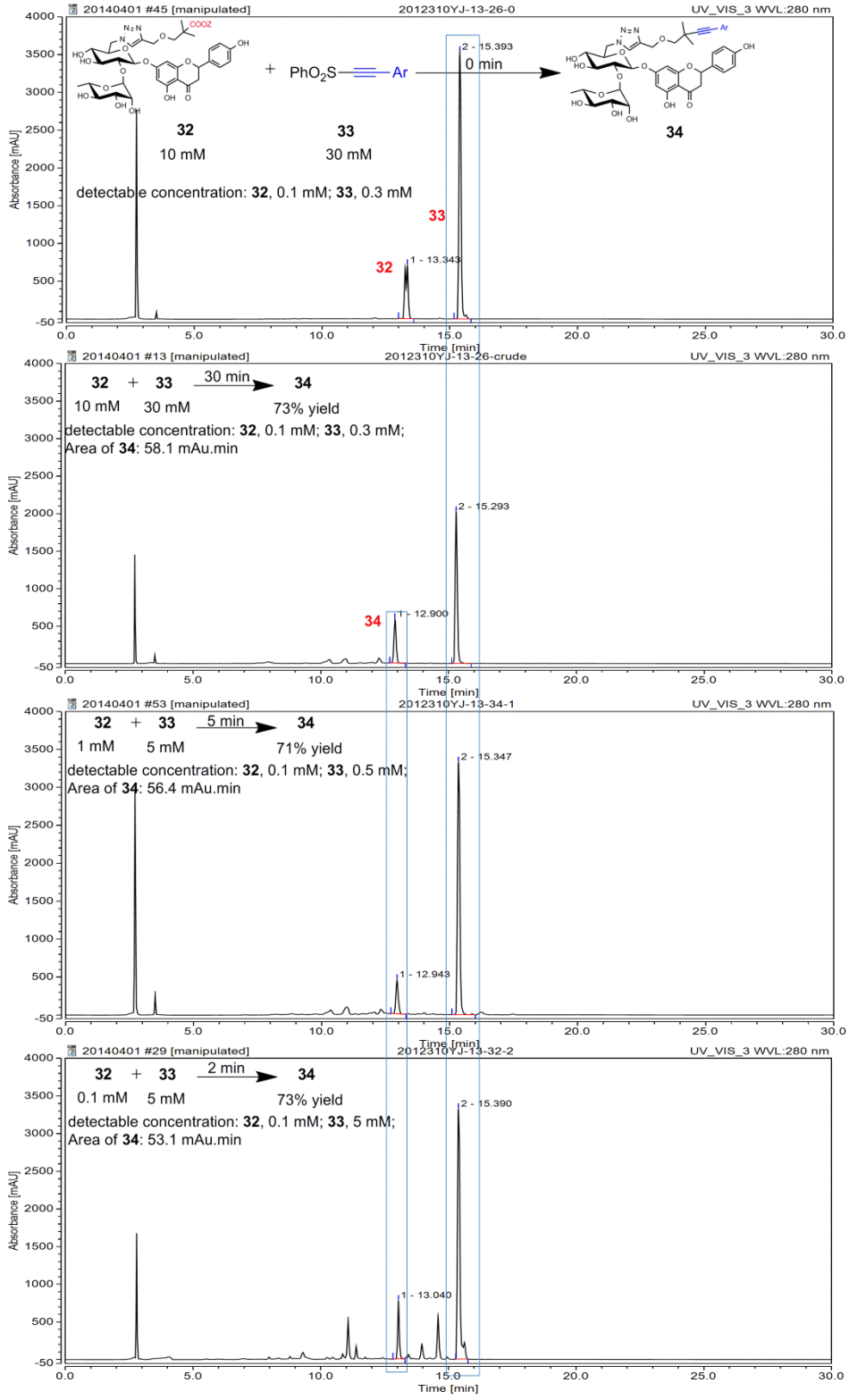
To a solution of naringin-conjugated *N*-acyloxyphthalimide **32**, PEG-conjugated alkynyl sulfones **33** and $Ru(bpy)_3Cl_2$ in 10 mL pH 7.4 CH_3CN/Tris buffer (v/v, 1/1) was added ascorbic acid under nitrogen, and stirred under blue LED at room temperature for indicated time. The reaction mixture was subjected to HPLC analysis monitored at 210 nm, 254 nm and 280 nm.

Table S7. Oligosaccharides Alkynylation at Different Concentrations.

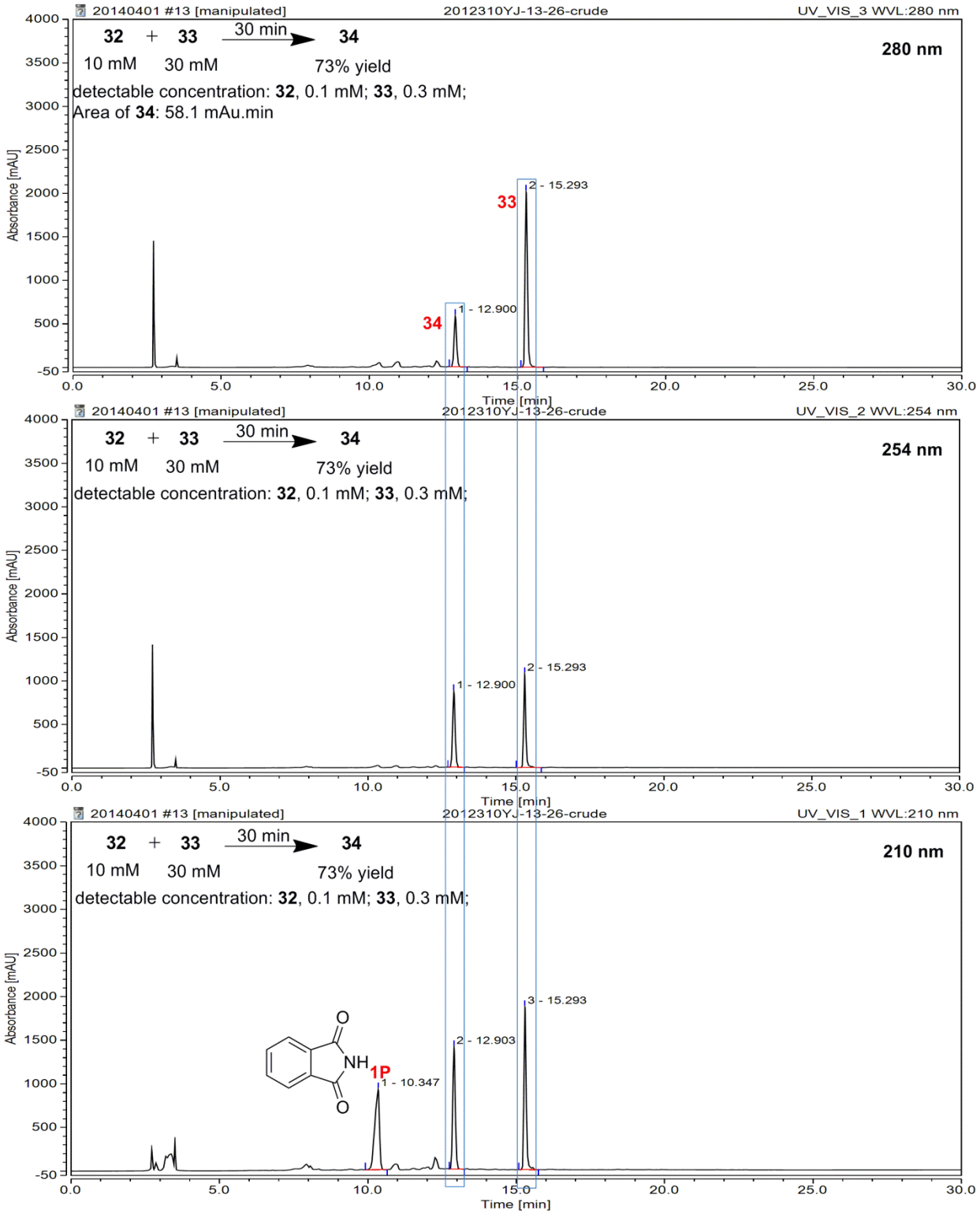


[a] Reaction conditions: **32** (100 μM), **33** (5 mM), $Ru(bpy)_3Cl_2$ (100 μM), and ascorbates (1 mM) in 1:9 CH_3CN/aqueous buffer (20 mM pH 7.4 Tris) under nitrogen with blue LED irradiation for 2 min. [b] Conversions and yields were determined by HPLC analysis at 280 nm in the indicated concentration. [c] In CH_3CN/Tris (v/v, 1/1; 0.3 M; pH 7.4), *N*/mol = (-9.16E-11) + (1.11E-10) x *Area*/(mAu.min) for **32** (280 nm), *N*/mol = (8.24E-12) + (1.25E-10) x *Area*/(mAu.min) for product **34** (280 nm). [d] In CH_3CN/Tris (v/v, 1/9; 0.02 M; pH 7.4), *N*/mol = (5.29E-10) + (1.50E-10) x *Area*/(mAu.min) for **32** (280 nm), *N*/mol = (1.61E-11) + (1.38E-10) x *Area*/(mAu.min) for product **34** (280 nm).

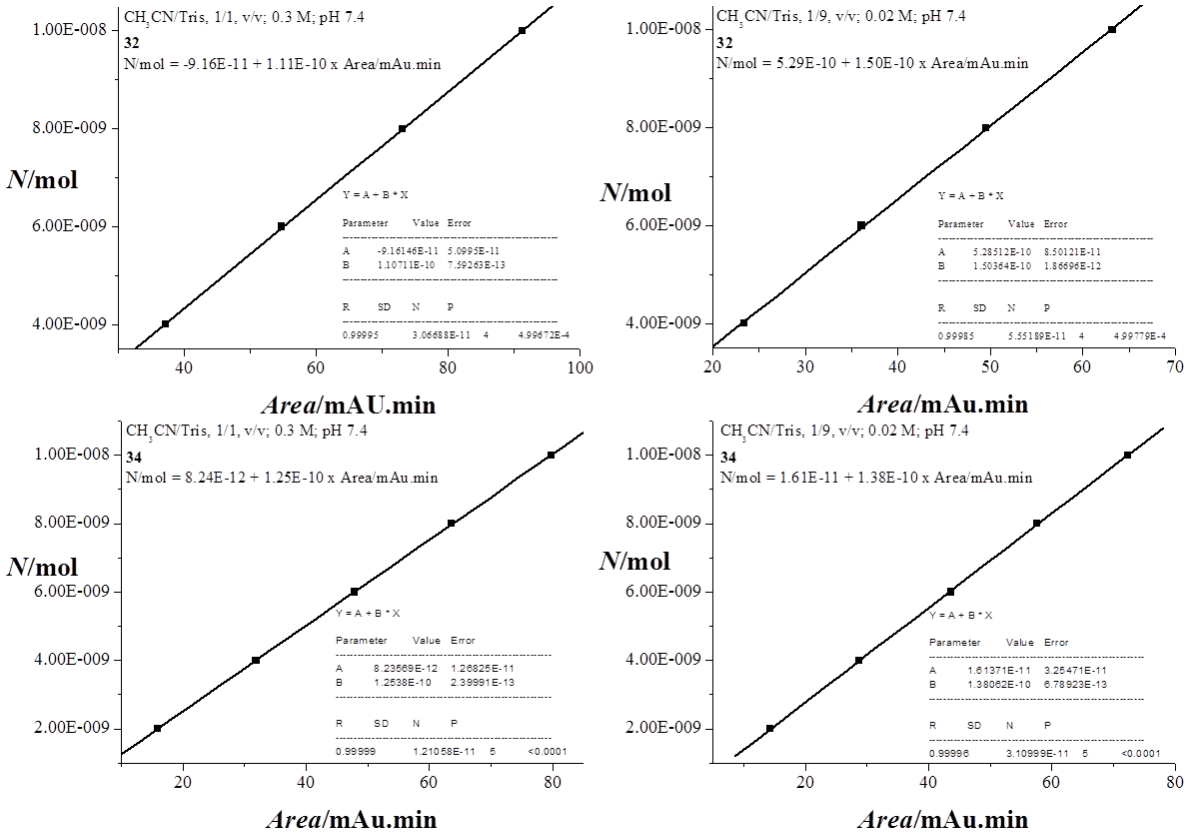
Entry	**32**	**33**	VcH	$Ru(bpy)_3Cl_2$	CH_3CN/Tris	Time	Conversion[b]	Yield[b]
1	10 mM	30 mM	23 mM	0.5 mM	1/1, v/v; 0.3M, pH 7.4	30 min	>95%	73%
2	1 mM	5 mM	10 mM	0.1 mM	1/1, v/v; 0.3M, pH 7.4	5 min	>95%	71%
3[a]	0.1 mM	5 mM	1 mM	0.1 mM	1/9, v/v; 0.02M, pH 7.4	2 min	>95%	73%



Scheme S11. HPLC Traces for Oligosaccharides Alkynylation at 280 nm.

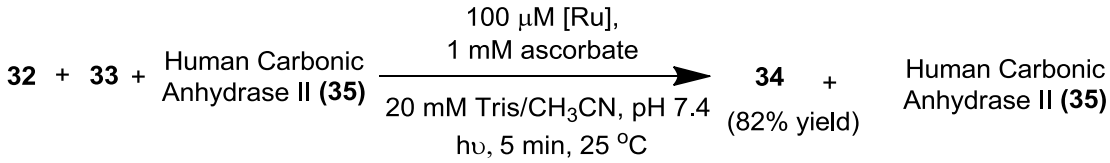


Scheme S12. HPLC Traces for Oligosaccharides Alkynylation at Different Wave Lengths.



Scheme S13. The Standard Curves for 32 and 34.

Oligosaccharides Alkynylation in the Presence of Human Carbonic Anhydrase II



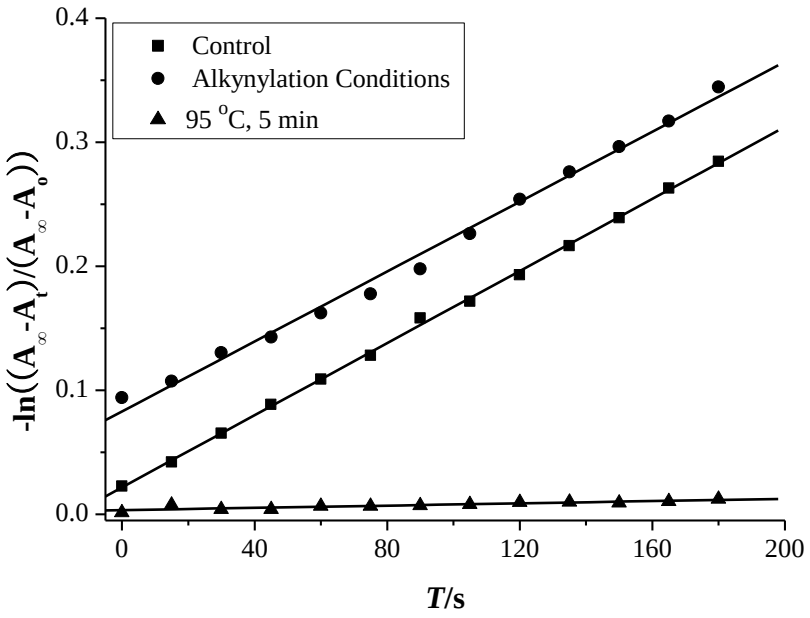
Human carbonic anhydrase II (HCA II) was expressed in *E. coli* BL21 strain with a 6*His tag at its N terminal. Purification by Ni-NTA (ThermoFisher Scientific) afforded greater than 95% purity determined by SDS-gel electrophoresis.

To a solution of PEG-conjugated alkynyl sulfones **33** (5 mM), $Ru(bpy)_3Cl_2$ (100 μM), and ascorbic acid (1 mM) in 2 mL acetonitrile/aqueous buffer (1/9, 20 mM Tris, pH 7.4), was added naringin-conjugated *N*-acyloxyphthalimide **32** and Human carbonic anhydrase II (HCA II) **35** under nitrogen to final concentrations of 100 μM and 1.6 μM, respectively. The reaction mixture was stirred at 25 ^{o}C at a distance of 10 cm from blue LED for 5 min. HCA II was collected through ultrafiltration (Amicon, Ultra-0.5 mL, 3K) and HCA II enzyme activity was assayed by following 4-nitrophenyl acetate hydrolysis spectrophotometrically, as described previously[6]. The oligosaccharide alkynylation was analyzed directly by reverse-phase HPLC.

The 4-nitrophenyl acetate (4-NPA) hydrolysis kinetic assay was initiated by injecting 10 μL of 5 mM fresh acetonitrile solution of 4-NPA into 990 μL of 50 mM Tris-HCl (pH 8.0, NaCl 0.1 M) buffer containing 1.6 μM HCA II with rapid mixing. The hydrolysis of 4-NPA was followed by monitoring the appearance of 4-nitrophenolate at 400 nm over a 3 min period using a UV-Vis spectrophotometer (Thermo scientific NanoDrop 2000c).The positive control group underwent no alkynylation condition treatment, and the negative control group underwent heating at 95 ^{o}C for 5 min. Error bars represented the standard deviation of results from three independent reaction runs. The k_{obs} (first order rate constant) values was calculated by the following equation.

$-\ln[(A_\infty - A_t)/(A_\infty - A_o)] = k_{obs}t$

$k_{obs} = k_{enz}C_{enz} + k_{negative}$



Scheme S14 Typical First-Order Rate Plots of 4-NPA Hydrolysis with HCA II at 25 °C.

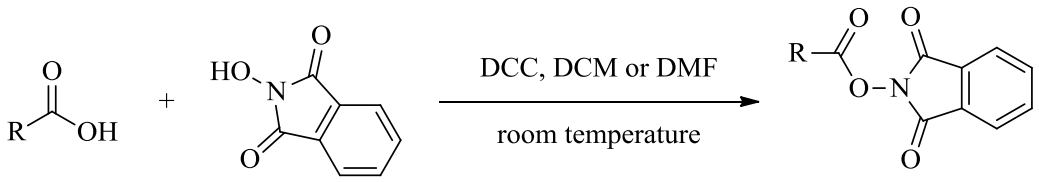
Table S8 Hydrolysis of p-NPA as Catalyzed by Human CA-II.

	k_{obs}/ s^{-1}	$k_{enz}/M^{-1}s^{-1}$
Control	$1.47 \times 10^{-3} \pm 4.36 \times 10^{-5}$	878.32 ± 27.07
Alkynylation Conditions	$1.38 \times 10^{-3} \pm 4.16 \times 10^{-5}$	820.35 ± 25.86
95 °C, 5 min	$5.59 \times 10^{-5} \pm 4.94 \times 10^{-6}$	34.71 ± 3.07

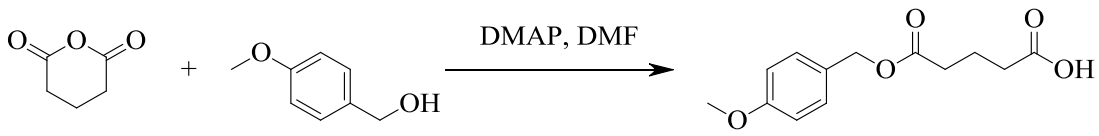
V. Substrates Preparation and Characterization

i. Synthesis of *N*-acyloxyphthalimides

General procedure[7]

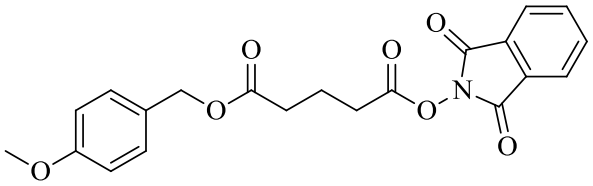


To a solution of alkyl carboxylic acid (1.0 equiv.) and *N*-hydroxyphthalimide (NOP, 1.1 equiv.) in DCM or DMF (about 0.2 M) was added N,N'-dicyclohexylcarbodiimide (DCC, 1.1 equiv.) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 30 min and continued stirring at 25 ^{o}C until TLC indicated the complete consumption of alkyl carboxylic acid. The resulting suspension was filtered and the filtrate was concentrated in vacuo, and subjected to silica gel chromatography.

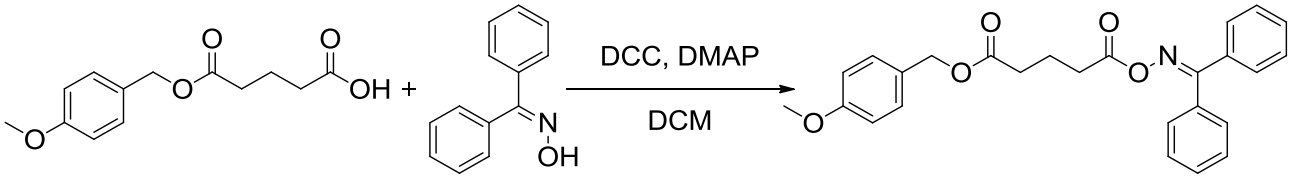


4-((4-methoxybenzyloxy)carbonyl)butanoic acid S1(CAS: 549509-19-5). To a solution of 4-methoxybenzyl alcohol (2.78 g, 20 mmol) and glutaricanhydride (2.30 g, 20.2 mmol) in DMF (40 mL) was added 4-dimethylamiopyridine (DMAP, 0.25 g, 2 mmol). The reaction mixture was stirred at 0 ^{o}C for 1 h, allowed to warm to room temperature and stirred at this temperature for 5.5 h until TLC indicated the complete consumption of 4-methoxybenzyl alcohol. The resulting reaction mixture was added NaOH solution (1.2 equiv.), and extracted with EtOAc. The pH of the aqueous phase was adjusted to 1 by adding 1N (aq.) HCl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and subjected to silica gel. A white solid **S1** (1.62 g, 32%) was obtained after flash chromatography: TLC R_f = 0.40 (EtOAc/hexanes = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.29 (d, J = 5.0 Hz, 2H), 6.89 (d, J = 5.0 Hz, 2H), 5.05 (s, 2H), 3.80 (s, 3H), 2.42 (dt, J =7.5, 5.0 Hz, 4H), 1.93-1.92 (m,

2H); ^{13}C NMR (500 MHz, $CDCl_3$), δ178.8, 172.8, 159.6, 130.1, 128.0, 114.0, 66.2, 55.3, 33.2, 32.9, 19.8.

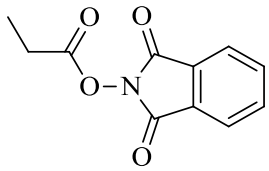


***N*-(4-((4-methoxybenzyloxy)carbonyl)butanoyloxy)phthalimide 1**. Following the general procedure, the reaction of **S1** (1.31 g, 5.0 mmol), NOP (0.87 g, 5.25 mmol) and DCC (1.08 g, 5.25 mmol) in DCM for 11 h afforded **1** as a white solid (0.90 g, 43%) after flash chromatography: TLC R_f = 0.14 (EtOAc/hexanes = 1/10); IR (KBr, thin film) 2950, 1814, 1787, 1516, 1248, 1185, 1162, 878, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ7.88-7.87 (m, 2H), 7.79-7.77 (m, 2H), 7.30 (d, *J* =10.0 Hz, 2H), 6.89 (d, *J* =10.0 Hz, 2H), 5.08 (s, 2H), 3.80 (s, 3H), 2.75 (t, *J* =7.5 Hz, 2H),2.52 (t, *J* =7.5 Hz, 2H), 2.13-2.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 172.4, 169.0, 161.9, 159.6, 134.8, 130.1, 128.9, 128.0, 124.0, 114.0, 66.2, 55.3, 32.8, 30.0, 19.9; HRMS-ESI (m/z) calculated for $C_{21}H_{19}NO_7$ $[M+Na]^+$: 420.1056, found 420.1054.

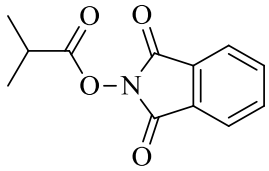


4-methoxybenzyl 5-(((diphenylmethylene)amino)oxy)-5-oxopentanoate 1-oxime. To a solution of **S1** (0.4 g, 1.59 mmol, 1.0 equiv.), benzophenone oxime (0.34 g, 1.75 mmol, 1.1 equiv.) and DCC (0.36 g, 1.75 mmol, 1.1 equiv.) in DCM (10 mL) was added DMAP (23 mg, 0.19 mmol, 0.1 equiv.), and the reaction mixture was stirred at 25 ^{o}C overnight until TLC indicated the complete consumption of **S1**. The resulting suspension was filtered and the filtrate was concentrated in vacuo, and afforded 1-oxime as a colorless oil (0.43 g, 63%) after flash chromatography (15%, EtOAc/hexanes): TLC R_f = 0.25 (EtOAc/hexanes = 1/5); IR (KBr, thin film) 3647, 3523, 3447, 3060, 3000, 2955, 2837, 2359, 2250, 2057, 1965, 1893, 1768, 1736, 1613, 1587, 1515, 1445, 1418, 1304, 1076, 914, 822, 732, 698, 672, 646, 562, 522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ7.58 (d, *J* = 7.2 Hz, 2H), 7.44-7.40 (m, 4H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.29-7.25 (m, 4H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.02 (s, 2H), 3.76 (s, 3H), 2.40 (t, *J* = 7.2 Hz, 2H),

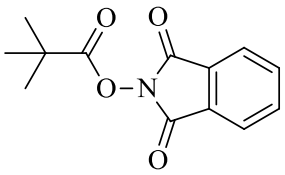
2.35 (t, *J* = 7.6 Hz, 2H), 1.91 (quint, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 172.4, 170.2, 164.8, 159.4, 134.4, 132.3, 130. 7, 129.8, 129.4, 128.8, 128.5, 128.2, 128.1, 128.0, 127.8, 113.7, 65.8, 55.0, 32.9, 31.7, 19.6; HRMS-ESI (m/z) calculated for $C_{26}H_{25}NO_5$ $[M+Na]^+$: 454.1627, found 454.1625.



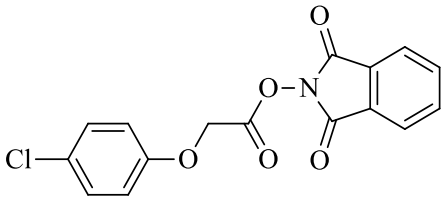
***N*-(n-propionoyloxy)phthalimide 4a** (CAS: 90467-37-1). Following the general procedure, the reaction of propionic acid (0.83 g, 11 mmol), NOP (1.63 g, 10 mmol) and DCC (2.31 g, 11 mmol) in DCM for 3.5 h afforded **4a** as a white solid (1.7 g, 69%) after flash chromatography (20% EtOAc/hexanes): TLC R_f = 0.25 (EtOAc/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.90-7.86 (m, 2H), 7.80-7.77 (m, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 170.3, 161.9, 134.7, 128.9, 123.9, 24.5, 8.7.



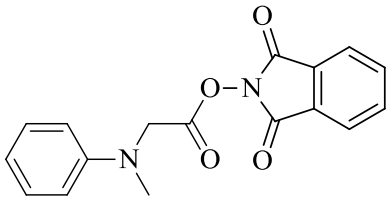
***N*-(isobutyryloxy)phthalimide 5a**. Following the general procedure, the reaction of isobutyric acid (0.99 g, 11 mmol), NOP (1.69 g, 10 mmol) and DCC (2.06 g, 10 mmol) in DCM for 13 h afforded **5a** as a white solid (2.38 g, 72%) after flash chromatography (20% EtOAc/hexanes): TLC R_f = 0.33 (EtOAc/hexanes = 1/20); IR (KBr, thin film) 2991, 1813, 1781, 1743, 1189, 1055, 877, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.90-7.86 (m, 2H), 7.81-7.77 (m, 2H), 3.02 (m, *J* = 6.8 Hz, 1H), 1.39 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 173.0, 162.0, 134.7, 128.9, 123.9, 31.7, 18.79; HRMS-ESI (m/z) calculated for $C_{12}H_{11}NO_4$ $[M+Na]^+$: 256.0569, found 256.0580.



***N*-(pivalyloxy)phthalimide 6a** (CAS: 84379-72-6). Following the general procedure, the reaction of pivalic acid (2.04 g, 20 mmol), NOP (3.59 g, 22 mmol) and DCC (4.53 g, 22 mmol) in DCM for 24 h afforded **6a** as a white solid (2.91 g, 58%) after flash chromatography (1/15/15, MeOH/DCM/hexanes): TLC R_f = 0.41 (EtOAc/hexanes = 1/20); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.88 (dd, J = 5.4 and 3.1 Hz, 2H), 7.78 (dd, J = 5.4 and 3.1 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 174.4, 162.1, 134.7, 129.1, 123.9, 38.4, 27.0.

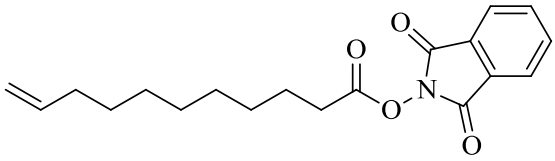


***N*-((2-(4-chlorophenoxy)acetoyloxy)phthalimide 7a** (CAS: 109524-11-0). Following the general procedure, the reaction of 2-(4-chlorophenoxy)acetic acid (1.86 g,10 mmol), NOP (1.79 g, 11 mmol) and DCC (2.27 g, 11 mmol) in DMF for 24 h afforded **7a** as a white solid (2.60 g, 79%) after flash chromatography (15%,EtOAc/hexanes): TLC R_f = 0.50 (EtOAc/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.90 (m, 2H), 7.81 (m, 2H), 7.29 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 5.02 (s, 2H); ^{13}C NMR (100MHz, $CDCl_3$), δ 165.3, 161.5, 155.9, 135.0, 129.7, 128.8, 127.5, 124.2, 116.2, 63.7.

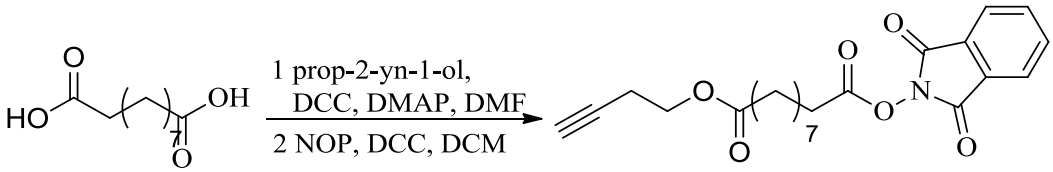


***N*-(2-(*N*-methyl-*N*-phenylamino))acetoyloxy)phthalimide 8a**. Following the general procedure, the reaction of 2-(*N*-methyl-*N*-phenylamino)acetic acid[8] (0.50 g, 3 mmol), NOP (0.53 g, 3.3 mmol) and DCC (0.706 g, 3.3 mmol) in DCM for 15 h afforded **8a** as a white solid (0.56 g, 60%) after flash chromatography (15%, EtOAc/hexanes): TLC R_f = 0.36 (20% EtOAc

/hexanes); IR (KBr, thin film) 2937, 1815, 1789, 1742, 1600, 1504, 1367, 1183, 1061, 764, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.91-7.82 (m, 2H), 7.81-7.71 (m, 2H), 7.35-7.26 (m, 2H), 6.81 (d, J = 8.2 Hz, 3H), 4.47 (s, 2H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.1, 161.7, 148.2, 134.8, 129.4, 128.9, 124.0, 118.4, 112.9, 52.2, 39.4; HRMS-ESI (m/z) calculated for $C_{17}H_{14}N_2O_4$ $[M+H]^+$: 311.1028, found 311.1026.

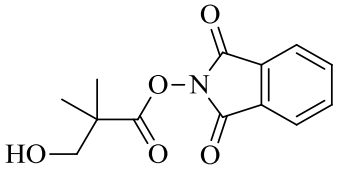


***N*-(undec-10-enoyloxy)phthalimide 14a**. Following the general procedure, the reaction of 10-undecenoic acid (1.88 g,10 mmol), NOP (1.70 g, 10.5 mmol) and DCC (2.19 g, 10.5 mmol) in DCM for 27 h afforded **14a** as a yellow oil (2.58 g, 77%) after flash chromatography (20%, EtOAc/hexanes): TLC R_f = 0.45 (EtOAc/hexanes = 1/20); IR (KBr, thin film) 3075, 2928, 2855, 1816, 1789, 1745, 1467, 1364, 1186, 1134, 1080, 969, 878, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.90-7.86 (m, 2H), 7.81-7.76 (m, 2H), 5.86-5.76 (m, 1H), 5.01 (md, J = 17.6 Hz, 1H), 4.93 (md, J = 10.4 Hz, 1H), 4.95 (dm, J = 10.4 Hz, 1H), 2.68 (t, J = 7.6 Hz, 2H), 2.07 (dd, J = 6.8 and 7.2 Hz, 2H), 1.82 (quint, J = 7.6 Hz, 2H), 1.46-1.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 169.6, 161.1, 139.1, 134.7, 128.9, 123.9, 114.1, 33.8, 31.0, 29.2, 29.0, 29.0, 28.8, 28.8, 24.6; HRMS-ESI (m/z) calculated for $C_{19}H_{23}NO_4$ $[M+Na]^+$: 352.1523, found 352.1519.



***N*-(10-(but-3-yn-1-yloxy)-10-oxodecanoyloxy)phthalimide 15a**. To a solution of sebacic acid (5.84 g, 2.5 mmol), DCC (1.59 g, 7.5 mmol), and DMAP (0.21 g, 1.5 mmol) in DMF (50 mL) was added 3-butyn-1-ol (0.37 g, 5.24 mmol), and stirred for 17.5 h until TLC indicated the complete consumption of sebacic acid. The solid was removed by filtration, and the filtrate was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield **S15a**. Following the general procedure, the reaction of **S15a**, NOP (1.66 g, 10.2 mmol) and DCC (2.22 g, 10.5 mmol) in DCM for 28 h afforded **15a** as a white oil (1.63 g, 82%,

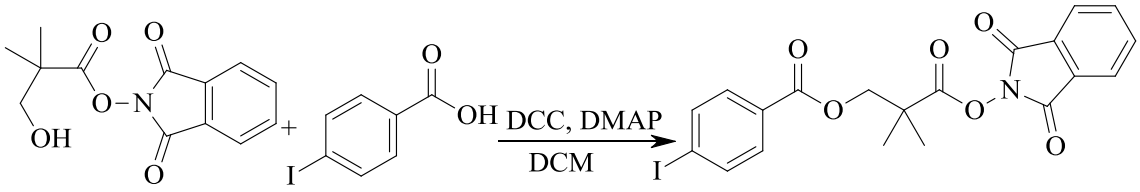
two steps) after flash chromatography (15%, EtOAc/hexanes): TLC R_f = 0.13 (EtOAc/hexanes = 1/10); IR (KBr, thin film) 3258, 2928, 2854, 1819, 1789, 1745, 1470, 1366, 1186, 1146, 1294, 1104, 1072, 962, 879, 864, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.91-7.87 (m, 2H), 7.81-7.77 (m, 2H), 4.20 (t, *J* = 6.8 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.55 (dt, *J* = 2.4 and 6.8 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.01 (t, *J* = 2.8 Hz, 1H), 1.82 (q, *J* = 7.2 Hz, 2H), 1.66-1.60 (m, 2H), 1.46-1.41 (m, 2H), 1.34 (br, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 173.5, 169.6, 162.0, 134.7, 128.9, 123.9, 80.1, 69,8, 61.9, 34.1, 30.9, 28.9, 28.9, 28.7, 24.8, 24.6, 19.0; HRMS-ESI (m/z) calculated for $C_{22}H_{25}NO_6$ $[M+Na]^+$: 422.1575, found 422.1574.



***N*-(3-hydroxypivaloxy)phthalimide S16a**. Following the general procedure, the reaction of 3-hydroxypivalic acid (3.56 g, 30 mmol), NOP (5.88 g, 36 mmol) and DCC (6.81 g, 33 mmol) in DCM for 1.5 h afforded **S16a** as a white solid (5.90 g, 75%) after flash chromatography (20%, EtOAc/hexanes): TLC R_f = 0.14 (EtOAc/hexanes = 1/10); ^1H NMR (400 MHz, $CDCl_3$), δ 7.90 (dd, *J* = 5.4 and 3.2 Hz, 2H), 7.81 (dd, *J* = 5.5 and 3.1 Hz, 2H), 3.77 (d, *J* = 7.3 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 1H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 173.0, 162.2, 134.9, 128.8, 124.1, 69.8, 45.0, 21.6.

***N*-(3-((4-bromobenzoyl)oxy)-2,2-dimethylpropanoyloxy)phthalimide 16a**. A solution of **S16a** (2.60 g, 10 mmol), 4-Bromobenzoic acid (2.23 g, 11 mmol), DCC (2.31 g, 11 mmol) and DMAP (0.12 g, 1 mmol) in DCM (20 mL) was stirred at 25 ^oC for 2 h until TLC indicated the complete consumption of **S16a**. The solid was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by flash-column chromatography (33%, DCM/hexanes), affording **16a** as a white solid (2.43 g, 51%): TLC R_f = 0.26 (EtOAc/hexanes = 1/20); IR (KBr, thin film) 2982, 1786, 1810, 1724, 1467, 1269, 1186, 1061, 878, 756, 696, 518

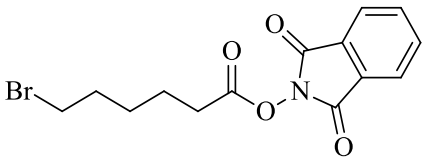
cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.01 (d, J = 9.0 Hz, 2H), 7.90-7.87 (m, 2H), 7.81-7.77 (m, 2H), 7.63 (d, J = 8.5 Hz, 2H), 4.51 (s, 2H), 1.53 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 171.8, 165.4, 161.7, 134.7, 131.8, 131.4, 128.9, 128.5, 128.4, 123.9, 70.0, 42.7, 22.3; HRMS-ESI (m/z) calculated for $C_{20}H_{16}BrNO_6$ $[M+Na]^+$: 468.0046, found 468.0053.



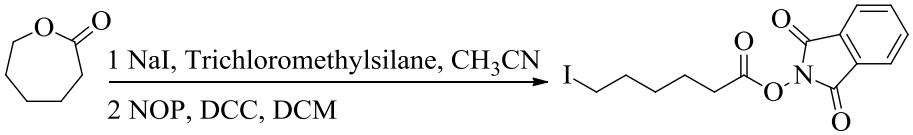
***N*-(3-((4-Iodobenzoyl)oxy)-2,2-dimethylpropanoyloxy)phthalimide 17a**. A solution of **S16a** (2.64g, 10 mmol), 4-iodobenzoic acid (2.73 g, 11 mmol), DCC (2.34 g, 11 mmol) and DMAP (0.13 g, 1 mmol) in DCM (20 mL) was stirred at 25 ^{o}C for 1.5 h until TLC indicated the complete consumption of **S16a**. The solid was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by flash-column chromatography (33%, DCM/hexanes), affording ester **17a** as a white solid (1.61 g, 33%): TLC R_f = 0.26 (EtOAc/hexanes = 1/20) ; IR (KBr, thin film) 2982, 1786, 1810, 1745, 1586, 1369, 1268, 1117, 1030, 1007, 753, 696, 518 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.88-7.85 (m, 2H), 7.84-7.82 (m, 4H), 7.78-7.75 (m, 2H), 4.51 (s, 2H), 1.53 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 171.7, 165.5, 161.6, 137.7, 134.6, 131.2, 129.0, 128.7, 123.8, 101.1, 69.8, 42.5, 22.3; HRMS-ESI (m/z) calculated for $C_{20}H_{16}INO_6$ $[M+Na]^+$: 515.9916, found 515.9915.

***N*-(6-azidohexanoyloxy)phthalimide 18a**. A solution of 6-bromohexanoic acid (2.17 g, 11.1 mmol) and sodium azide (1.37 g, 21.1 mmol) in DMF was stirred at 50 ^{o}C for 20.5 h until TLC indicated the complete consumption of 6-bromohexanoic acid. The resulting reaction mixture was cooled to the room temperature, diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford **S18a** (1.51 g, 86%). Following the general procedure, the reaction of 6-azidohexanoic acid (1.50 g, 9.5 mmol), NOP (1.65 g, 10.1 mmol) and DCC (2.06 g, 10.1 mmol) in DCM for 24 h afforded **18a** as a white solid (1.51 g,

53%) after flash chromatography (1/15/15, MeOH/DCM/hexanes): TLC R_f = 0.26 (EtOAc/hexanes = 1/20); IR (KBr, thin film) 2939, 2866, 2097, 1815, 1745, 1787, 1467, 1363, 1186,1135, 1064, 968, 878, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.88 (dd, J = 5.3 and 3.1 Hz, 2H), 7.79 (dd, J = 5.4 and 3.1 Hz, 2H), 3.32 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 7.3 Hz, 2H), 1.83 (quint, J = 7.4 Hz, 2H), 1.67 (m, 2H), 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 169.3, 161.9, 134.8, 128.9, 124.0, 51.1, 30.8, 28.4, 25.9, 24.2; HRMS-ESI (m/z) calculated for $C_{14}H_{14}N_4O_4$ $[M+Na]^+$: 325.0905, found 325.0907.

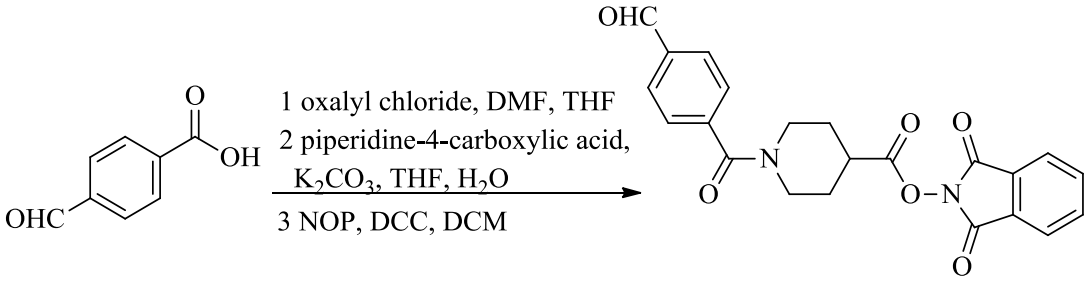


***N*-(6-bromohexanoyloxy)phthalimide 19a** (CAS: 329379-01-3). Following the general procedure, the reaction of 6-bromohexanoic acid (1.98 g,10 mmol), NOP (1.68 g, 10.3 mmol) and DCC (2.08 g, 10.1 mmol) in DCM overnight afforded **19a** as a white solid (2.4 g, 71%) after flash chromatography (1/15/15, MeOH/DCM/hexanes): TLC R_f = 0.33 (EtOAc/hexanes = 1/20); ^1H NMR (400 MHz, $CDCl_3$), δ 7.89 (dd, J = 5.3 and 3.2 Hz, 2H), 7.80 (dd, J = 5.4 and 3.1 Hz, 2H), 3.44 (t, J = 6.7 Hz, 2H), 2.70 (t, J = 7.3 Hz, 2H), 1.93 (quint, J = 6.9 Hz, 2H), 1.83 (quint, J = 7.4 Hz, 2H), 1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 169.3, 162.0, 134.8, 128.9, 124.0, 33.2, 32.2, 30.8, 27.4, 23.9.



***N*-(6-iodohexanoyloxy)phthalimide 20a**. To a stirred solution of sodium iodide (3.75 g, 25 mmol) in 40 mL CH_3CN were successively added ε-caprolactone (2.13 mL, 20 mmol) and trichloromethylsilane (2.33 mL, 20 mmol). The reaction mixture was refluxed for 3 h and then was poured into the ice water. The resulting mixture was extracted with ether (3 × 50 mL), and the combined organic layers were washed with the sodium thiosulfate solution, water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the 6-iodohexanoic acid **S20a**. The crude product was directly thrown to the next steps without further purification. Following the general procedure, the reaction of 66-iodohexanoic acid, NOP (3.26

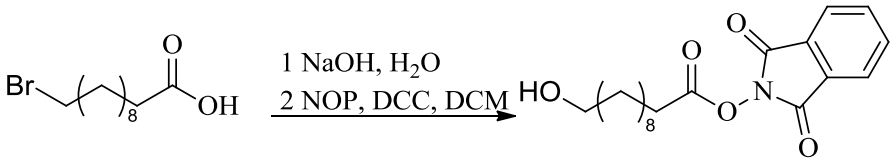
g, 20 mmol) and DCC (4.12 g, 20.2 mmol) in DCM for 10 h afforded **20a** as a white solid (5.69 g, 73%) after flash chromatography (20%, EtOAc/hexanes): TLC R_f = 0.50 (EtOAc/hexanes = 1/4); IR (KBr, thin film) 3520, 3061, 2935, 2860, 1788, 1745, 1467, 1366, 1186, 1081, 1015, 878, 785, 697, 518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.89 (dd, J = 5.5 and 3.1 Hz, 2H), 7.80 (dd, J = 5.5 and 3.1 Hz, 2H), 3.22 (t, J = 7.0 Hz, 2H), 2.70 (t, J = 7.4 Hz, 2H), 1.93-1.78 (m, 4H), 1.60-1.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 169.5, 162.1, 134.9, 129.0, 124.1, 33.1, 30.9, 29.8, 23.8, 6.3; HRMS-ESI (m/z) calculated for $C_{14}H_{14}INO_4$ $[M+Na]^+$: 409.9857, found 409.9860.



N-(**1-(4-formylbenzoyl)piperidine-4-carboxylyloxy)phthalimide 21a**. To a solution of 4-formylbenzoic acid (3.00 g, 20 mmol) and DMF (60 μL) in THF (50 mL) was added oxalyl chloride (2.25 mL, 24 mmol) at 0 ^oC, and stirred for 30 min. Then the reaction mixture was allowed to warm to the room temperature, and stirred for 14 h until TLC indicated the complete consumption of 4-formylbenzoic acid. The resulting reaction mixture was concentrated in vacuo to afford 4-formylbenzoyl chloride **S21a**. To a solution of isonipecotic acid (2.66 g, 20.7 mmol) and K_2CO_3 (5.70 g, 40 mmol) in H_2O (60 mL) was added slowly a solution of **S21a** in THF (20 mL) at 0 ^oC, and stirred for 30 min at 0 ^oC. Then the reaction mixture was warmed to the room temperature, and stirred for 18 h until TLC indicated the complete consumption of **S21a**. To the resulting reaction mixture was added K_2CO_3 adjusted pH to 10, and extracted with EtOAc. To the aqueous phase was added 1N (aq.) HCl adjusted pH to 3, extracted with EtOAc, dried over anhydrous Na_2SO_4, concentrated in vacuo and subjected to silica gel (50%, EtOAc/DCM) to afford a white solid 1-(4-formylbenzoyl)piperidine-4-carboxylic acid **S21a'** (2.85 g, 55%). Following the general procedure, the solution of **S21a'** (2.85 g, 11 mmol), NOP (1.98 g, 12 mmol) and DCC (2.53 g, 12 mmol) in DMF for 13 h afforded **21a** as a white solid (2.76 g, 62%) after flash chromatography (50%, EtOAc/hexanes): TLC R_f = 0.11 (EtOAc/hexanes = 1/2); IR (KBr, thin film) 2864, 2016, 1893, 1813, 1785, 1742, 1632, 1439, 1020, 878, 697; ^1H NMR (400

MHz, DMSO-d_6), δ 10.07 (s, 1H), 8.01-7.95 (m, 6H), 7.66 (d, J = 8.4 Hz, 2H), 4.41 (br, 1H), 3.54 (br, 1H), 3.32-3.13 (br, 3H), 2.13 (br, 1H), 2.00 (br, 1H), 1.75 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6), δ 192.7, 170.9, 168.0, 161.8, 141.6, 136.4, 135.5, 129.6, 128.1, 127.4, 124.0, 37.5; HRMS-ESI (m/z) calculated for $C_{22}H_{18}N_2O_6$ $[M+Na]^+$: 429.1051, found 429.1057.

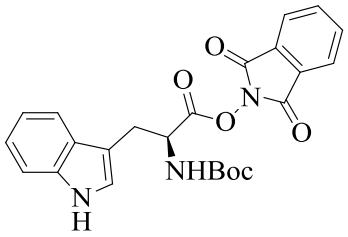
Note: CH_2 of piperidine ring is difficult to be determined by ^{13}C NMR, while CH of piperidine ring is successfully determined by ^{13}C NMR.



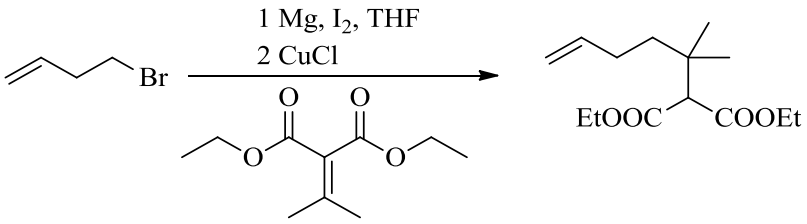
***N*-(11-hydroxyundecanolyloxy)phthalimide 22a**. A solution of 11-Bromoundecanoic acid (5.94 g, 30 mmol) and NaOH solution (210 mL, 2M) was refluxed and stirred for 18 h. The resulting reaction mixture was cooled to 0 ^{o}C, and added 1N (aq.) HCl adjusted pH to 3. The white solid was filtered, washed with water, and dried affording **S22a** (5.82 g, 96%). Following the general procedure, the reaction of **S22a** (1.01 g, 5.0 mmol), NOP (0.82 g, 5.0 mmol) and DCC (1.08 g, 5.25 mmol) in DMF for 1 h afforded **22a** as a white solid (0.83 g, 48%) after flash chromatography (20%, EtOAc/hexanes): TLC R_f = 0.22 (EtOAc/hexanes = 1/5); IR (KBr, thin film) 3328, 2921, 2851, 1827, 1789, 1743, 1466, 1375, 1186, 1078, 1054, 963, 880, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.91-7.88 (m, 2H), 7.81-7.80 (m, 2H), 3.6 (t, *J* = 8.4 Hz, 2H), 2.69 (t, *J* = 9.6 Hz, 2H), 1.83-1.74 (m, 2H), 1.59-1.55 (m, 2H), 1.44-1.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 169.6, 162.0, 134.7, 128.9, 123.9, 63.0, 32.8, 31.0, 29.4, 29.3, 29.2, 29.0, 28.7, 25.7, 24.6; HRMS-ESI (m/z) calculated for $C_{19}H_{25}NO_5$ $[M+Na]^+$: 370.1627, found 370.1625.

5-((1,3-dioxoisoindolin-2-yl)oxy)-5-oxopentanoic acid 23a (CAS: 1104567-88-5). To a solution of glutaric anhydride (1.27 g, 11 mmol) in DCM (10 mL) was added NOP (1.65 g, 10 mmol) and DMAP (1.49 g, 12 mmol) in DMC (10 mL) at 0 ^{o}C, and stirred at 0^{o}C for 28 h until TLC indicated the complete consumption of NOP. The reaction mixture was washed with 1N (aq.) HCl, dried over anhydrous Na_2SO_4, concentrated in vacuo and subjected to silica gel (20%,

EtOAc/DCM). A white solid **23a** (1.62 g, 48%) was obtained after flash chromatography: TLC R_f = 0.16 (EtOAc/hexanes = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.90-7.87 (m, 2H), 7.81-7.78 (m,2H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.69 (d, *J* = 7.0 Hz, 2H), 2.16 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 178.3, 168.9, 161.9, 134.8, 128.8, 124.0, 32.4, 30.0, 19.5.

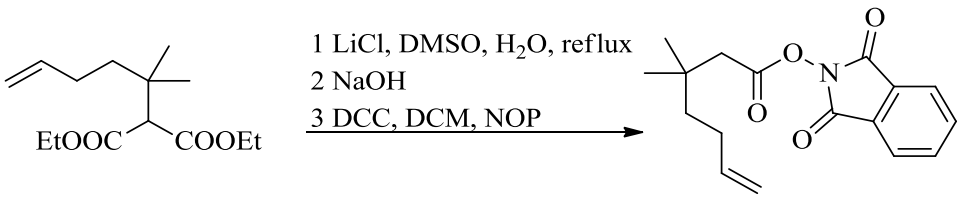


(S)-1,3-dioxoisoindolin-2-yl 2-((tert-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoate 24a. Following the general procedure, the reaction of *N*-Boc-*L*-Tryptophan (1.04 g, 3.4 mmol), NOP (0.62 g, 3.8 mmol) and DCC (0.78 g, 3.8 mmol) overnight afforded **24a** as a white solid (1.2 g, 78%) after flash chromatography (10%, EtOAc/DCM): TLC R_f = 0.1 (EtOAc/hexanes = 1/5); IR (KBr, thin film) 3409, 1735, 1703, 1508, 1152, 1052, 889, 689, 652, 486 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6), δ 8.00-7.99 (m, 4H), 7.72(d, *J* = 7.5 Hz, 1H), 7.46-7.43 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.08 (m, 1H), 6.50 (d, *J* = 8.0 Hz, 0.72H), 6.05 (br, 0.21H), 4.99-4.95 (m, 0.77H), 4.83 (br, 0.23H), 3.63 (dd, *J* = 5.5 and 15 Hz, 1H), 3.45 (dd, *J* = 8.5 and 15 Hz, 1H), 1.41 and 1.38 (s and s, 9H); ^{13}C NMR (125 MHz, Acetone-d_6), δ 169.3, 161.6, 155.2, 136.7, 135.3, 128.8, 127.6, 124.2, 123.8, 121.5, 119.0, 118.2, 111.5, 109.1, 79.0, 53.3, 27.6; HRMS-ESI (m/z) calcultated for $C_{24}H_{23}N_3O_6$ $[M+Na]^+$: 472.1478, found 472.1479.



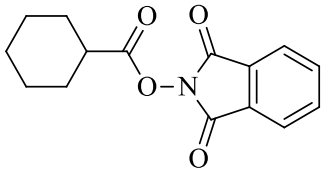
Diethyl 2-(2-methylhex-5-en-2-yl)malonate S25. To a mixture of Mg (553.5 mg, 23 mmol) and a small crystal of I_2 in THF (10 mL) at room temperature was added 4-bromobut-1-ene (2.0 mL, 19.7 mmol). The resulting mixture was heated to 50 ℃ and stirred for 1.5 h before it was cooled to room temperature. To a solution of this freshly prepared Grignard solution at -30 ℃ was added a suspension of CuCl (20 mg, 0.2 mmol) in THF (4 mL). To the resulting mixture was

added a solution of diethylisopropylidenemalonate (2.0 g, 10 mmol) in THF (3 mL). The resulting mixture was warmed to room temperature and stirred for 1.5 h before it was quenched with saturated NH_4Cl solution (100 mL). The resulting mixture was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in *vacuo* affording diester **S25** (2.0 g, 78 % over two steps) as a colorless oil after flash column chromatography (5%, EtOAc/ hexanes): TLC R_f = 0.20 (EtOAc/ Hexanes = 1/19); ^{1}H NMR (500 MHz, $CDCl_3$), δ 5.77 (m, 1H), 4.99 (dd, J = 17.1 and 1.5 Hz, 1H), 4.95-4.88 (m, 1H), 4.16 (q, J = 7.1 Hz, 4H), 3.32 (s, 1H), 2.08 (m, 2H), 1.55 (m, 2H), 1.25 (t, J = 7.1 Hz, 6H), 1.11 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$), δ 168.3, 138.8, 114.3, 60.9, 59.7, 40.1, 36.2, 28.3, 25.0, 14.1.

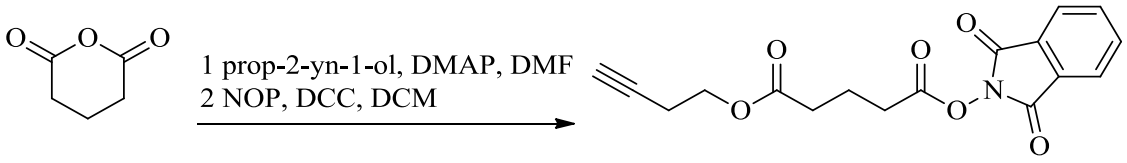


1,3-dioxoisoindolin-2-yl 3,3-dimethylhept-6-enoate 25. To the solution of the **S25** (1.0 g, 3.9 mmol) in 10 mL DMSO and 1mL H_2O was added LiCl (164 mg, 3.9 mmol). The mixture was refluxed until the complete consumption of **S25**. The reaction mixture was allowed to cool down to room temperature, and the crude mixture was diluted with 50 mL H_2O and 100 mL ether. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved with 10 mL ethanol, and was added 5 mL 2 N NaOH. The mixture was heated to 50 ^{o}C under vigorous stirring. After the reaction reached completion based on TLC monitoring, the reaction was adjusted to pH = 1 with 2 N HCl. The mixture was extracted with EtOAc (30 mL × 3). The organic layer was separated, washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Following the general procedure, the reaction of the residue, NOP (0.66 g, 4.0 mmol) and DCC (0.87 g, 4.2 mmol) in DCM for 3 h afforded **25** as a yellow solid 0.56 g, 48% over three steps) after flash chromatography (10%, EtOAc/hexanes); TLC R_f = 0.60 (EtOAc/hexanes = 1/4); IR (KBr, thin film) 3522, 3064, 2964, 2933, 2874, 2855, 1813, 1788, 1744, 1641, 1468, 1371, 1186, 1067, 973, 878, 739, 697, 518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.88 (m, 2H), 7.79 (m, 2H), 5.84 (m, 1H), 5.05 (m, 1H), 4.99 (m, 1H), 2.55 (s, 2H), 2.18-2.04 (m, 2H), 1.58-

1.49 (m, 2H), 1.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.8, 162.0, 138.8, 134.7, 129.0, 123.9, 114.4, 42.6, 41.2, 33.8, 28.6, 27.1; HRMS-ESI (m/z) calculated for $C_{17}H_{19}NO_4$ $[M+Na]^+$: 324.1207, found 324.1206.

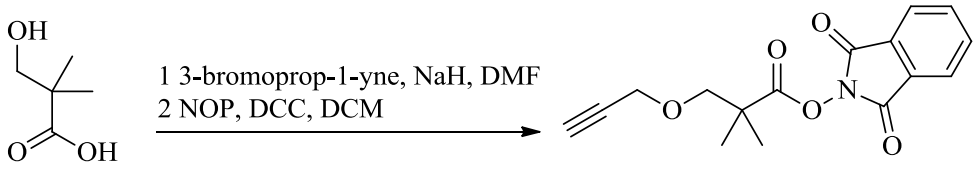


***N*-(cyclohexanecarboxylyloxy)phthalimide 28** (CAS: 126812-30-4). Following the general procedure, the reaction of cyclohexanecarboxylic acid (1.06 g, 8 mmol), NOP (1.45 g, 8.8 mmol) and DCC (1.92 g, 8.8 mmol) in DCM overnight afforded **28** as a white solid (1.56 g, 69%) after flash chromatography (15% EtOAc/hexanes): TLC R_f = 0.30 (EtOAc/hexanes = 1/20); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.90-7.86 (m, 2H), 7.80-7.76 (m, 2H), 2.78 (tt, J = 11.2 and 3.6 Hz, 2H), 2.12-2.08 (m, 2H), 1.86-1.82 (m, 2H), 1.71-1.61 (m, 3H), 1.44-1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 172.8, 162.1, 134.6, 129.0, 123.9, 40.4, 28.8, 25.4, 25.0.

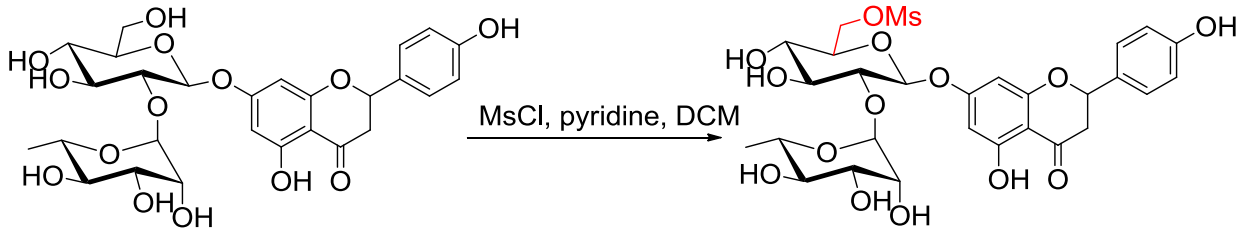


***N*-(4-((but-3-ynyloxy)carbonyl)butanoyloxy)phthalimide S32'-Alkyne**. To a stirred solution of but-3-yn-1-ol (5.0 g, 71 mmol) and glutaricanhydride (8.19 g, 71.7 mmol) in DMF (100 mL) was added DMAP (0.88 mg, 7.2 mmol) at 0 ^{o}C. After 1 h, the reaction mixture was stirred at room temperature for 17 h. The resulting mixture was concentrated in vacuo, and was added EtOAc (100 mL). The organic phase was washed with 1N HCl solution twice and saturated brine once, and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the 5-(but-3-yn-1-yloxy)-5-oxopentanoic acid (7.02 g) which was directly thrown to the next steps without further purification. Following the general procedure, the reaction of 5-(but-3-yn-1-yloxy)-5-oxopentanoic acid (3.0 g, 16.3 mmol), NOP (2.80 g, 17.1mmol) and DCC (3.52 g, 17.1 mmol) in DCM for 17 h afforded **S32'** as a white solid (2.67 g, 50% over two steps) after flash chromatography (50%, EtOAc/hexanes): TLC R_f = 0.65 (EtOAc/hexanes = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.90-7.88 (m, 2H), 7.81-7.79 (m, 2H), 4.24 (t, J = 6.8 Hz, 2H), 2.81 (t, J = 7.2

Hz, 2H), 2.58-2.52 (m, 4H), 2.16-2.0 (m, 2H), 2.05 (t, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ172,1, 169.0, 161.8, 134.8, 128.8, 123.9, 80.0, 70.1, 62.1, 32.6, 30.0, 19.8, 18.9.

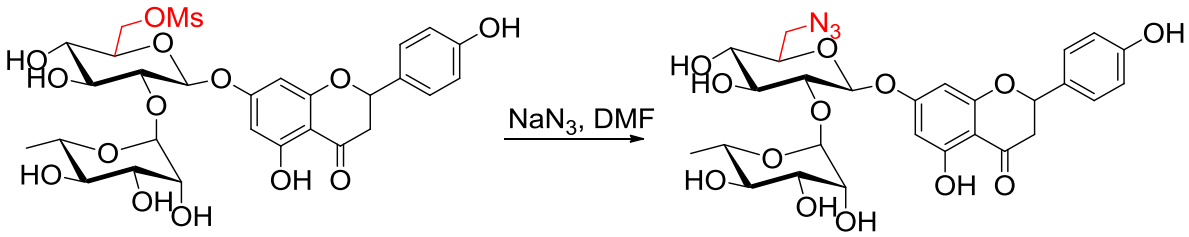


***N*-(2,2-dimethyl-3-(prop-2-ynyloxy)propanoyloxy)phthalimide S32-Alkyne**. To the solution of 2-(hydroxymethyl)-2-methylpropanoic acid (1.18 g, 10 mmol) in DMF (50 mL) was added NaH (0.89, 22 mmol) at 0 ^{o}C, and was stirred for 10 min. The 3-bromoprop-1-yne (1.31 g, 11 mmol) in toluene (10 mL) was added to the reaction mixture, and stirred for 30 min. The resulting mixture was stirred at room temperature for 5 h. 200 mL H_2O was added to the reaction mixture, and was extracted with EtOAc (50 mL). The aqueous phase was added 1N (aq.) HCl adjusted pH to 3, and then was extracted with EtOAc (50 mL x 3). The organic phase was dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford 2,2-dimethyl-3-(prop-2-ynyloxy)propanoic acid which was directly thrown to the next steps without further purification. Following the general procedure, the reaction of 2,2-dimethyl-3-(prop-2-ynyloxy)propanoic acid, NOP (1.63 g, 10 mmol) and DCC (2.06 g, 10 mmol) for 13 h afforded **S32** as a white solid (0.3 g, 10% over two steps) after flash chromatography (15%, EtOAc/hexanes): TLC R_f = 0.55 (EtOAc/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$), δ7.89-7.86 (m, 2H), 7.79-7.77 (m, 2H), 4.28 (d, J = 2.4 Hz, 2H), 3.71 (s, 2H), 2.46 (t, J = 2.4 Hz, 1H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ172.4, 161.9, 134.7, 129.0, 123.9, 79.4, 75.7, 74.6, 58.8, 43.3, 22.2.

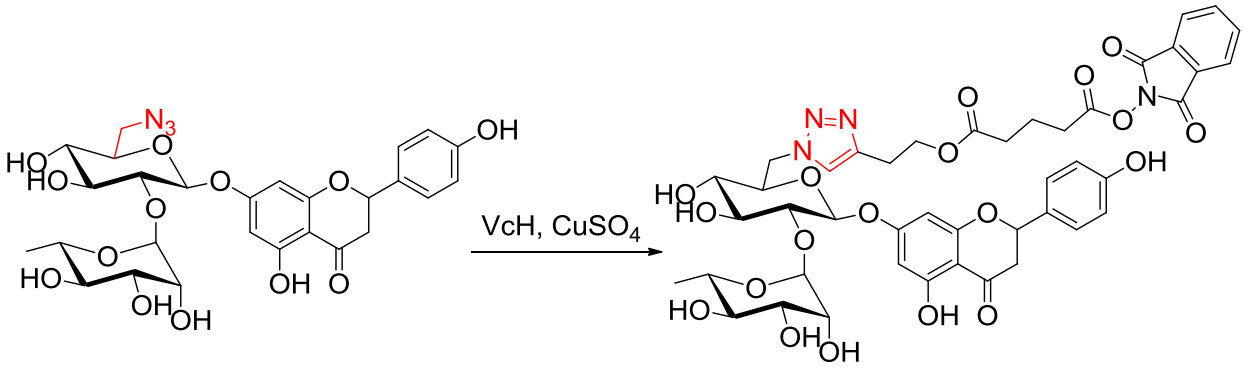


6-*O*-Methanesulfonylnaringin, **S32-OMs**. To a solution of naringin (5.18 g, 8.9 mmol, the commercially available naringin was a mixture of (2R) and (2S)-naringin, dr~1:1[9]) in DCM (150 mL) and pyridine (40 mL) was added methanesulfonyl chloride (0.80 mL, 9.8 mmol) at 0 ^{o}C. The reaction mixture was slowly warmed to room temperature and stirred for 12 h. The

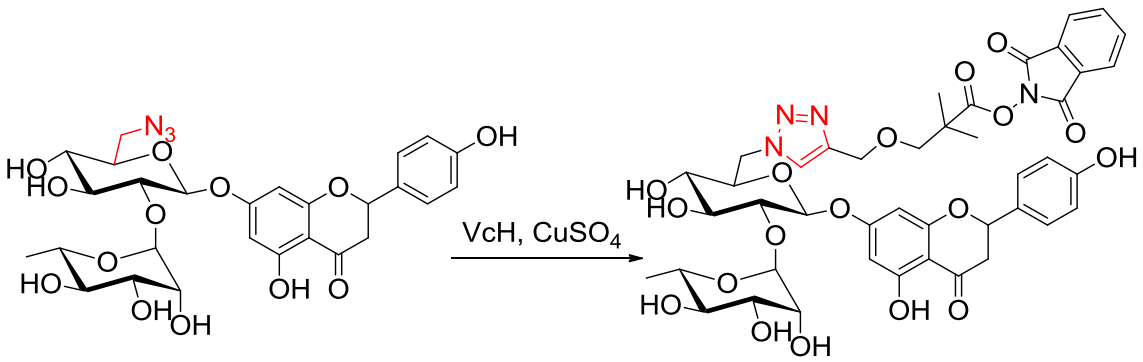
resulting mixture was concentrated in vacuo and added H_2O (200 mL). The aqueous phase was extracted with EtOAc (300 mL), then the organic phase was washed with saturated brine twice, dried over anhydrous Na_2SO_4. and concentrated in vacuo to afford **S32-OMs** (1.52 g, 26%) as a yellow solid after flash chromatography (10%, MeOH/EtOAc): TLC R_f = 0.25 (MeOH/EtOAc = 1/10); ^{1}H NMR (400 MHz, CD_3OD), δ 7.33 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 6.8 Hz, 2H), 6.20-6.16 (m, 2H), 5.41-5.36 (m, 1H), 5.25-5.24 (m, 1H), 5.18 (m, 1H), , 4.59-4.53 (m, 1H(CH_2)), 4.36-4.31 (m, 1H(CH_2)), 3.94 (t, J = 1.6 Hz, 1H), 3.90-3.84 (m, 1H), 3.78-3.73 (m, 1H), 3.68-3.57 (m, 3H), 3.41-3.37 (m, 2H), 3.24-3.13 (m, 1H), 2.98 and 2.97 (s, 3H(OMs)), 2.79 (m, 1H), 1.30 (d, J = 6.4 Hz, 3H).



6-Azido-6-deoxynaringin, **S32-N_3**. The solution of **S32-OMs** (1.52 g, 2.3 mmol) and NaN_3 (0.75 g, 11.5 mmol) in DMF (20 mL) was stirred at 50 ^{o}C under nitrogen for 80 h. After cool to room temperature, DMF was removed under vacuum, and the residue was dissolved in *n*-BuOH (50 mL). The organic phase was washed with saturated brine (50 mL) and H_2O (50 mL), and dried over Na_2SO_4 and concentrated in vacuo to afford **S32-N_3** (1.28 g, 91%) after flash chromatography (20%, MeOH/EtOAc): TLC R_f = 0.30 (MeOH/EtOAc = 1/4); IR (KBr, thin film) 3388, 2918, 2106, 1642, 1578, 1519, 1448, 1177, 1061, 978, 835, 557 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD), δ 7.33 (d, J = 7.6 Hz, 2H), 6.829 and 6.826 (d, J = 8.4 Hz, 2H), 6.18-6.15 (m, 2H), 5.41-5.35 (m, 1H), 5.25 (m, 1H), 5.16 (m, 1H), 3.93 (t, J = 1.6 Hz, 1H), 3.90-3.85 (m, 1H), 3.67-3.53 (m, 5H), 3.44-3.33 (m, 3H), 3.20-3.12 (m, 1H), 2.78 (m, 2 H), 1.30 (d, J = 6.0 Hz, 3H); HRMS-ESI (m/z) calculated for $C_{27}H_{37}N_3O_{13}$ $[M+Na]^+$: 628.1744, found 628.1749.



Oligosaccharides Modification 32'. A solution of **S32-N_3** (0.50 g, 0.83 mmol), **S32'-Alkyne** (0.55 g, 1.66 mmol), sodium ascorbates (34.4 mg, 0.17 mmol) and $CuSO_4$ (29.8 mmol, 0.17 mmol) in t-BuOH/H_2O (24/8 mL) was stirred at 50 ^oC under nitrogen for 3 h. The solvent was removed under vacuum to afforded **32'** (0.59 g, 75%) after flash chromatography (20%, MeOH/EtOAc): TLC R_f = 0.28 (MeOH/EtOAc = 1/4); IR (KBr, thin film) 3365, 2970, 2914, 1783, 1740, 1636, 1577, 1370, 1186, 1055, 834, 698 cm^{-1}; ^1H NMR (500 MHz, CD_3OD), δ 7.95-7.90 (m, 4H), 7.71 (s, 0.46H(CH)), 7.68 (s, 0.52H(CH)), 7.33 (m, 2H), 6.83 (m, 2H), 5.87-5.86 (m, 1H), 5.841 (d, *J* = 2.0 Hz, 0.51H), 5.818 (d, *J* = 2.0 Hz, 0.46H), 5.42 (m, 1H), 5.20 (m, 1H), 5.02 (m, 1H), 4.96-4.93 (m, 1H), 4.43-4.37 (m, 1H), 4.27-4.18 (m, 2H), 3.86-3.76 (m, 2H), 3.61-3.54 (m, 2H), 3.51 (m, 1H), 3.39 (m, 1H), 3.25-3.12 (m, 2H), 2.99-2.87 (m, 2H), 2.79-2.73 (m, 1H), 2.72-2.69 (m, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.02-1.95 (m, 2H), 1.301 and 1.296 (d, *J* = 6.0 Hz, 3H); HRMS-ESI (m/z) calculated for $C_{44}H_{46}N_4O_{19}$ $[M+Na]^+$: 957.2629, found 957.2648.

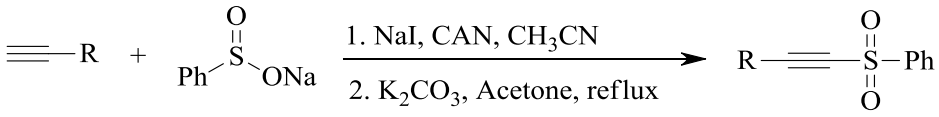


Oligosaccharides Modification 32. A solution of **S32-N_3** (0.70 g, 1.15 mmol), **S32-Alkyne** (0.693 g, 2.3 mmol), sodium ascorbates (45 mg, 0.23 mmol) and $CuSO_4$ (36 mmol, 0.23 mmol) in t-BuOH/H_2O (20/6 mL) was stirred at 50 ^oC under nitrogen for 2.5 h. The solvent was removed under vacuum to afford **32** (0.39 g, 67%) after flash chromatography (20%,

MeOH/EtOAc): TLC R_f = 0.28 (MeOH/EtOAc = 1/4); IR (KBr, thin film) 3544, 2387, 2232, 2100, 1993, 1843, 1771, 1683, 1558, 945, 750, 590 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 8.126 (s, 0.46H(CH)), 8.063 (s, 0.47H(CH)), 7.89-7.88 (m, 4H), 7.311 and 7.304 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.75-5.74 (m, 1H), 5.700 (d, *J* = 2.4 Hz, 0.46H), 5.580 (d, *J* = 2.4 Hz, 0.47H), 5.33-5.24 (m, 1H), 5.23-5.21 (m, 1H), 5.03-4.94 (m, 2H), 4.60-4.43 (m, 3H), 3.91-3.90 (m, 1H), 3.84-3.76 (m, 2H), 3.63-3.58 (m, 3H), 3.55-3.46 (m, 2H), 3.39-3.33 (m, 1H), 3.20-3.01 (m, 1H), 2.73-2.64 (m, 1H), 1.32-1.22 (m, 6H); HRMS-ESI (m/z) calculated for $C_{43}H_{46}N_4O_{18}$ $[M+H]^+$: 907.2877, found 907.2880.

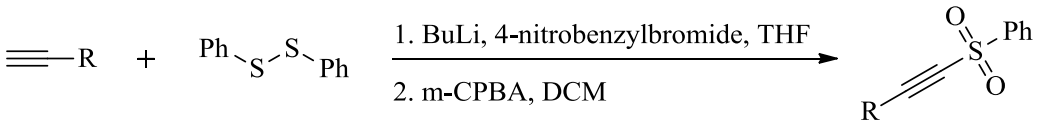
ii. Synthesis of Alkynyl Sulfones

Procedure A[10]



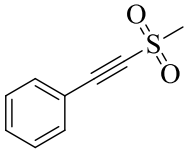
To a solution of terminal alkyne (1.0 equiv.), NaI (1.2 equiv.), and sodium benzenesulfinate (1.2 equiv.) in acetonitrile (0.1 M) was added ceric ammonium nitrate (CAN, 2.5 equiv.) at 25 ^{o}C under nitrogen, and stirred for 2 h until TLC indicated the complete consumption of the terminal alkyne. The resulting reaction mixture was filtered, diluted with water, and extracted with DCM twice. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo to yield the vinyl iodide. The vinyl iodide was directly dissolved in acetone (0.5 M), added K_2CO_3 (4.0 equiv.), and heated to reflux until TLC or NMR indicated the complete consumption of the vinyl iodide. The reaction mixture was cooled to 0 ^{o}C, diluted with H_2O, and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography to afford the alkynyl sulfone.

Procedure B[11]

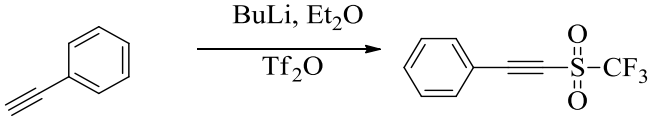


To a solution of terminal alkyne (1.0 equiv.) in THF (0.5 M) was added *n*-BuLi (1.1 equiv., 2.5 M in THF) at -78 ^{o}C. After stirring for 30 min, a solution of dimethyl disulfide (1.1 equiv.) in THF (0.75 M) was added. The reaction mixture was warmed to 25 ^{o}C and stirred for additional 2 h. To trap the resulting phenyl thiol, 4-nitrobenzyl bromide (1.2 equiv.) was added after cooling to -40 ^{o}C, and then the reaction mixture was warmed to 25 ^{o}C and stirred for additional 1 h. After quenched with saturated NH_4Cl, extracted with EtOAc, and dried over anhydrous Na_2SO_4, the organic layer was concentrated in vacuo to afford the alkynyl thioether. The crude alkynyl thioether was dissolved in DCM (0.5 M), added 3-chloroperbenzoic acid (mCPBA, 2.4 equiv., 80%) at 0 ^{o}C, and stirred until TLC indicated the complete consumption of the thioether (typically with 3 h). The resulting reaction mixture was quenched with saturated $Na_2S_2O_8$

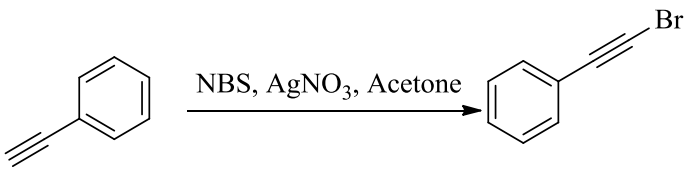
solution, extracted with DCM, washed with saturated Na_2CO_3 and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography to afford the alkynyl sulfone.



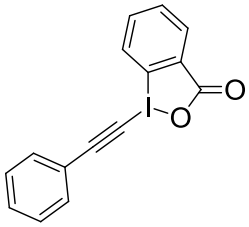
1-(2-(methylsulfonyl)ethynyl)benzene 2a (CAS: 24378-05-0). Following the general procedure B, the reaction of phenylacetylene (1.55 g, 15 mmol), *n*-BuLi (6.6 mL, 16.5 mmol, 2.5 M in THF), dimethyldisulfide (1.5 mL, 1.6 mmol), 4-Nitrobenzylbromide (3.84 g, 18 mmol) and mCPBA (10.5 g, 36 mmol, 80%) afforded a white solid **2a** (0.86 g, 45%) after flash chromatography (15%, EtOAc/hexanes): R_f = 0.22 (EtOAc/hexanes = 1/10); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.61 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 3.31 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$), δ 132.8, 131.8, 128.8, 117.5, 91.5, 84.4, 46.8.



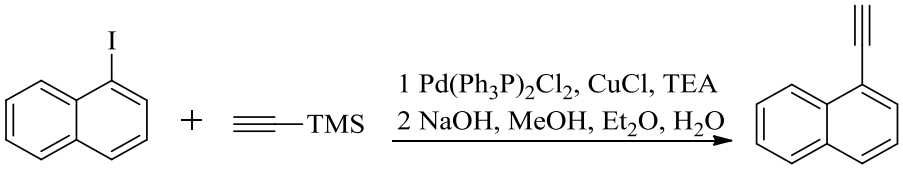
1-(2-(trifluoromethylsulfonyl)ethynyl)benzene 2b (CAS: 52843-77-3).[12] Phenylacetylene (2.0 mL, 18 mmol) was added to the solution of *n*-BuLi (8 mL, 19.2 mmol, 2.5 M in THF) in Et_2O (30 mL) at -78 ^{o}C, and stirred for 1 h. The resulting reaction mixture was added to the solution of trifluoroacetic anhydride (3.5 mL, 18 mmol) in Et_2O (10 mL) at -78^{o}C, and stirred for 1 h. Then, the reaction mixture was warmed to 0 ^{o}C, and stirred for 30 min. The resulting reaction mixture was quenched and diluted with H_2O, extracted with Et_2O, dried over anhydrous Na_2SO_4, concentrated in vacuo and subjected to silica gel. A white solid **2b** (3.99 g, 95%) was obtained after flash chromatography (100%, hexanes); R_f = 0.42 (Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.70 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 133.7, 133.4, 129.1, 122.8 (q, J_{C-F} = 321, CF_3), 115.8, 100.8, 77.3; F NMR (400 MHz, $CDCl_3$), δ -79.65.



1-(2-bromoethynyl)benzene 2c (CAS: 932-87-6). To a solution of phenylacetylene (2.05 g, 20 mmol) and *N*-bromosuccinimide (NBS, 10.5 g, 89 mmol) in acetone (130 mL) was added $AgNO_3$ (0.7 g, 4 mmol), and stirred at 25 ^oC until NMR indicated the complete consumption of phenylacetylene. The resulting reaction mixture was concentrated in vacuo, and filtered through a pad of silica gel with hexanes. The resulting mixture was concentrated in vacuo and subjected to silica gel chromatography. A yellow solid **2c** (2.05 g, 56%) was obtained after flash chromatography (100%, hexanes): TLC R_f = 1.0 (Hexanes); ^1H NMR (500 MHz, $CDCl_3$), δ 7.46-7.44 (m, 2H), 7.36-7.29 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 132.0, 128.7, 128.4, 122.7, 80.1, 49.8.

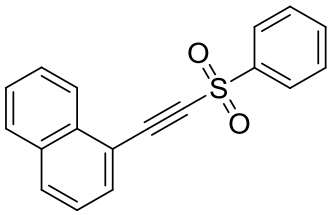


1-(Phenylethynyl)-1,2-benziodoxol-3(1H)-one 2d (CAS:181934-31-6). It was prepared according to the literature [3]. ^1H NMR (400 MHz, $CDCl_3$), δ 8.46–8.39 (m, 1H), 8.29–8.22 (m, 1H), 7.77 (td, *J* = 7.3, 6.8, 4.3 Hz, 2H), 7.64–7.56 (m, 2H), 7.54–7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.8, 135.0, 133.0, 132.6, 131.7, 131.5, 130.9, 128.9, 126.4, 120.7, 116.3, 106.7, 50.3.

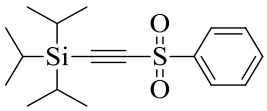


1-ethynylnaphthalene S4b (CAS: 15727-65-8). To a solution of 1-naphthyliodide (3.61 g, 14 mmol), cuprous iodide (0.14 g, 0.42 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.30 g, 0.42 mmol) in triethylamine (10 mL) was added (trimethylsilyl)acetylene (1.61 g, 15.4 mmol), and stirred at 25 ^oC for 40 min. The resulting reaction mixture was concentrated in vavuo

to yield the triisopropyl(naphthalen-1-ylethynyl)silane. The triisopropyl(naphthalen-1-ylethynyl)silane was dissolved in MeOH (100mL) and Et_2O (100 mL) solution, and added a solution of NaOH (2.5 M) in H_2O (40 mL). The reaction mixture was stirred at 25 ^oC for 18 h until NMR indicated the complete consumption of material. The resulting reaction mixture was added 1N (aq.) HCl solution adjusted pH to 5, and extracted with Et_2O. The combined organic phase was washed with water, dried over anhydrous Na_2SO_4, concentrated in vacuo and subjected to silica gel. A yellow oil **S4b** (2.11 g, 97%) was obtained after flash chromatography (100%, hexanes).^{1}H NMR (400 MHz, $CDCl_3$), δ 8.37 (d, J = 10.8 Hz, 1H), 7.86 (d, J = 10.8 Hz, 2H), 7.75 (d, J = 9.6 Hz, 1H), 7.60 (m, 2H), 7.44 (t, J = 10 Hz, 1H), 3.47 (s, 1H).

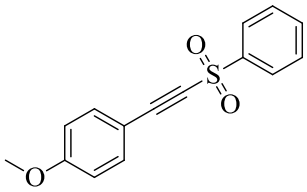


1-(2-(phenylsulfonyl)ethynyl)naphthalene 4b (CAS: 908290-02-8). Following the general procedure A, the reaction of **S4b** (2.11 g, 13.8 mmol), NaI (2.48 g, 16.6 mmol), sodium benzenesulfinate (2.73 g, 16.6 mmol), CAN (19.0 g, 34.5 mmol) and K_2CO_3 (3.83 g, 27.6 mmol) for 2 h, respectively, afforded a white solid **4b** (2.73 g, 67%) after flash chromatography (10%, EtOAc/hexanes): R_f = 0.33 (EtOAc/hexanes = 1/20); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.17 (d, J = 7.5 Hz, 2H), 8.10 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 6.5 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.64-7.53 (m, 4H), 7.46 (t, J = 8.0 Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$), δ 142.0, 134.2, 133.1, 132.8, 132.3, 129.4, 128.6, 128.0, 127.4, 127.1, 125.2, 125.0, 115.3, 92.5, 89.8.

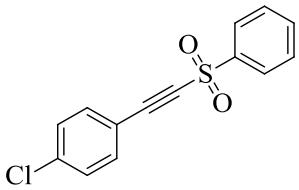


Triisopropyl(2-(phenylsulfonyl)ethynyl)silane 7b (CAS: 120948-15-4). Following the general procedure B, the reaction of triisopropylsilylacetylene (1.81 g, 10 mmol), *n*-BuLi (4.6 mL, 11 mmol, 2.5 M in THF), diphenyldisulfide (2.6 g, 12 mmol), 4-Nitrobenzylbromide (2.57 g, 12 mmol) and mCPBA (4.98 g, 27 mmol, 80%) afforded a colorless oil **7b** (2.52 g, 83%) after flash

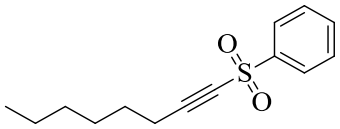
chromatography (2%, EtOAc/hexanes): R_f = 0.43 (EtOAc/hexanes = 1/50); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 1.12-0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 142.1, 134.0, 129.2, 127.2, 100.9, 100.6, 18.3, 10.8.



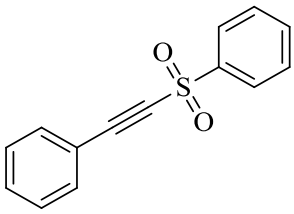
1-(2-(4-methoxyphenyl)ethynylsulfonyl)benzene 10b (CAS: 126613-16-9). Following the general procedure B, the reaction of 4-methoxyphenylacetylene (1.08 g, 8.2 mmol), *n*-BuLi (3.5 mL, 9.0 mmol, 2.5 M in THF), diphenyldisulfide (1.71 g, 7.8 mmol) 4-nitrobenzylbromide (1.91 g, 8.8 mmol) and mCPBA (8.43 g, 36 mmol, 80%) afforded a white solid **10b** (1.34 g, 61%) after flash chromatography (15%, EtOAc/hexanes): R_f = 0.22 (EtOAc/hexanes = 1/10); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 9.2 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 162.1, 142.1, 134.7, 133.9, 129.3, 127.2, 114.4, 109.4, 94.7, 84.6, 55.4.



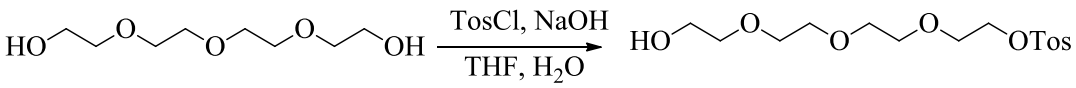
1-(2-(4-chlorophenyl)ethynylsulfonyl)benzene 11b (CAS: 126613-18-1). Following the general procedure A, the reaction of 4-chlorophenylacetylene (1.83 g, 13.5 mmol), NaI (2.46 g, 16.4 mmol), sodium benzenesulfinate (2.74 g, 16.7 mmol) and CAN (19.3 g, 35.2 mmol) for 2 and 14 h, respectively, afforded a white solid **11b** (1.32 g, 35%) after flash chromatography (20%, EtOAc/hexanes): R_f = 0.27 (EtOAc/hexanes = 1/20); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.09 (d, *J* = 7.2 Hz, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 141.5, 138.1, 134.3, 133.9, 129.4, 129.8, 127.5, 116.3, 92.0, 86.1.



1-(oct-1-ynylsulfonyl)benzene 12b (CAS: 120948-15-4). Following the general procedure B, the reaction of 1-octyne (1.67 g, 15 mmol), *n*-BuLi (6.6 mL, 16.5 mmol, 2.5 M in THF), diphenyldisulfide (3.68 g, 17 mmol), 4-Nitrobenzylbromide (3.84 g, 17.9 mmol) and mCPBA (8.85 g, 36 mmol, 80%) afforded a white oil **12b** (1.84 g, 58%) was obtained after flash chromatography (15%, EtOAc/hexanes); R_f = 0.40 (EtOAc/hexanes = 1/20); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.01 (d, J = 7.2 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 7.6 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 1.58 (q, J = 7.2 Hz, 2H), 1.36-1.21 (m, 6H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 142.0, 133.9, 129.2, 127.1, 98.0, 78.1, 31.0, 28.3, 26.8, 22.3, 18.9, 13.9.

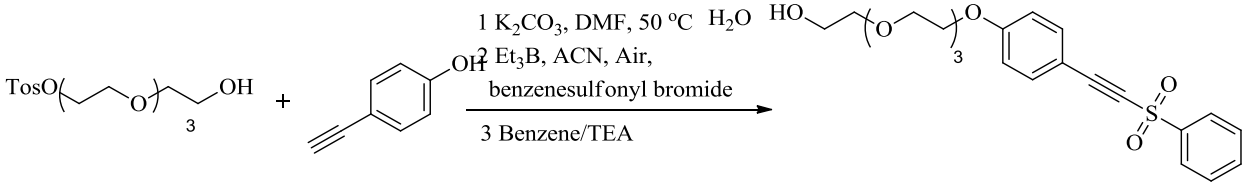


1-(2-phenylethynylsulfonyl)benzene 27 (CAS: 5324-64-1). Following the procedure A, the reaction of phenyl acetylene (2.70 g, 26.5 mmol), NaI (4.85 g, 32.3 mmol), sodium benzenesulfinate (5.34 g, 32.6 mmol) and CAN (37.2 g, 67.9 mmol) for 2h and 18 h, respectively, afforded **27** (3.79 g, 97%) as a white solid after flash chromatography (20%, EtOAc/hexanes): TLC R_f = 0.36 (EtOAc/hexanes = 1/20); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.09 (d, J = 8.0 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 8.0 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 141.7, 134.1, 132.6, 131.5, 129.3, 128.6, 127.3, 117.7, 93.4, 85.2.



2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethanol S33b (CAS: 77544-60-6). To a solution of tetraethyleneglycol (26.85 g, 138 mmol) and NaOH (0.95 g, 23.8 mmol) in THF/H_2O (10/10 mL) was added p-toluenesulfonyl chloride (3.94 g, 20.7 mmol) in THF (60 mL) slowly at 0 ^{o}C for 1 h.

Then the reaction mixture was stirred at room temperature for 14 h. The resulting mixture was extracted with EtOAc and saturated NH_4Cl solution, and the organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **S33b** (6.10 g, 84%) without further puritification: TLC R_f = 0.1 (EtOAc/hexanes = 1/1); ^{1}H NMR (400 MHz, Acetone-d_6), δ 7.83 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 4.18-4.15 (m, 2H), 3.68-3.65 (m, 14H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6), δ 145.8, 134.3, 130.8, 128.7, 73.5, 71.2, 71.2, 71.1, 71.1, 70.7, 69.3, 62.0, 21.6.



2-(2-(2-(2-(4-((phenylsulfonyl)ethynyl)phenoxy)ethoxy)ethoxy)ethoxy)ethanol 33. A solution of 4-hydroxyphenylacetylene[13] (1.07 g, 9.1 mmol), **S33b** (2.60 g, 7.5 mmol) and K_2CO_3 (3.10 g, 22.5 mmol) in DMF (25 mL) was heated to 50 ^{o}C and stirred for 15 h under nitrogen. The solvent was removed under vacuum, and the residue was purified by flash chromatography to afford 2-(2-(2-(2-(4-ethynylphenoxy)ethoxy)ethoxy)ethoxy)ethanol (1.86 g, 85%): TLC R_f = 0.12 (EtOAc/hexanes = 1/1). Then to the solution of 2-(2-(2-(2-(4-ethynylphenoxy)ethoxy)ethoxy)ethoxy)ethanol (1.40 g, 4.8 mmol), benzenesulfonyl bromide[14] (1.35 g, 6.1 mmol) in ACN (50 mL) was add Et_3B solution (1.40 mL, 1M in THF), and the reaction mixture was stirred for 12 h under air. The resulting mixture was concentrated in vacuo to afford (E)-bromo vinylsulfones through a SiO_2 pad (100%, EtOAc), which was directly thrown to the next steps without further purification. Then (E)-bromo vinylsulfones was dissolved in benzene and TEA (10 and 10 mL), and stirred for 48 h at room temperature. After removing the solvent, the residue was purified by flash chromatography (75% to 100%, EtOAc/hexanes) to afford **33** (0.51 g, 25% over two steps): TLC R_f = 0.25 (EtOAc/hexanes = 3/1); IR (KBr, thin film) 3409, 2874, 2174, 2093, 1602, 1508, 1472, 1448, 1327, 1309, 1159, 1085, 861, 786, 724, 637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.08-8.06 (m, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.0 Hz, 2H), 7.47 (dt, J = 9.0 and 2.0 Hz, 2H), 6.91 (dt, J = 9.0 and 2.0 Hz, 2H), 4.16 (t, J = 4.5 Hz, 2H), 3.86 (t, J = 5.0 Hz, 2H), 3.72-3.65 (m, 10 H), 3.60-3.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 161.3, 142.0, 134.6, 133.9, 129.2, 127.2, 115.0, 109.5, 94.6, 84.5,

72.4, 70.7, 70.5, 70.4, 70.1, 69.3, 67.6, 61.6; HRMS-ESI (m/z) calculated for $C_{22}H_{26}O_7S$ $[M+Na]^+$: 457.1293, found 457.1291.

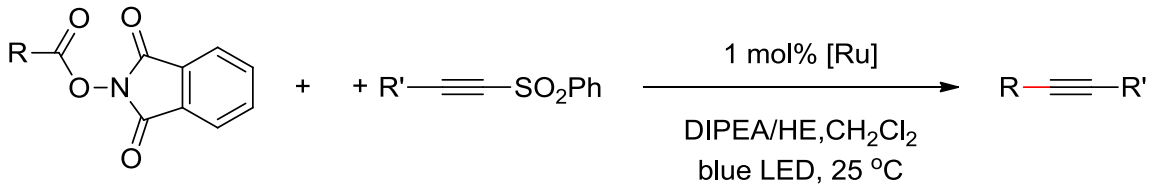
iii. Synthesis of Catalysts

Tris(bipyridyl)ruthenium(II) bis(hexafluorophosphate) $Ru(bpy)_3(PF_6)_2$[15]. Following a slightly modified literature procedure, a solution of 2,2'-bipyridine (5.648 g, 36 mmol) and $RuCl_3 \cdot 2H_2O$ (1.76 g, 6.7 mmol) in ethylene glycol (80 mL) was stirred at 180 ^oC for 2 h. After cooling to room temperature, a solution of KPF_6 (4.85 g, 26.3 mmol) in H_2O (20 mL) was added and the red solid precipitated out. The red solid was filtered and washed with water to remove the excess ruthenium salts. The resulting solid was recrystallized in acetone/ethyl ether (1/1, v/v) to afford $Ru(bpy)_3(PF_6)_2$ as a red solid (4.84 g, 81%). ^1H NMR (400 MHz, DMSO-d_6), δ 8.85 (d, J = 8.4 Hz, 6H), 8.20 (dt, J = 1.2 and 8.0 Hz, 6H), 7.74 (d, J = 4.8 Hz, 6H), 7.55 (dt, J = 1.2 and 6.6 Hz, 6H).

Tris(bipyridyl)ruthenium(II) dichloride $Ru(bpy)_3Cl_2$. A solution of 2, 2'-bipyridine (6.5 g, 41.6 mmol) and $RuCl_3 \cdot 2H_2O$ (2.20 g, 8.3 mmol) in DMF (100 mL) was refluxed for 6 h. After cooling to room temperature, the resulting reaction mixture was concentrated to 15 mL before added to the saturate solution of tetrabutylammonium chloride in acetone (50 mL).The precipitated red solid was filtered and recrystallized in H_2O to afford $Ru(bpy)_3Cl_2$ as a red solid (3.1 g, 51%); ^1H NMR (400 MHz, D_2O), δ 8.43 (d, J = 8.0 Hz, 6H), 7.95 (dt, J = 1.6 and 8.0 Hz, 6H), 7.72 (dt, J = 0.8 and 5.2 Hz, 6H), 7.26 (dt, J = 1.2 and 6.6 Hz, 6H).

VI. Decarboxylative Alkynylation Product Characterization

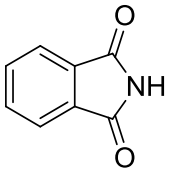
Standard Procedure:



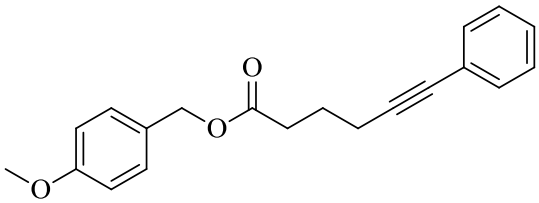
To a solution of alkyl *N*-acyloxyphthalimides (0.1 mmol, 1.0 equiv.), alkynyl sulfone (0.15 mmol, 1.5 equiv.), $Ru(bpy)_3(PF_6)_2$ (0.86 mg, 0.001 mmol, 0.01 equiv.) and hantzsch ester (HE, 38 mg, 0.15 mmol, 1.5 equiv.) in 1.0 mL DCM in a 5 mL clear-colored glass vial was added diisopropylethylamine (DIPEA, 35 μL, 0.2 mmol, 2.0 equiv.). The vial was sealed and exposed to 468 nm blue LED (two 4 W light bulbs 10 cm away from the vial, Figure S1) at room temperature with stirring until TLC indicated the complete consumption of alkyl *N*-acyloxyphthalimides (typically less than 30 min). The reaction mixture was concentrated and purified directly by column chromatography to afford the alkynylation adduct (Each reaction was performed in duplicates or triplicates).

*The heating effect from LED irradiation conditions above was minimal. With 12 hours irradiation, the increase of temperature was less than 3 ^{o}C.

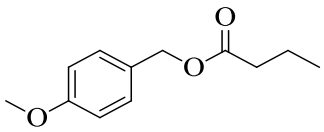
Figure S15 The Visible-Light-Induced Reaction Setup



Phthalimide 1P (CAS: 85-41-6). Following the standard procedure, the reaction of **1** (39.6 mg, 0.1 mmol) and **27** (37.0 mg, 0.15 mmol) for 30 min afforded phthalimide as a white solid (15.5 mg, >99% yield) after flash chromatography: TLC R_f = 0.10 (EtOAc/Hexanes = 1/5); ^{1}H NMR (500 MHz, Acetone-d_6), δ 10.1 (br, 1H), 7.86 (s, 4H); ^{13}C NMR (100 MHz, Acetone-d_6), δ 168.4, 134.1, 133.1, 122.9.

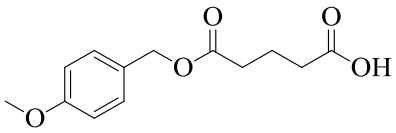


4-Methoxybenzyl 6-phenylhex-5-ynoate 3. Following the standard procedure, the reaction of **1** (39.5 mg, 0.1 mmol) and **27** (40.8 mg, 0.15 mmol) for 30 min afforded **3** as a colorless oil (23.6 mg, 77% yield) after flash chromatography: TLC R_f = 0.31 (EtOAc/hexanes = 1/20); IR (KBr, thin film) 2961, 2030, 1895, 1730, 1611, 1514, 1384, 1246, 1030, 756, 692, 558 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.39-7.36 (m, 2H), 7.31-7.25 (m, 5H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.06 (s, 2H), 3.80 (s, 3H), 2.55 (t, *J*= 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.97 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 173.1, 159.6, 131.5, 130.0, 128.2, 128.1, 127.6, 123.7, 113.9, 88.8, 81.4, 66.1, 55.3, 33.2, 23.9, 18.9; HRMS-ESI (m/z) calculated for $C_{20}H_{20}O_3$ $[M+Na]^+$: 331.1309, found 331.1305.

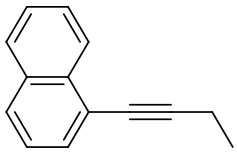


4-methoxybenzyl butyrate 3H (CAS: 6963-56-0). Following the standard procedure, the reaction of **1** (39.2 mg, 0.1 mmol) for 0.5 h afforded **3H** as a colorless oil (14.5 mg, 71% yield) after flash chromatography: TLC R_f = 0.30 (EtOAc/hexanes = 1/100); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.31 (dt, *J* = 8.8 and 2.8 Hz, 2H), 6.91 (dt, *J* = 8.4 and 3.2 Hz, 2H), 5.05 (s, 2H), 3.81

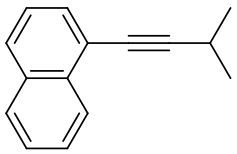
(s, 3H), 2.33 (t, J = 7.6 Hz, 2H), 1.71-1.61 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 173.6, 159.6, 130.0, 128.3, 113.9, 65.8, 55.3, 36.2, 18.4, 13.6.



4-((4-methoxybenzyloxy)carbonyl)butanoic acid 3C. Same as **S1**.

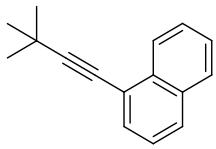


1-(but-1-ynyl)naphthalene 4. Following the standardprocedure, the reaction of **4a** (22.3 mg, 0.1 mmol) with **4b** (45.0 mg, 0.15 mmol) for 0.5 h afforded **4** as a colorless oil (12.9 mg, 70% yield) after flash chromatography: TLC R_f = 0.55 (Hexane); IR (KBr, thin film) 3058, 2975, 2936, 2231, 1930, 1810, 1586, 1506, 1432, 1375, 1318, 1017, 798, 773, 668, 568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.35 (d, J = 8.0 Hz, 1H),7.83 (d, J = 8.0 Hz, 1H),7.78 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.57-7.47 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 1.36 (t, J = 8.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 133.5, 133.2, 129.9, 128.2, 127.9, 126.4, 126.3, 126.2, 125.2, 121.7, 96.74, 77.9, 14.1, 13.4; HRMS-EI (m/z) calculated for $C_{14}H_{12}$ $[M]^+$: 180.0939, found 180.0941.

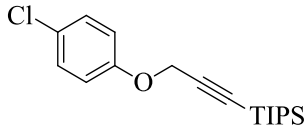


1-(3-methylbut-1-ynyl)naphthalene 5. Following the standard procedure, the reaction of **5a** (24.0 mg, 0.1 mmol) with **4b** (42.5 mg, 0.15 mmol) for 0.5 h afforded **5** as a colorless oil (14.7 mg, 74% yield) after flash chromatography: TLC R_f = 0.74 (Hexanes); IR (KBr, thin film) 3057, 2969, 2924, 2869, 2320, 2030, 1586, 1459, 1395, 1319, 1015, 798, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.34 (d, J = 10 Hz, 1H), 7.83 (d, J = 10 Hz, 1H), 7.78 (d, J = 10.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.57 (dt, J = 9.3 and 1.5 Hz, 1H), 7.51 (dt, J = 9.3 and 1.5 Hz, 1H), 7.41 (t, J = 9.5 Hz, 1H), 3.00-2.92 (m, 1H), 1.38 (d, J = 8.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ

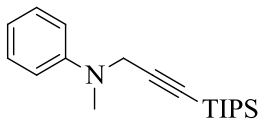
133.4, 133.2, 129.9, 128.2, 127.9, 126.4, 126.2, 125.2, 121.6, 100.9, 77.7, 23.2, 21.5; HRMS-EI (m/z) calculated for $C_{15}H_{14}$ $[M]^+$: 194.1096, found 194.1092.



1-(3,3-dimethylbut-1-ynyl)naphthalene 6 (CAS: 124153-66-8). Following the standard procedure, the reaction of **6a** (24.8 mg, 0.1 mmol) with **4b** (43.2 mg, 0.15 mmol) for 0.5 h afforded **6** as a colorless oil (16.5 mg, 79% yield) after flash chromatography: TLC R_f = 0.74 (Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.32 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 1.2 and 6.8 Hz, 1H), 7.57 (dt, J = 1.2 and 7.4 Hz, 1H), 7.51 (dt, J = 1.2 and 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 133.4, 133.2, 129.8, 128.2, 127.8, 126.4, 126.2, 126.1, 125.2, 121.7, 103.7, 77.03, 31.2, 28.4.

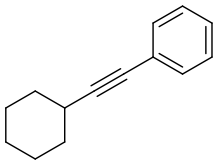


(3-(4-chlorophenoxy)prop-1-yn-1-yl)triisopropylsilane 7. Following the standard procedure, the reaction of **7a** (33.4 mg, 0.1 mmol) with **7b** (46.0 mg, 0.15 mmol) for 0.5 h afforded **7** as a colorless oil (23.1 mg, 73% yield) after flash chromatography: TLC R_f = 0.90 (EtOAc/hexanes = 1/100); IR (KBr, thin film) 2943, 2865, 2180, 1590, 1491, 1367, 1220, 1037, 882, 822, 678, 626 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.24 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 4.70 (s, 2H), 1.04 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 156.2, 129.1, 126.2, 116.6, 101.5, 89.7, 57.0, 18.5, 11.1; HRMS-ESI (m/z) calculated for $C_{18}H_{27}ClOSi$ $[M+Na]^+$: 345.1411, found 345.1412.

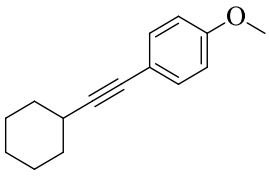


***N*-methyl-*N*-(3-(triisopropylsilyl)prop-2-yn-1-yl)aniline 8**. Following the standard procedure, the reaction of **8a** (30.7 mg, 0.1 mmol) with **7b** (50.0 mg, 0.15 mmol)for 0.5 h afforded **8** as a colorless oil (25.3 mg, 85% yield) after flash chromatography: TLC R_f = 0.52 (EtOAc/hexanes = 1/100); IR (KBr, thin film) 2942, 2890, 2864, 2166, 1601, 1503, 1462, 1237, 1110, 1033, 883,

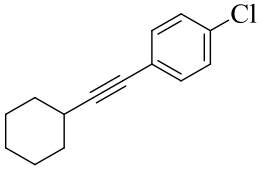
753, 689, 590 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ 7.25 (t, J = 8.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 2H), 4.06 (s, 2H), 2.96 (s, 3H), 0.99 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 149.4, 128.9, 118.3, 114.9, 103.1, 85.0, 43.8, 38.6, 18.5, 11.1; HRMS-ESI (m/z) calculated for $C_{19}H_{31}NSi$ $[M+H]^+$: 302.2297, found 302.2299.



1-(2-cyclohexylethynyl)benzene 9 (CAS: 33414-83-4). Following the standard procedure, the reaction of **28** (27.1 mg, 0.1 mmol) with **27** (37.3 mg, 0.15 mmol) for 0.5 h afforded **9** as a colorless oil (14.6 mg, 80% yield) after flash chromatography: TLC R_f = 0.74 (Hexanes); ^1H NMR (500 MHz, $CDCl_3$), δ 7.40 (dd, J = 8.0 and 2.0 Hz, 2H), 7.28-7.27 (m, 3H), 2.63-2.58 (m, 1H), 1.91-1.89 (m, 2H), 1.79-1.77 (m, 2H), 1.59-1.53 (m, 3H), 1.39-1.35 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 131.5, 128.1, 127.4, 124.1, 94.4, 80.5, 32.7, 29.7, 25.9, 24.9.

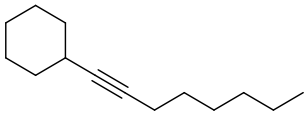


1-(2-cyclohexylethynyl)-4-methoxybenzene 10 (CAS: 870007-59-3). Following the standard procedure, the reaction of **28** (26.4 mg, 0.1 mmol) with **10b** (44.7 mg, 0.15 mmol) for 0.5 h afforded **10** as a colorless oil (17.6 mg, 85% yield) after flash chromatography: TLC R_f = 0.30 (Hexanes); ^1H NMR (400 MHz, $CDCl_3$), δ 7.34 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 2.59 (m, J = 4.0 Hz, 1H), 1.87-1.85 (m, 2H), 1.77-1.74 (m, 2H), 1.56-1.48 (m, 3H), 1.39-1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 158.9, 132.9, 116.3, 113.7, 92.8, 80.1, 55.2, 32.8, 29.7, 25.9, 25.0.

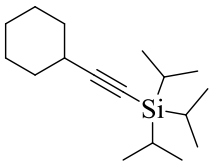


1-chloro-4-(2-cyclohexylethynyl)benzene 11 (CAS: 870007-54-8). Following the standard

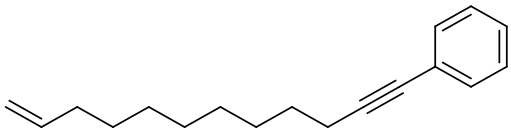
procedure, the reaction of **28** (26.4 mg, 0.1 mmol) with **11b** (41.7 mg, 0.15 mmol) for 0.5 h afforded **11** as a colorless oil (16.3 mg, 72% yield) after flash chromatography: TLC R_f = 0.84 (Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.33 (dt, J = 9.0 and 2.0 Hz, 2H), 7.27 (d, J = 8.5 and 2.5 Hz, 2H), 2.61 (m, J = 2.8 Hz, 1H), 1.91-1.87 (m, 2H), 1.79-1.73 (m, 2H), 1.56-1.50 (m, 3H), 1.38-1.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 133.3, 132.8, 128.4, 122.6, 96.5, 79.5, 32.6, 29.7, 25.9, 24.9.



(Oct-1-ynyl)cyclohexane 12 (CAS: 125641-94-3). Following the standard procedure, the reaction of **28** (26.4 mg, 0.1 mmol) with **12b** (80.0 mg, 0.3 mmol) for 0.5 h afforded **12** as a colorless oil (16.1 mg, 83% yield) after flash chromatography: TLC R_f = 0.89 (Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.34-2.30 (m, 1H), 2.17 (dt, J = 2.4 and 7.2 Hz, 2H), 1.80-1.75 (m, 2H), 1.72-1.65 (m, 2H), 1.51-1.23 (m, 14H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 84.6, 80.1, 33.2, 31.4, 29.2, 29.2, 28.5, 26.0, 25.0, 22.6, 18.8, 14.0.

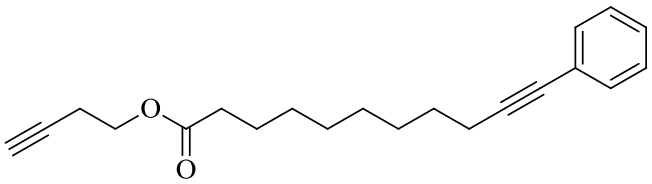


(2-cyclohexylethynyl)triisopropylsilane 13 (CAS: 196789-87-4). Following the standard procedure, the reaction of **28** (26.9 mg, 0.1 mmol) with **7b** (48.4 mg, 0.15 mmol) for 0.5 h afforded **13** as a colorless oil (18.8 mg, 72% yield) after flash chromatography: R_f = 1.00 (Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.48-2.43 (m, 1H), 1.80-1.67 (m, 4H), 1.54-1.43 (m, 3H), 1.38-1.26 (m, 3H), 1.09-0.96 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 113.6, 79.5, 32.7, 29.8, 26.0, 24.5, 18.6, 11.3.

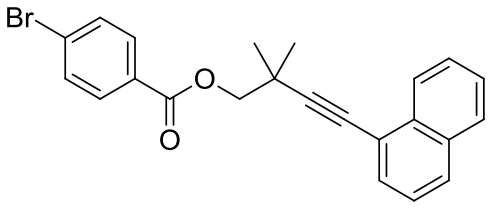


1-(dodec-11-en-1-ynyl)benzene 14. Following the standard procedure, the reaction of **14a** (33.2

mg, 0.1 mmol) with **27** (36.3 mg, 0.15 mmol) for 0.5 h afforded **14** as a colorless oil (17.8 mg, 73% yield) after flash chromatography: TLC R_f = 0.71 (Hexanes); IR (KBr, thin film) 3077, 2927, 2854, 2220, 2102, 1640, 1490, 1442, 910, 755, 691, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.40-7.37 (m, 2H), 7.30-7.25 (m, 3H), 5.86-5.76 (m, 1H), 5.02-4.96 (m, 1H), 4.94-4.92 (m, 1H), 2.42 (t, J = 7.2 Hz, 2H), 2.07-2.02 (m 2H), 1.64-1.56 (m, 2H), 1.48-1.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 139.2, 131.5, 128.1, 127.4, 124.1, 114.1, 90.4, 80.6, 33.8, 29.4, 29.1, 29.1, 28.9, 28.9, 28.7, 19.4; HRMS-EI (m/z) calculated for $C_{18}H_{24}$ $[M]^+$: 240.1878, found 240.1880.

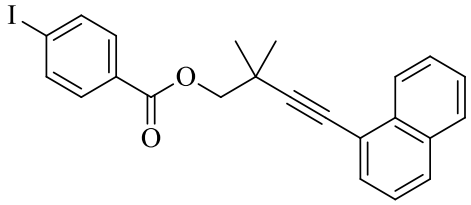


but-3-ynyl 12-phenyldodec-11-ynoate 15. Following the standard procedure, the reaction of **15** (39.6 mg, 0.1 mmol) with **27** (39.3 mg, 0.15 mmol) for 0.5 h afforded **15** as a colorless oil (26.2 mg, 72% yield) after flash chromatography: TLC R_f = 0.29 (EtOAc/hexanes = 1/100); IR (KBr, thin film) 3298, 2929, 2855, 2099, 1736, 1490, 1167, 756, 692, 637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ 7.40-7.37 (m, 2H), 7.30-7.25 (m, 3H), 4.20 (t, J = 6.5 Hz, 2H), 2.54 (dt, J = 6.5 and 2.5 Hz, 2H), 2.41 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 2.00 (t, J = 2.5 Hz, 1H), 1.67-1.57 (m, 4H), 1.46-1.43 (m, 2H), 1.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 173.5, 131.5, 128.1, 127.4, 124.0, 90.3, 80.6, 80.1, 69.8, 61.9, 29.1, 29.0, 28.9, 28.8, 28.7, 24.9, 19.4, 19.0; HRMS-ESI (m/z) calculated for $C_{21}H_{26}O_2$ $[M+Na]^+$: 333.1827, found 333.1825.

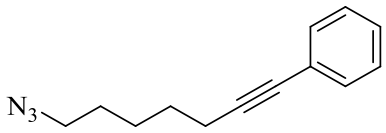


2,2-dimethyl-4-(naphthalen-1-yl)but-3-ynyl 4-bromobenzoate 16. Following the standard procedure, the reaction of **16a** (44.9 mg, 0.1 mmol) with **4b** (43.1 mg, 0.15 mmol) for 0.5 h afforded **16** as a white solid (35.7 mg, 89% yield) after flash chromatography: TLC R_f = 0.40 (EtOAc/hexanes = 1/100); IR (KBr, thin film) 3060, 2971, 2926, 2866, 2020, 1915, 1722, 1590,

1396, 1267, 1114, 1012, 799, 755, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.28 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7,83 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.61-7.57 (m, 3H), 7.59 (t, J = 7.6 Hz, 1H), 7.44-7.37 (m, 2H), 4.39 (s, 2H), 1.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.7, 133.3, 133.1, 131.8, 131.2, 130.1, 129.1, 128.3, 128.2, 128.2, 126.5, 126.3, 126.0, 125.2, 120.9, 98.8, 79.5, 72.4, 32.9, 26.3; HRMS-ESI (m/z) calculated for $C_{23}H_{19}BrO_2$ $[M+Na]^+$: 429.0466, found 429.0461.

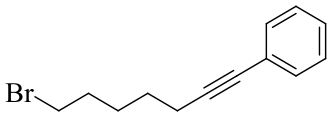


2,2-dimethyl-4-(naphthalen-1-yl)but-3-ynyl 4-iodobenzoate 17. Following the standard procedure, the reaction of **17a** (49.4 mg, 0.1 mmol) with **4b** (41.3 mg, 0.15 mmol) for 0.5 h afforded **17** as a white solid (36.0 mg, 81% yield) after flash chromatography: TLC R_f = 0.39 (EtOAc/hexanes = 1/100); IR (KBr, thin film) 3057, 2965, 2010, 1895, 1720, 1586, 1393, 1265, 1114, 1008, 799, 773, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.27 (d, J = 8.4 Hz, 1H), 7.85-7.77 (m, 6H), 7.61 (d, J = 6.8 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.44-7.37 (m, 2H), 4.38 (s, 2H), 1.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.9, 137.8, 133.3, 133.1, 131.1, 130.1, 129.6, 128.3, 128.2, 126.5, 126.3, 126.0, 125.1, 120.9, 100.9, 98.8, 79.5, 72.4, 32.9, 26.3; HRMS-ESI (m/z) calculated for $C_{23}H_{19}IO_2$ $[M+Na]^+$: 477.0328, found 477.0322.

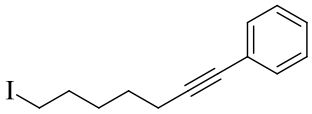


1-(7-azidohept-1-ynyl)benzene 18. Following the standard procedure, the reaction of **18a** (33.0 mg, 0.1 mmol) with **27** (33.9 mg, 0.15 mmol) for 0.5 h afforded **18** as a colorless oil (16.0 mg, 69% yield) after flash chromatography: TLC R_f = 0.26 (Hexanes); IR (KBr, thin film) 2938, 2860, 2095, 1508, 1490, 1260, 1070, 756, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.40-7.37 (m, 2H), 7.30-7.26 (m, 3H), 3.31 (t, J = 6.4 Hz, 2H), 2.45 (t, J = 6.5 Hz, 2H), 1.70-1.61 (m, 4H), 1.60-1.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 131.5, 128.2, 127.6, 123.9, 89.7, 80.9, 51.3, 28.4, 28.2, 26.0, 19.3; HRMS-ESI (m/z) calculated for $C_{13}H_{15}N_3$ $[2M+Na]^+$: 449.2418, found

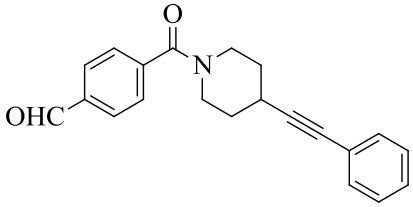
449.2424.



1-(7-bromohept-1-ynyl)benzene 19 (CAS: 92078-65-4). Following the standard procedure, the reaction of **19a** (33.2 mg, 0.1 mmol) with **27** (39.0 mg, 0.15 mmol) for 0.5 h afforded **19** as a colorless oil (19.4 mg, 79% yield) after flash chromatography: TLC R_f = 0.50 (Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.40-7.38 (m, 2H), 7.30-7.26 (m, 3H), 3.45 (t, J = 7.0 Hz, 2H), 2.45 (t, J = 6.5 Hz, 2H), 1.95 (quint, J = 6.5 Hz, 2H), 1.66-1.61 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 131.5, 128.2, 127.6, 123.9, 89.7, 80.9, 33.6, 32.3, 27.8, 27.4, 19.25.



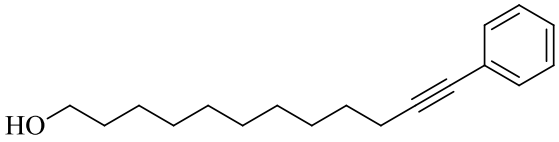
1-(7-iodohept-1-ynyl)benzene 20 (CAS: 57718-14-6). Following the standard procedure, the reaction of **20a** (38.5 mg, 0.1 mmol) with **27** (36.4 mg, 0.15 mmol) for 0.5 h afforded **20** as a colorless oil (22.8 mg, 77% yield) after flash chromatography: TLC R_f = 0.80 (EtOAc/hexanes = 1/5); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.40-7.38 (m, 2H), 7.30-7.26 (m, 3H), 3.23 (t, J = 7.0 Hz, 2H), 2.44 (t, J = 6.5 Hz, 2H), 1.91 (m, 2H), 1.66-1.56 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 131.5, 128.2, 127.5, 123.9, 89.7, 80.9, 33.0, 29.7, 27.6, 19.2, 6.70.



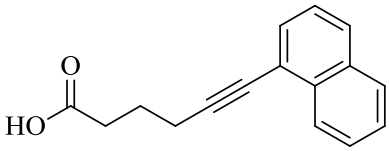
4-(4-(phenylethynyl)piperidine-1-carbonyl)benzaldehyde 21. Following the standard procedure, the reaction of **21a** (40.2 mg, 0.1 mmol) with **27** (38.7 mg, 0.15 mmol)for 0.5 h afforded **21** as a colorless oil (31.7 mg, 99% yield) after flash chromatography: TLC R_f = 0.11 (EtOAc/hexanes = 1/5); IR (KBr, thin film) 2924, 2855, 2220, 2010, 1900, 1810, 1700, 1623, 1570, 1442, 1303, 1255, 1168, 1145, 1087, 999, 842, 693, 555 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*), δ 7.99 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.42-7.40 (m, 2H), 7.36-7.35

(m, 2H), 4.06 (br, 1H), 3.48 (br, 2H), 3.21 (br, 1H), 3.02-2.95 (m, 1H), 1.95 (br, 1H), 1.83 (br, 1H), 1.69 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6), δ 192.7, 167.8, 141.9, 136.4, 131.3, 129.6, 128.6, 128.1, 127.3, 122.8, 92.2, 81.6, 26.9; HRMS-ESI (m/z) calculated for $C_{21}H_{19}NO_2$ $[M+Na]^+$: 340.1304, found 340.1308.

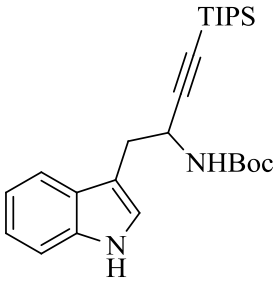
Note: CH_2 of piperidine ring is difficult to be determined by ^{13}C NMR, while CH of piperidine ring is successfully determined by ^{13}C NMR.



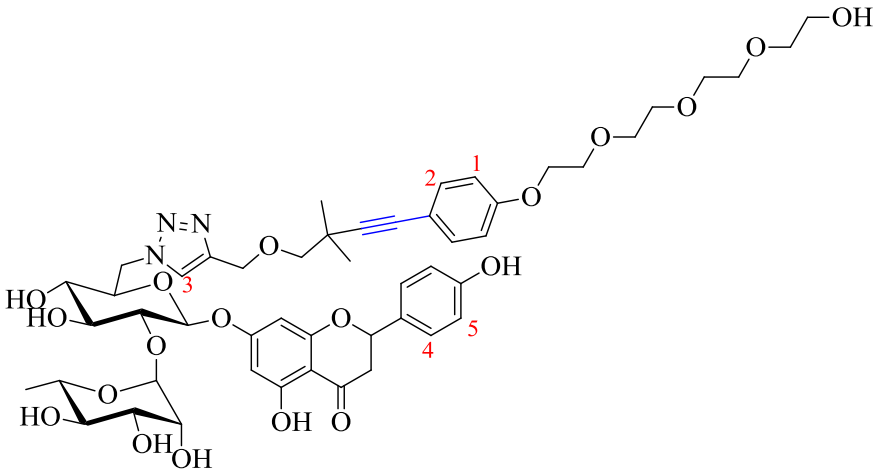
12-phenyldodec-11-yn-1-ol 22. Following the standard procedure, the reaction of **22a** (34.3 mg, 0.1 mmol) with **27** (36.5 mg, 0.15 mmol) for 0.5 h afforded **22** as a colorless oil (16.5 mg, 73% yield) after flash chromatography: TLC R_f = 0.14 (EtOAc/hexanes = 1/20); IR (KBr, thin film) 3346, 2925, 2854, 2233, 1598, 1490. 1465, 1330, 1057, 912, 722, 691, 525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.40-7.38 (m, 2H), 7.30-7.26 (m, 3H), 3.65 (t, J = 6.4 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H), 1.64-1.54 (m, 4H), 1.46-1.42 (m, 2H), 1.31 (br, 10H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 131.5, 128.2, 127.4, 124.1, 90.5, 80.6, 63.1, 32.8, 29.5, 29.4, 29.4, 29.1, 28.9, 28.7, 25.7, 19.4; HRMS-ESI (m/z) calculated for $C_{18}H_{26}O$ $[M+Na]^+$: 281.1876, found 281.1876.



6-(naphthalen-1-yl)hex-5-ynoic acid 23 (CAS: 540803-87-0). Following the standard procedure, the reaction of **23a** (28.1 mg, 0.1 mmol) with **4b** (42.7 mg, 0.15 mmol) for 0.5 h afforded **23** as a white solid (15.9 mg, 83% yield) after flash chromatography: TLC R_f = 0.16 (EtOAc/hexanes = 1/5); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.32 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.57 (dt, J = 7.5 and 1.0 Hz, 1H), 7.51 (dt, J = 7.5 and 1.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 2.68-2.62 (m, 4H), 2.07 (q, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 179.0, 133.4, 133.2, 130.2, 128.2, 128.1, 126.6, 126.2, 126.2, 125.2, 121.3, 93.6, 79.6, 32.9, 23.8, 19.1.



tert-butyl 1-(1H-indol-3-yl)-4-(triisopropylsilyl)but-3-yn-2-ylcarbamate 24. Following the standard procedure, the reaction of **24a** (44.3 mg, 0.1 mmol) with **7b** (43.0 mg, 0.15 mmol)for 0.5 h afforded **24** as a colorless oil (33.7 mg, 78% yield) after flash chromatography: TLC R_f = 0.5 (EtOAc/hexanes = 1/5); IR (KBr, thin film) 3423, 3342, 2942, 2865, 2180, 1695, 1494, 1366, 1167, 1071, 1017, 883, 739. 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ8.13 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.20 (m, 3H), 4.77 (br, 1H), 3.16 (d, *J* = 5.6 Hz, 2H), 1.42 (s, 9H), 1.00 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$), δ154.8, 136.0, 128.1, 123.2, 121.9, 119.4, 119.1, 110.9, 107.4, 83.8, 79.7, 44.7, 31.7, 28.3, 10.5, 11.1; HRMS-ESI (m/z) calculated for $C_{26}H_{40}N_2O_2Si$ $[M+Na]^+$: 463.2754, found 463.2751; ee = 0.2%.



Standard compound 34. ^1H NMR (500 MHz, CD_3OD), δ7.800 (s, 0.46H (H-3)), 7.783 (s, 0.52H (H-3)), 7.31 (d, *J* = 11 Hz, 2H (H-4)), 7.22 (d, *J* = 11 Hz, 2H (H-2)), 6.84-6.81 (m, 4H (H-1 and H-5)), 5.84-5.83 (m, 2H), 5.39-5.28 (m, 1H), 5.24 (d, *J* = 2.0 Hz, 1H), 5.0 (m, 1H), 4.61-4.35 (m, 1H), 4.11-4.09 (m, 2H), 3.91-3.90 (m, 1H), 3.87-3.78 (m, 4H), 3.71-3.53 (m, 16H), 3.39-3.34 (m, 2H), 3.27-3.01 (m, 2H), 2.73-2.65 (m, 1H), 1.287 (d, *J* = 7.5 Hz, 3H), 1.20 (m, 6H); TLC R_f = 0.28 (MeOH/EtOAc = 1/4); IR (KBr, thin film) 3363, 2925, 2873, 2100, 1638, 1577,

1508, 1456, 1348, 1173, 1126, 1088, 1057, 835 cm^{-1}; HRMS-ESI (m/z) calculated for $C_{50}H_{62}N_3O_{19}$ $[M+Na]^+$: 1032.3943, found 1032.3948.

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