Supporting Information, Part A

Small-Molecule Inhibitors of Protein Geranylgeranyltransferase Type I

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Contents

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List of Abbreviations

APCI	atmospheric pressure chemical ionization
Ar	aryl
n-BuLi	*n*-butyllithium
Bs	benzenesulfonyl
Br	bromo
Bu	butyl
CI	chemical ionization
Cl	chloro
4-ClBs	*p*-chlorobenzenesulfonyl
calcd.	calculated
CN	cyano
cond.	condition(s)
DCM	dichloromethane
DIPEA	diisopropylethylamine (Hünig's base)
DMF	*N,N*-dimethylformamide
EI	electron ionization
equiv	equivalents
ES	electrospray
Et	ethyl
EtO	ethoxy
F	fluoro
h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
incl.	included
IR	infrared
L-lantern	L-series lantern, capacity 15 μmol/lantern
L-	attached to L-lantern solid support
LC	liquid chromatography
2-MCBs	2-methoxycarbonylbenzenesulfonyl
Me	methyl
MeO	methoxy
Ms	methanesulfonyl
MS	mass spectrometry
nd	not determined
nm	nanometer
NMR	nuclear magnetic resonance
Ns	*p*-nitrobenzenesulfonyl
2-Ns	*o*-nitrobenzenesulfonyl
3-Ns	*m*-nitrobenzenesulfonyl
Ph	phenyl
i-Pr	isopropyl
R_f	retention factor
rt	room temperature
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	time of flight
Ts	*p*-toluenesulfonyl
2-Ts	*o*-toluenesulfonyl

General. Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without purification. Synphase lanterns (L-series lantern; capacity: 15 μmol/lantern), spindles, and cogs were purchased from Mimotopes Pty. Ltd., Clayton, Australia. Prior to their first use, the lanterns were washed (3×) with the reaction solvent. Each washing was left to settle for at least 5 min, unless otherwise stated. The solid phase washings were performed using PA-grade solvents. For reactions, benzene and CH_2Cl_2 were freshly distilled from calcium hydride. THF and diethyl ether were freshly distilled from Na using benzophenone as indicator. Triethylamine was stored over KOH pellets and used as such. All air- and moisture-sensitive reactions were performed under an inert atmosphere of dry Ar. Column chromatography was performed using EMD silica gel 60 (230–400 mesh). R_f values were obtained from thin layer chromatography (TLC) on silica gel-coated glass plates (E. Merck silica gel plates 60F-254) using the indicated solvents. Infrared spectra were recorded on a Perkin–Elmer pargon 1600 FT-IR spectrometer. NMR spectra were obtained in $CDCl_3$ (unless otherwise noted) on a Bruker AV300, Bruker ARX 400, or Bruker DRX 500 spectrometer. Spectra are reported in units of ppm on the δ scale, relative to chloroform (7.26 ppm for ^{1}H NMR; 77.0 ppm for ^{13}C NMR). High-resolution EI mass spectra were recorded after rapid thermal vaporization of samples deposited on a desorption ionization filament that was directly inserted into the electron ionization (EI, 70 eV, 200ºC) source of a triple-sector high-resolution instrument (VG/Micromass Autospec) tuned to 8000 static resolution (M/DM, 10% valley) using perfluorinated kerosene (formula weight: 705; Lancaster Synthesis, Inc., NH) as an internal calibrant. High-resolution chemical ionization (CI) mass spectra were recorded using a Micromass GCT Gas Chromatograph EI/CI TOF spectrometer. Atmospheric pressure chemical ionization (APCI) was performed on a SCIEX II instrument equipped with an optional Applied Biosystems/MSD Sciex QSTAR-XL hybrid Quad-TOF. Uncorrected melting points were determined using an Electrothermal capillary melting point apparatus. LCMS data were obtained on an Agilent 1100 HPLC using a Phenomenex Synergi 4μ max–RP 80Å 50 × 3 mm column, an Agilent MSD single-quadrupole mass spectrometer in ESI mode, and water/acetonitrile with formic acid as co-additive as the eluent.

Enzyme Assay. [^{3}H]Farnesyl diphosphate (FPP) and [^{3}H]geranylgeranyl diphosphate (GGPP) were purchased from Perkin–Elmer. Rat FTase and GGTase-I were purchased from JENA Biosciences. GGTI298 and GGTI2166 were purchased from Calbiochem. Full-length cDNAs of K-Ras4B and RhoA were subcloned into pMAL-p2 vector (NEB) to generate MBP-tagged K-Ras4B and RhoA. The preparation of pCDNA3-mycHARheb (M184L) was described previously.[2] FTase and GGTase-I activities were determined using the method in which radiolabeled isoprenoid is transferred from [^{3}H]FPP and [^{3}H]GGPP into a substrate protein. In brief, FTase or GGTase-I (50 ng) were used to initiate reactions containing 50.0 mM Tris-HCl (pH 7.5), 10.0 mM $MgCl_2$, 50.0 μM $ZnCl_2$, 1.0 mM DTT, 0.1 μM [^{3}H]FPP or [^{3}H]GGPP, 50.0 ng GGTase-I, and a concentration of 0.25 μM of appropriately purified MBP-tagged protein substrates (K-Ras4B for FTase; RhoA and K-Ras4B for GGTase-I). The final DMSO concentration was 5% for each sample. Reactions were performed for 30 min at 37 °C, after which time the reaction mixtures were added onto a piece of Whatmann 3 filter paper. Filters were fixed twice with 10% trichloroacetic acid (TCA) for 10 min and then washed twice with ethanol and acetone for 5 min, respectively. After drying, the filters were mixed with scintillation fluid (2 mL) and counted in a Beckman LS6500 scintillation counter.

Protein Processing Assay. Human embryonic kidney (HEK293) cells were maintained in Dulbecco's modified Eagle's medium (DMEM; Invitrogen) supplemented with 10% (vol/vol) heat-inactivated fetal bovine serum, penicillin (100 IU mL^{-1}), and streptomycin (100 μg mL^{-1}). Cells were transfected using Polyfect (Qiagen) according to the manufacturer's instructions. In brief, the plasmid DNA was incubated in serum-free media with the Polyfect reagent for 10 min, diluted in serum-free media, and added to the cells with fresh media. After 24 h of transfection, the cells were treated with DMSO or our GGTIs, GGTI-298, and GGTI-2166 for 48 h. The cells were then harvested and lysed in lysis buffer: 150 mM NaCl, 50 mM Tris-HCl (pH 8.0), 1% SDS, 1% NP-40, and 1x Protease Inhibitor Mixture (Roche Applied Science). The lysates were electrophoresed using a 10% SDS-PAGE system, transferred to nitrocellulose membranes, and immunoblotted with anti-Rheb antibody (GenWay).

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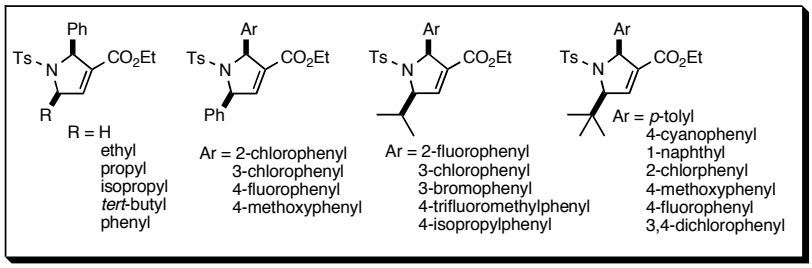
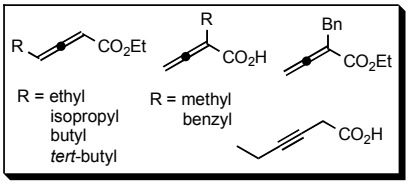
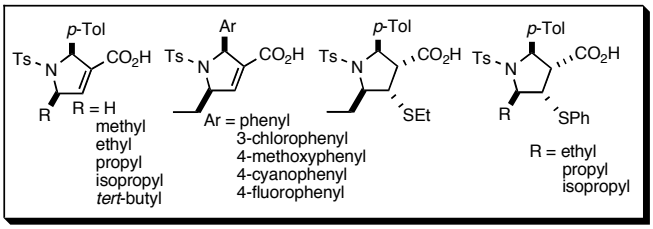
[2] Gau, C. L.; Kato-Stankiewicz, J.; Jiang, C.; Miyamoto, S.; Guo. L.; Tamanoi, F. *Mol. Cancer Ther*. **2005**, *4*, 918.



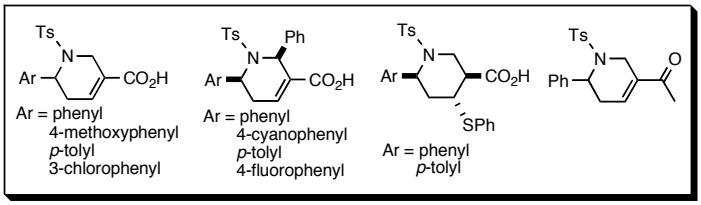
dihydropyrroles synthesized in solution



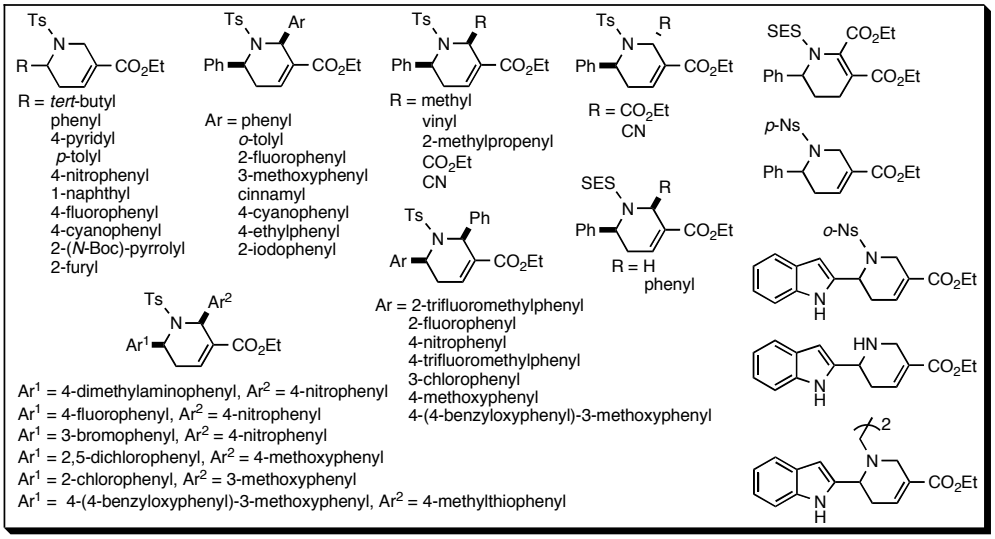
Allenes



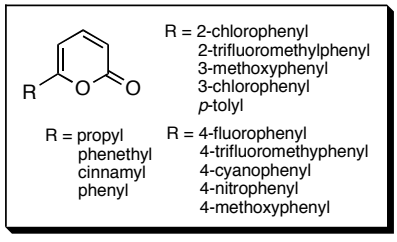
pyrrolines/pyrrolidines synthesized on solid support



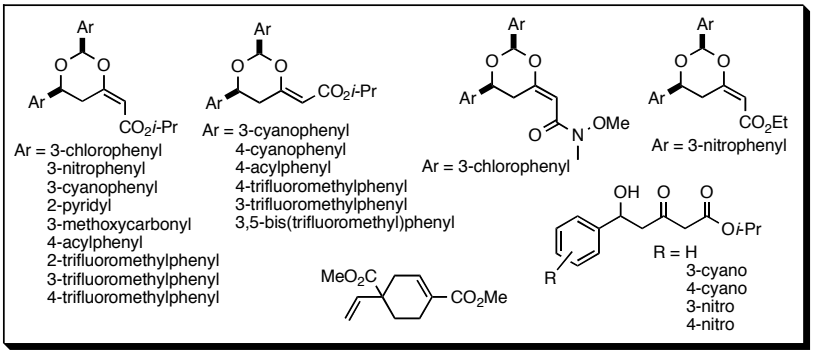
(didehydro)piperidines synthesized on solid phase



tetrahydropyridines synthesized in solution



2-pyrones



small molecules from dioxanylidene project

Figure S1. Structures of 138 compounds screened against GGTase I.

Screening the Pilot Library of 138 Compounds

Filter Binding Assays to Identify the Initial Protein Geranylgeranyltransferase Type I Inhibitors. The pilot library (Figure S1) was screened for inhibitors of protein geranylgeranyltransferase type I (GGTase I). Protein prenyltransferase assays were performed through filter binding.[3] Two different substrates, RhoA and K-Ras4B, were used for the assay. RhoA ends with the CaaL motif and is an exclusive substrate for GGTase I, while K-Ras4B ends with the CaaX motif and is modified by both GGTase I and protein farnesyltransferase (FTase). The presence of a polybasic domain consisting of a stretch of lysine residues close to the CaaX motif enables this CaaX motif to be recognized by GGTase I. Thus, RhoA and K-Ras4B are two very different substrates for this enzyme. Screening of the 138-compound pilot library resulted in the identification of the two groups of compounds presented in Figure S2. In the assay, we used a fixed concentration of 100 μM for the small molecules; the results are plotted for the inhibition of RhoA (vertical axis) as well as for K-Ras4B (horizontal axis).

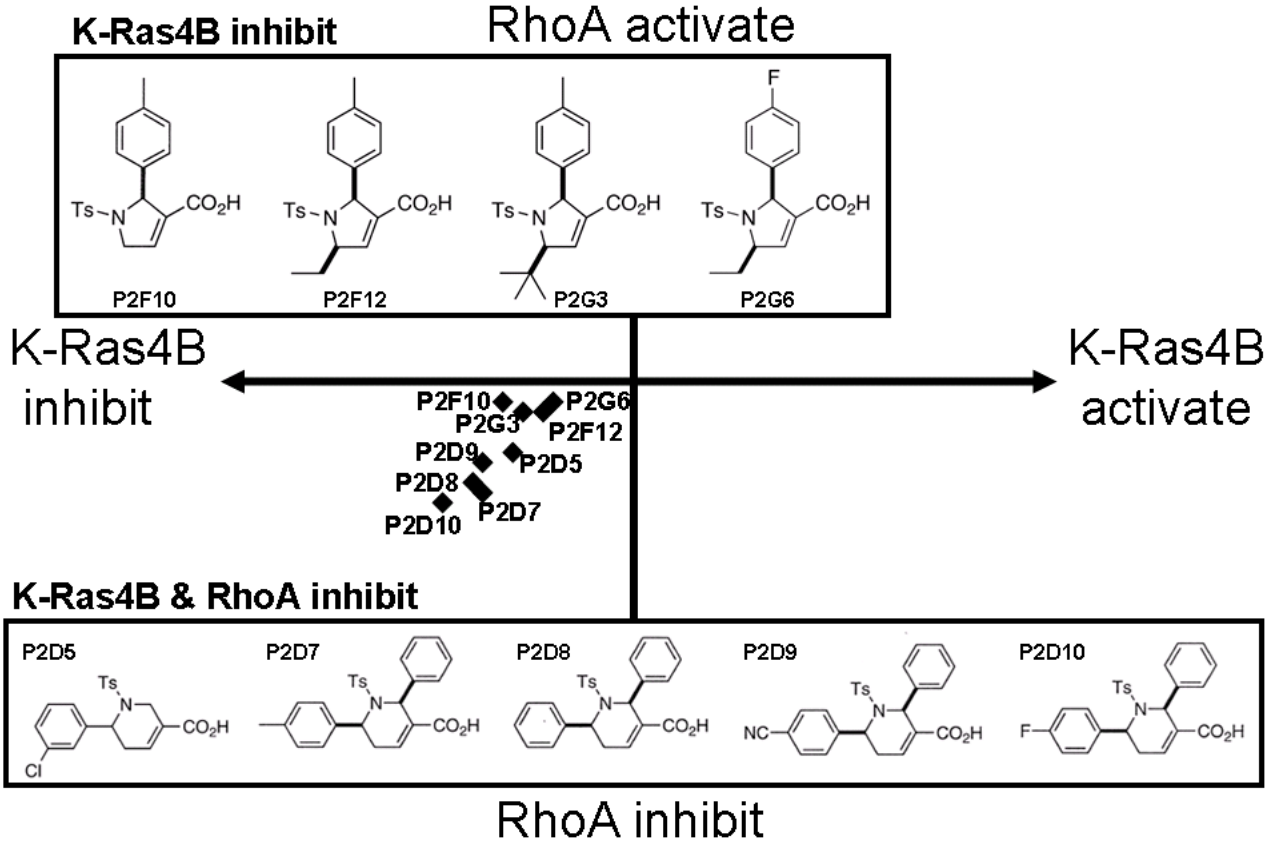


Figure S2. Impact of GGTIs on the GGTase-I activity, and their structures.

To determine IC_{50} values, the percentage activity of GGTase I was measured in the presence of the inhibitors of GGTase I (GGTIs) at various concentrations. Figure S3 displays dose–response curves for compounds **1 (P2G6)** and **2 (P2D10)**.

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[3] Finegold, A. A.; Johnson, D. I.; Farnsworth, C. C.; Gelb, M. H.; Judd, S. R.; Glomset, J. A.; Tamanoi, F. *Proc. Natl. Acad. Sci., USA* **1991**, *88*, 4448.

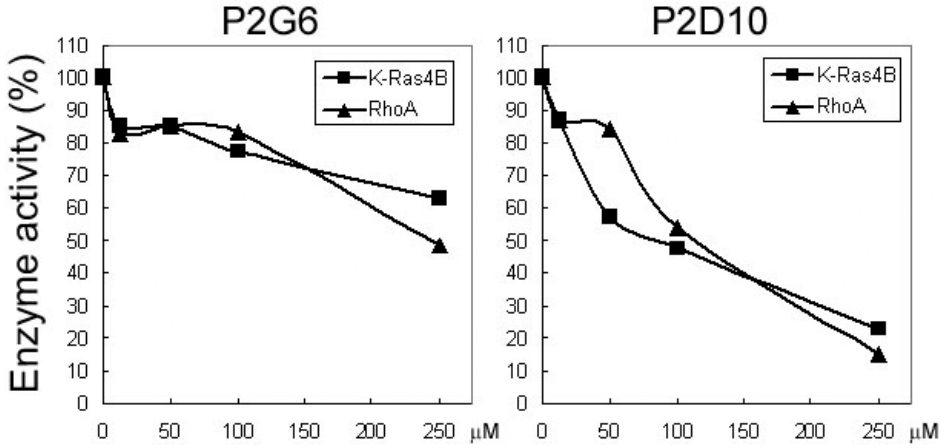
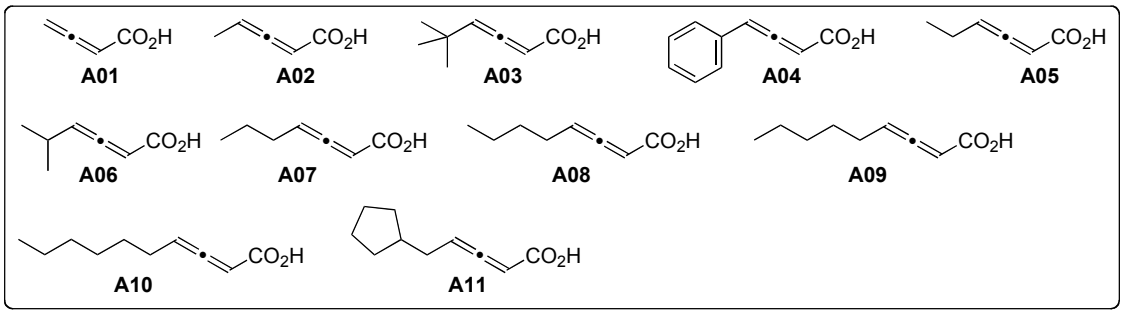
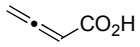


Figure S3. Dose dependency of GGTase-I activity in the presence of compound **1** or **2**.

Synthesis of 4-Substituted 2,3-Butadienoic Acids A(01–11)

Chart 1. 4-Substituted 2,3-butadienoic acid building blocks **A(01–11)**.





A01

2,3-Butadienoic Acid (A01). 2,3-Butadienoic acid was synthesized from 3-butyn-1-ol through Jones oxidation and subsequent isomerization according to a literature procedure.[4] Later, we found out that the Jones oxidation product, 3-butynoic acid, could be used directly for coupling to the benzyl alcohol units of Wang resin, resulting in the resin-bound allenoate. Presumably the initial 3-butynoate product was isomerized to the allenoate under the coupling reaction conditions. Subsequently, we employed a mixture of an allenoic acid and the isomeric alkynoic acid in the formation of resin-bound allenoates (vide infra).

4-Alkyl-2,3-butadienoic Acids A(02–11). Most of the 4-alkyl-2,3-butadienoic acids **A(02–11)** and their ethyl esters are known in literature,[5] except for **A05** and **A11**. These 4-alkyl-butadienoic acids were synthesized according to the procedures described below.

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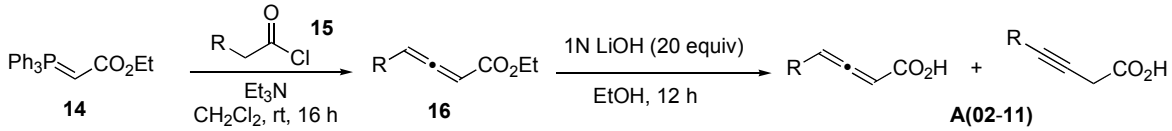
4. For Jones oxidation, see: (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc*. **1946**, 39. (b) Heibron, I.; Jones, R. H.; Sondheimer, F. *J. Chem. Soc*. **1949**, 604. For isomerization, see: (c) Egliton, G.; Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc*. **1954**, 3197.

5. For ethyl esters, see: (a) Lang, R. W.; Hansen, H.-J. H. *Helv. Chim. Acta* **1980**, *63*, 438. (b) Tsuboi, S.; Kuroda; Takatsura, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem*. **1993**, *58*, 5952. (c) Gandhi, R. P.; Ishar, M. P. S. Wali, A. *Tetrahedron Lett*. **1987**, *28*, 6679. (d) Dieter, R. K.; Lu, K. *Tetrahedron Lett*. **1999**, *40*, 4011. (e) Nishibayashi, Y.; Singh, J. D.; Fukuzawa, S.; Uemura, S. *J. Org. Chem*. **1995**, *60*, 4114. (f) Ahmar, M.; Chabanis, O.; Gauthier, J.; Cazes, B. *Tetrahedron Lett*. **1997**, *38*, 5277. (g) Bestmann, H. J.; Hartung, H. *Angew. Chem., Int. Ed. Engl*. **1963**, *2*, 214. (h) Ramaswamy, S.; Hui, R. A. H. F.; Jones, J. B. *J. Chem. Soc., Chem. Commun*. **1986**, 1545. (i) Lang, R. W.; Hansen, H.-J. *Org. Synth. Coll. Vol. 7*, **1990**, 232. For acids, see: (j) Jones, E. R. H.; Whitham, G. H.; Whiting, M. C. *J. Chem. Soc*. **1954**, 3201. (k) Ma, S.-M.; Shi, Z.-J. *Chin. J. Chem*. **2001**, *19*, 1280. (l) Pansard, J.; Gaudemar, M. *Bull. Soc. Chim. Fr*. **1968**, *8*, 3332. (m) Gill, G. B.; Idris, M. S. H.; Kirollos, K. S.



General Procedure. Et_3N (63 mmol, 1.1 equiv) was added to a stirred solution of (carbethoxymethylene)triphenylphosphorane (57.5 mmol, 1 equiv) in CH_2Cl_2 (200 mL). After stirring for 10 min, the required acyl chloride (57.5 mmol, 1 equiv) was added dropwise over 30 min at room temperature. After stirring overnight, the resulting mixture was poured unto a Büchner funnel packed with silica gel and was washed with CH_2Cl_2 several times. The combined filtrate was carefully concentrated and the resulting crude oil was purified by flash column chromatography (hexane/EtOAc, 20:1) to provide the 4-substituted 2,3-butadienoates. For the hydrolysis, a round-bottom flask was charged with the 4-substituted 2,3-butadienoate in EtOH (10 mL/g of ester). LiOH (1 N aqueous solution, 20 equiv) was added over a period of 5 min at room temperature. The reaction mixture was stirred overnight at room temperature. The products were extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts dried (Na_2SO_4) and concentrated to afford a mixture of allenoic and alkynoic acids. This crude mixture of allenoic and alkynoic acids was used for loading to obtain the resin-bound γ-substituted allenoates. The reaction yields and literature references for the allenoates and their hydrolysis products are listed in Tables 1 and 2. Spectroscopic data of ethyl 4-cyclopentylmethyl-2,3-butadienoate and its hydrolysis product are also provided.

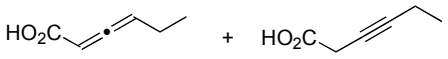
Table 1. Synthesized 4-Substituted 2,3-Butadienoic Acid Ethyl Esters **Et-A(01–11)**.

Entry	Allenoate	R	Yield (%)	Reference
1	**Et-A02**	methyl	–	*Helv. Chim. Acta* **1980**, *63*, 438
2	**Et-A03**	*tert*-butyl	75	*Helv. Chim. Acta* **1980**, *63*, 438
3	**Et-A04**	phenyl	53	*J. Org. Chem.* **1993**, *58*, 5952
4	**Et-A05**	ethyl	100	*Tetrahedron Lett.* **1987**, *28*, 6679
5	**Et-A06**	isopropyl	74	*Tetrahedron Lett.* **1999**, *40*, 4011
6	**Et-A07**	*n*-propyl	74	*J. Org. Chem.* **1995**, *60*, 4114
7	**Et-A08**	*n*-butyl	86	*Tetrahedron Lett.* **1997**, *38*, 5277
8	**Et-A09**	*n*-pentyl	75	*Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 214
9	**Et-A10**	*n*-hexyl	84	*J. Chem. Soc., Chem. Commun.* **1986**, 1545
10	**Et-A11**	cyclopentylmethyl	55	Unknown in the literature

Table 2. Hydrolyses of 4-Substituted 2,3-Butadienoic Acid Ethyl Esters **Et-A(01–11)**.

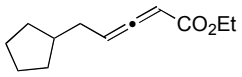
Entry	Acid	R	Yield (%)	Ratio Allenoic/alkynoic acid	Reference
1	**A02**	methyl	91	1:2.9	*J. Chem. Soc.* **1954**, 3201
2	**A03**	*tert*-butyl	96–100	2.7:1	*Chin. J. Chem.* **2001**, *19*, 1280
3	**A04**	phenyl	80–100	2.7:1	*J. Chem. Soc., Chem. Commun.* **1986**, 1545
4	**A05**	ethyl	96–98	1:1.2	Unknown in the literature
5	**A06**	isopropyl	98–100	1.4:1	*Bull. Soc. Chim. Fr.* **1968**, *8*, 3332
6	**A07**	*n*-propyl	98–100	1.1:1	*J. Chem. Soc, Perkin Trans 1* **1992**, 2367
7	**A08**	*n*-butyl	95–100	1:1.8	*Tetrahedron Lett.* **1999**, *40*, 2393
8	**A09**	*n*-pentyl	95–98	1:2.1	*Synthesis* **1981**, 875
9	**A10**	*n*-hexyl	95–98	1:1.5	*J. Am. Chem. Soc.* **1985**, *107*, 6046
10	**A11**	cyclopentylmethyl	90–100	1:3.6	Unknown in the literature

J. Chem. Soc., Perkin Trans 1 **1992**, 2367. (n) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393. (o) Clinet, J.-C.; Linstrumelle, G. *Synthesis* **1981**, 875. (p) Schwab, J. M.; Lin, D. C. T. *J. Am. Chem. Soc.* **1985**, *107*, 6046.



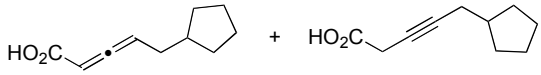
A5

4-Ethylbuta-2,3-dienoic Acid and Hex-3-ynoic Acid (A05). According to the general procedure (90 mmol scale), a mixture of 4-ethylbuta-2,3-dienoic acid and hex-3-ynoic acid was obtained as a light-yellow oil. Yield: 13.5 g (88 mmol, 98%). IR (neat) ν 3400–2500, 2976, 1956, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.43 (s, 1H), 5.67 (q, *J* = 6.25 Hz, 1H), 5.44 (dt, *J* = 6.25, 3.52 Hz, 1H), 3.24 (t, *J* = 2.40, 2H), 2.15–2.07 (m, 5H), 1.04 (t, *J* = 7.55, 3H), 1.00 (t, *J* = 7.40, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 175.3, 172.4, 97.3, 88.2, 85.4, 69.9, 25.6, 20.4, 13.5, 12.7, 12.1; GCMS (Agilent) calcd. for $C_6H_8O_2$ [M^+] 112.05, found 112.10.



Et-A11

5-Cyclopentyl-2,3-pentadienoic Acid Ethyl Ester (Et-A11). The title compound was prepared in accordance with the general procedure described above (163 mmol scale), and was obtained in 55% yield as a yellow oil. IR (neat) ν 2948, 2868, 1716, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 3.90 Hz, 1H), 7.16 (d, *J* = 6.9 Hz 1H), 5.61–5.53 (m, 2H), 4.23–4.12 (m, 2H), 2.02–1.90 (m, 1H), 1.84–1.76 (m, 2H), 1.64–1.49 (m, 2H), 1.29 (t, *J* = 7.46 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 166.4, 94.6, 87.8, 60.7, 39.5, 33.9, 32.3, 25.3, 14.3; HRMS (EI) calcd. for $C_{12}H_{19}O_2$ [M + H]$^+$ 195.1388, found 195.1376.

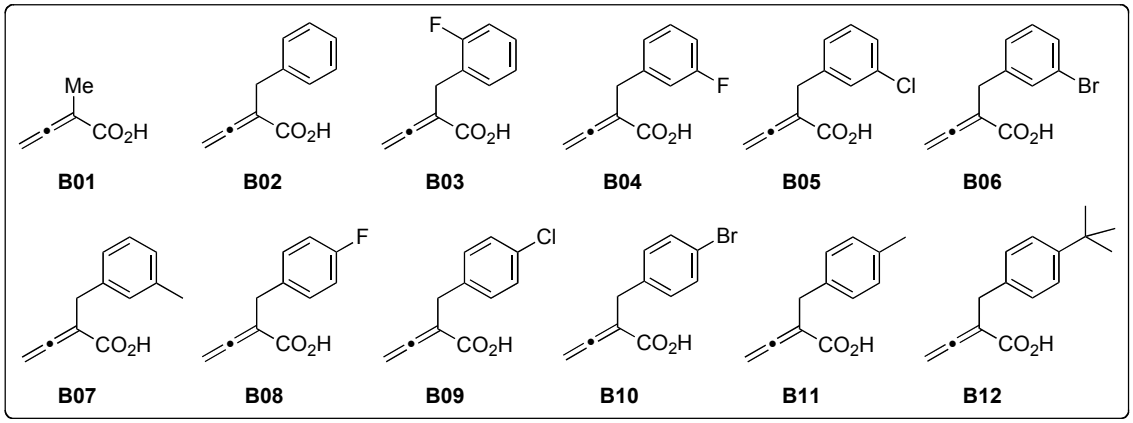


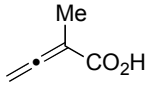
A11

5-Cyclopentyl-2,3-pentadienoic Acid and 5-Cyclopentyl-3-pentynoic Acid (A11). According to the general procedure (90 mmol scale), a mixture of 5-cyclopentylpenta-2,3-dienoic acid and 5-cyclopentylpent-3-ynoic acid was obtained as a light-yellow oil. Upon distillation of the crude mixture, 13.5 g (81 mmol, 90%) of the acids were obtained. IR (neat) ν 2950, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 3.90 Hz, 1H), 7.16 (d, *J* = 6.9 Hz 1H), 5.61–5.53 (m, 2H), 4.23–4.12 (m, 2H), 2.02–1.90 (m, 1H), 1.84–1.76 (m, 2H), 1.64–1.49 (m, 2H), 1.29 (t, *J* = 7.46 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 175.2, 172.3, 94.9, 87.2, 83.8, 70.5, 39.3, 38.9, 33.6, 32.1, 31.8, 25.8, 25.1, 25.1, 24.3; HRMS (ESI negative-ion mode) calcd. for $C_{10}H_{13}O_2$ [M – H]$^-$ 165.0928, found 165.0921.

Synthesis of 2-Substituted 2,3-Butadienoic Acids B(01–12)

Chart 2. 2-Substituted 2,3-butadienoic acid building blocks **B(01–12)**

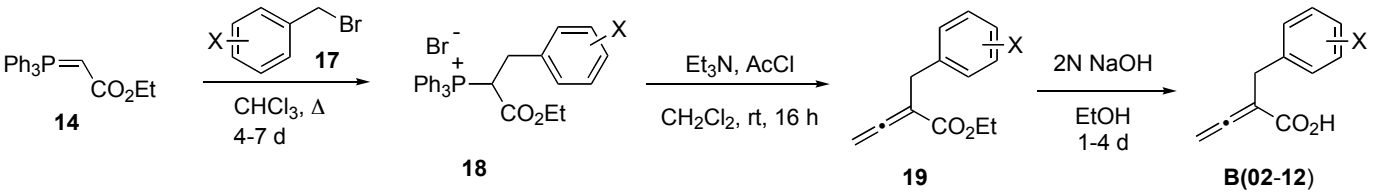




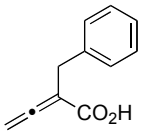
B01

2-Methyl-2,3-butadienoic Acid (B01). 2-Methyl-2,3-butadienoic acid was synthesized following a (slightly modified) literature procedure.[6]

2-Benzyl-2,3-butadienoic Acids B(02–12). All α-benzyl allenoic acids were synthesized according to the general procedure below, which is a combination of (slightly modified) literature procedures.[7]

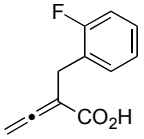


General Procedure. A solution of (carbethoxymethylene)triphenylphosphorane (80 g, 230 mmol) and the benzyl bromide (250 mmol, 1.1 equiv) in $CHCl_3$ (500 mL) was heated under reflux for 4–7 days until TLC (hexanes/EtOAc, 2:1) indicated the complete disappearance of the phosphorane. The mixture was concentrated and the crude oily foam was co-evaporated with CH_2Cl_2 (2 × 100 mL). The resultant crude phosphonium salt was dissolved in CH_2Cl_2 (500 mL) and Et_3N (64 mL, 460 mmol, 2 equiv) was added, followed by stirring for 30 min. AcCl (16.35 mL, 230 mmol, 1 equiv) was then slowly added over 30 min with vigorous stirring. The resultant suspension was stirred for 16 h and concentrated. The thick slurry was stirred with Et_2O (300 mL) for 2 h and then filtered over a pad of silica gel. The residue on the filter was washed with Et_2O (3 × 100 mL) and the combined organic fractions were concentrated. Column chromatography of the crude oil (hexanes/Et_2O, 40:1–20:1) afforded the pure allenoates. 2 N Aqueous NaOH (1L, 2 mol, 20 equiv) was added to a solution of the allenoate (100 mmol) in EtOH (50 mL) and stirred at the indicated temperature for 24–96 h until TLC (hexanes/EtOAc, 2:1) indicated complete hydrolysis. The solution was carefully acidified to ca. pH 1 using 6 N HCl and the product was then extracted with Et_2O (4 × 125 mL). The combined extracts were dried (Na_2SO_4) and concentrated. When necessary, column chromatography (hexanes/EtOAc, 8:1–0:1) afforded the pure butadienoic acid, often as a white solid.



B02

2-Benzyl-2,3-butadienoic Acid (B02).[7c] According to the general procedure (230 mmol scale), ethyl 2-benzyl-2,3-butadienoate (25.6 g, 127 mmol, 55%) was obtained as a colorless oil. The allenoate (25.6 g, 127 mmol) was hydrolyzed at room temperature to afford 2-benzylbuta-2,3-dienoic acid (18.0 g, 104 mmol, 82%) as a white solid. All spectroscopic data were in accordance with those reported in the literature.[7c]

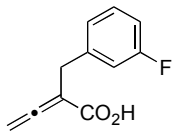


B03

2-(2-Fluorobenzyl)-2,3-butadienoic Acid (B03). According to the general procedure (86.1 mmol scale), ethyl 2-(2-fluorobenzyl)-buta-2,3-dienoate (10.1 g, 45.8 mmol, 53%) was obtained as a colorless oil. The allenoate (7.6 g, 34.7 mmol) was hydrolyzed at room temperature to give 2-(2-fluorobenzyl)-2,3-butadienoic acid (5.55 g, 28.9 mmol, 83%) as a white solid after column chromatography. IR (film) ν 2990, 1964, 1682, 1586, 1494, 1419, 1294, 1227, 1071, 911, 858, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.19 (m, 2H), 7.08–7.00 (m, 2H), 5.15 (t, J = 2.8 Hz, 2H), 3.59 (t, J = 2.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.1, 172.1, 161.1 (d, J = 246.2 Hz), 131.0 (d, J = 4.4

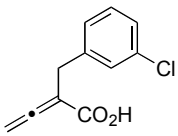
6. Harvey, G. R.; Ratts, K. W. *J. Org. Chem.* **1966**, *31*, 3907.
7. For the Wittig reaction, see: (a) Ref. 5a. For the hydrolysis, see: (b) Bestmann, H.-J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198. (c) Himbert, G.; Juergen, H. *Zeitschrift fur Naturforschung, B: Chemical Sciences* **1992**, *47*, 1785.

Hz), 128.2 (d, J = 8.3 Hz), 125.2 (d, J = 15.3 Hz), 123.7 (d, J = 3.3 Hz), 115.1 (d, J = 21.9 Hz), 98.6, 79.8, 27.8 (d, J = 2.5 Hz); HRMS (EI) calcd. for $C_{11}H_9O_2F$ [M^+] 192.0587, found 192.0594.



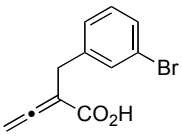
B04

2-(3-Fluorobenzyl)-2,3-butadienoic Acid (B04). Following the general procedure (86.1 mmol scale), ethyl 2-(3-fluorobenzyl)-2,3-butadienoate (10.5 g, 47.6 mmol, 55%) was obtained as a colorless oil. The allenoate (8.0 g, 36.3 mmol) was hydrolyzed at room temperature to give 2-(3-fluorobenzyl)-buta-2,3-dienoic acid (6.04 g, 31.4 mmol, 87%) as a white solid. IR (film) ν 2994, 1963, 1693, 1589, 1486, 1420, 1303, 1277, 1097, 931, 860, 787, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.21 (m, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.96–6.90 (m, 2H), 5.21 (t, J = 2.4 Hz, 2H), 3.54 (t, J = 2.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3, 172.2, 162.7 (d, J = 245.3 Hz), 141.1 (d, J = 7.4 Hz), 129.6 (d, J = 8.3 Hz), 124.4, 115.6 (d, J = 21.4 Hz), 113.3 (d, J = 20.9 Hz), 99.2, 79.7, 34.1; HRMS (EI) calcd. for $C_{11}H_9O_2F$ [M^+] 192.0587, found 192.0588.



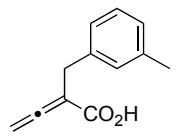
B05

2-(3-Chlorobenzyl)-2,3-butadienoic Acid (B05). Following the general procedure (48.8 mmol scale), ethyl 2-(3-chlorobenzyl)-2,3-butadienoate (18.14 g, 76.6 mmol, 55%) was obtained as a slightly yellow oil. The allenoate (18 g, 76.0 mmol) was hydrolyzed at room temperature to provide 2-(3-chlorobenzyl)-2,3-butadienoic acid (14.9 g, 71.4 mmol, 94%) as a white solid. IR (film) ν 2991, 1965, 1931, 1692, 1593, 1422, 1304, 1277, 1183, 1100, 915, 858, 785, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.18 (m, 3H), 7.13–7.11 (m, 1H), 5.21 (t, J = 2.4 Hz, 2H), 3.52 (t, J = 2.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 172.2, 140.6, 134.0, 129.5, 128.8, 126.9, 126.6, 99.2, 79.8, 34.0; HRMS (EI) calcd. for $C_{11}H_9O_2Cl$ [M^+] 208.0291, found 208.0286.



B06

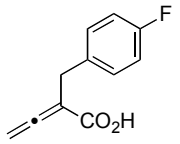
2-(3-Bromobenzyl)-2,3-butadienoic Acid (B06). Following the general procedure (86.1 mmol scale), ethyl 2-(3-bromobenzyl)-2,3-butadienoate (10.9 g, 38.6 mmol, 45%) was obtained as a slightly yellow oil. The allenoate (9.2 g, 32.7 mmol) was hydrolyzed at room temperature to afford 2-(3-bromobenzyl)-2,3-butadienoic acid (7.4 g, 29.2 mmol, 89%) as an off-white solid. IR (film) ν 2987, 2677, 1965, 1932, 1692, 1590, 1471, 1427, 1304, 1277, 1100, 915, 857, 785, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (m, 2H), 7.16–7.11 (m, 2H), 5.22 (s, 2H), 3.56 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 172.2, 140.9, 131.7, 129.8, 129.6, 127.4, 122.2, 99.2, 79.8, 34.0; HRMS (EI) calcd. for $C_{11}H_9O_2Br$ [M^+] 253.9765, found 253.9756.



B07

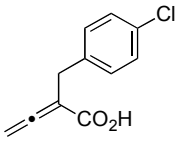
2-(3-Methylbenzyl)-2,3-butadienoic Acid (B07). Following the general procedure (97.6 mmol scale), ethyl 2-(3-methylbenzyl)-2,3-butadienoate (11.16 g, 51.6 mmol, 53%) was obtained as a slightly yellow oil. The allenoate (7.3 g, 33.8 mmol) was hydrolyzed at 100 °C to give 2-(3-methylbenzyl)-2,3-butadienoic acid (4.6 g, 24.4 mmol, 72%) as a white solid after column chromatography. IR (film) ν 3419, 3020, 1963, 1683, 1415, 1283, 850, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19–7.15 (m, 1H), 7.04–7.01 (m, 3H), 5.18 (t, J = 2.4 Hz, 2H), 3.52 (t, J = 2.2 Hz, 2H),

2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 172.0, 138.5, 137.8, 129.4, 128.1, 127.1, 125.7, 99.7, 79.4, 34.3, 21.3; HRMS (EI) calcd. for $C_{12}H_{12}O_2$ [M^+] 188.0837, found 188.0846.



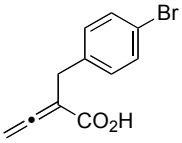
B08

2-(4-Fluorobenzyl)-2,3-butadienoic Acid (B08). Following the general procedure (86.1 mmol scale), ethyl 2-(4-fluorobenzyl)-2,3-butadienoate (9.9 g, 45 mmol, 52%) was obtained as a slightly yellow oil. The allenoate (8.2 g, 37.2 mmol) was hydrolyzed at room temperature to afford 2-(4-fluorobenzyl)-2,3-butadienoic acid (6.9 g, 35.8 mmol, 96%) as a white solid. IR (film) ν 2988, 1935, 1694, 1507, 1420, 1305, 1283, 1213, 859, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.16 (m, 2H), 6.98–6.93 (m, 2H), 5.18 (t, *J* = 2.5 Hz, 2H), 3.51 (t, *J* = 2.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 171.5, 161.5 (d, *J* = 244.4 Hz), 134.2, 130.2 (d, *J* = 7.9 Hz), 115.0 (d, *J* = 21.4 Hz), 99.7, 79.6, 33.6; HRMS (EI) calcd. for $C_{11}H_9O_2F$ [M^+] 192.0587, found 192.0592.



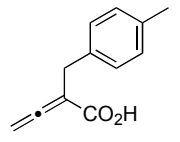
B09

2-(4-Chlorobenzyl)-2,3-butadienoic Acid (B09). Following the general procedure (230 mmol scale), ethyl 2-(4-chlorobenzyl)-2,3-butadienoate (28.3 g, 119.5 mmol, 52%) was obtained as a slightly yellow oil. The allenoate (23.0 g, 97 mmol) was hydrolyzed at room temperature to give 2-(4-chlorobenzyl)-2,3-butadienoic acid (19.0 g, 91 mmol, 94%) as an off-white solid. IR (film) ν 2982, 1932, 1691, 1492, 1421, 1303, 1277, 1087, 1013, 858 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.19 (t, *J* = 2.5 Hz, 2H), 3.51 (t, *J* = 2.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 171.7, 137.0, 132.2, 130.1, 128.3, 99.4, 79.7, 33.8; HRMS (EI) calcd. for $C_{11}H_9O_2Cl$ [M^+] 208.0291, found 208.0285.



B10

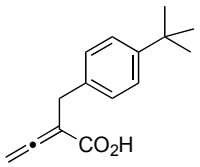
2-(4-Bromobenzyl)-2,3-butadienoic Acid (B10). Following the general procedure (230 mmol scale), ethyl 2-(4-bromobenzyl)-2,3-butadienoate (32.5 g, 115.7 mmol, 50%) was obtained as a slightly yellow oil. The allenoate (26.0 g, 92.5 mmol) was hydrolyzed at room temperature to give 2-(4-bromobenzyl)-2,3-buta-2,3-dienoic acid (24.1 g, 95 mmol, 100%) as an off-white solid. IR (film) ν 3059, 1933, 1691, 1487, 1419, 1301, 1275, 1176, 1067, 1008, 855, 799 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 5.19 (t, *J* = 2.4 Hz, 2H), 3.49 (t, *J* = 2.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 171.7, 137.6, 131.4, 131.3, 130.5, 130.0, 120.3, 99.3, 79.7, 33.9; HRMS (EI) calcd. for $C_{11}H_9O_2Br$ [M^+] 251.9787, found 251.9786.



B11

2-(4-Methylbenzyl)-2,3-butadienoic Acid (B11). Following the general procedure (97.6 mmol scale), ethyl 2-(4-methylbenzyl)-2,3-butadienoate (11.22 g, 52 mmol, 53%) was obtained as a slightly yellow oil. The allenoate (7.3 g, 33.8 mmol) was hydrolyzed at 100 °C to give 2-(4-methylbenzyl)-2,3-butadienoic acid (3.8 g, 19.7 mmol, 58%) as a solidifying oil after column chromatography. IR (film) ν 2980, 1962, 1675, 1515, 1420, 1281, 1065, 860 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.11 (m, 4H), 5.19 (s, 2H), 3.54 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 215.4, 172.7, 135.9, 135.6, 128.9, 128.6, 100.0, 79.4, 34.0, 21.0; HRMS (EI) calcd. for $C_{12}H_{12}O_2$ [M^+] 188.0837, found 188.0842.

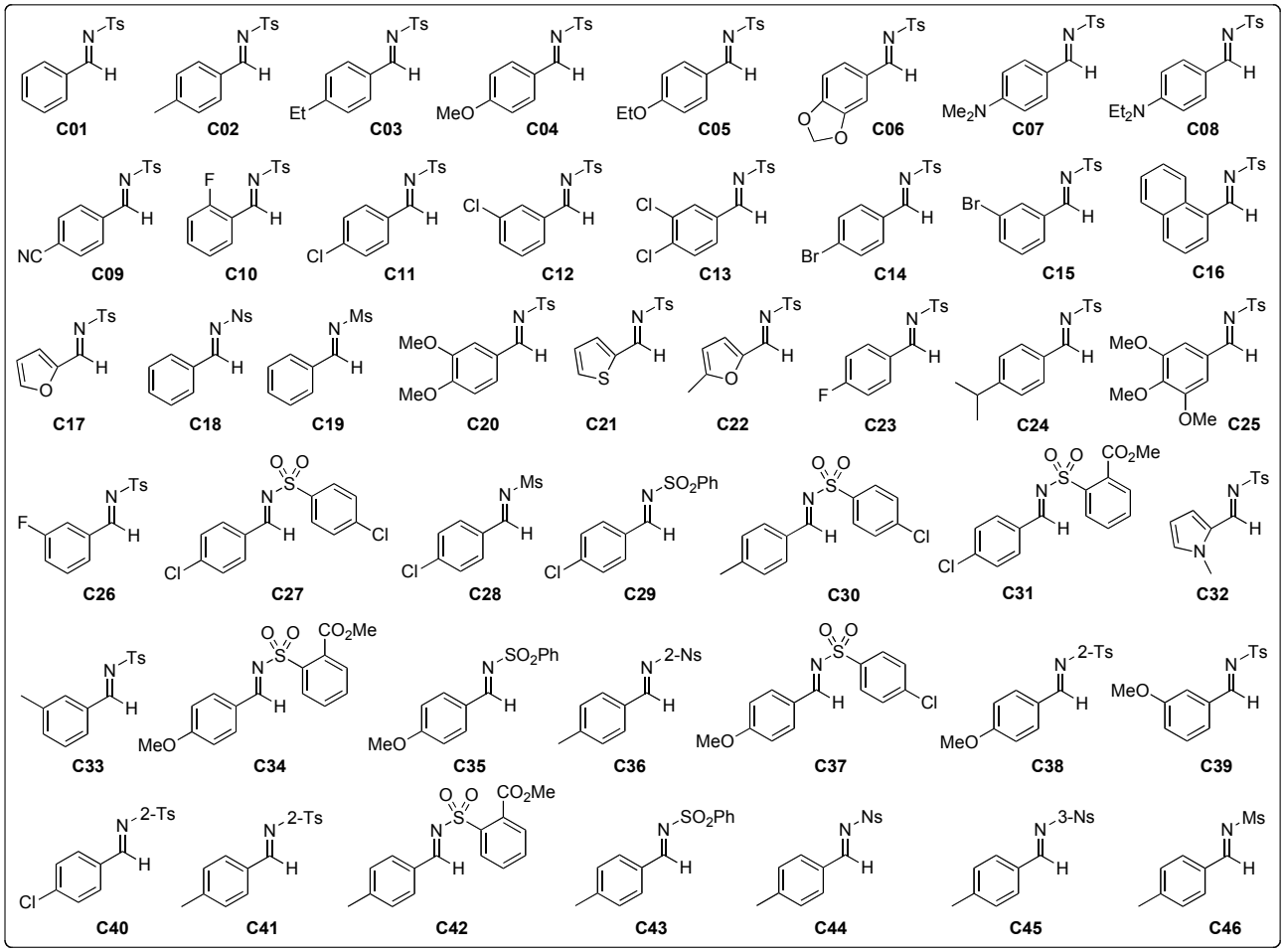


B12

2-(4-*tert*-Butylbenzyl)-2,3-butadienoic acid (B12). Following the general procedure (86.1 mmol scale), ethyl 2-(4-*tert*-butylbenzyl)-2,3-butadienoate (11.7 g, 45.1 mmol, 52%) was obtained as a slightly yellow oil. The allenoate (10.0 g, 38.7 mmol) was hydrolyzed at 100 °C to give 2-(4-*tert*-butylbenzyl)-2,3-butadienoic acid (6.9 g, 29.9 mmol, 77%) as a solidifying oil after column chromatography. IR (film) ν 2963, 1963, 1515, 1413, 1364, 1284, 907, 852, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 5.19 (t, *J* = 2.3 Hz, 2H), 3.52 (t, *J* = 2.1 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 172.7, 149.1, 135.6, 128.3, 125.1, 99.8, 79.3, 34.3, 33.9, 31.3; HRMS (EI) calcd. for $C_{15}H_{18}O_2$ [M^+] 230.1307, found 213.1318.

Synthesis of *N*-Sulfonylimines C(01–46)

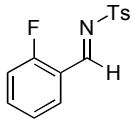
Chart 3. *N*-Sulfonylimine building blocks **C(01–46)**



The *N*-sulfonylimines **C01**, **C03**, **C06–C18**, **C20–C24**, **C26–C30**, and **C32–C42** were synthesized through the condensation of the corresponding aldehydes with the sulfonamides catalyzed by $BF_3{\cdot}OEt_2$ with azeotropic water

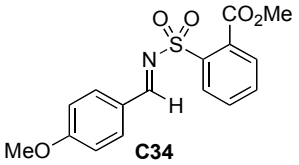
removal (Dean–Stark), according to the literature procedure.[8] The *N*-sulfonylimines **C02**, **C04**, **C05**, **C19**, **C25**, **C31**, and **C43–C46** were synthesized from the corresponding aldehydes and sulfonamides through the use of $TiCl_4$, according to a literature procedure.[9] The spectroscopic data for the following synthesized imines were in agreement with those reported in the literature (or cited therein): **C01**;[10a] **C02**, **C14**, and **C23**;[10b] **C03**;[10c] **C04** and **C16**;[10d] **C05**, **C30**, and **C43**;[10e] **C06**;[10f] **C07** and **C20**;[10g] **C09** and **C39**;[10h] **C11**, **C18**, and **C19**;[10i] **C12**;[10j] **C13**;[10k] **C15**;[10l] **C17**;[10m] **C21**;[10n] **C24**;[10o] **C26** and **C27**;[10p] **C28**;[10q] **C29** and **C35**;[10r] **C33**;[10s] **C46**.[10t]

The spectroscopic data for the previously unreported *N*-sulfonylimines **C10**, **C34**, **C36–C38**, and **C40–C42** that were used in the library synthesis are listed below.



C10

***N*-(2-Fluorobenzylidene)-4-methylbenzenesulfonamide (C10)**. Following the literature procedure,[8] 2-fluorobenzaldehyde (18.6 g, 150 mmol) was reacted with *p*-toluenesulfonamide (24.7 g, 144.0 mmol) in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) to afford **C10** as a white solid after crystallization from hexanes/EtOAc. Yield: 39.6 g (142.8 mmol, 99%). M.p. 136–140 °C; IR (film) ν 1611, 1572, 1456, 1321, 1157, 1087, 871, 814, 762 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 9.53 (s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.80–7.76 (m, 1H), 6.81–6.77 (m, 3H), 6.54–6.47 (m, 2H), 1.88 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 164.3 (d, J = 260 Hz), 163.7, 144.9, 137.1 (d, J = 9.1 Hz), 134.8, 129.9, 129.4, 128.2, 124.9, 120.5 (d, J = 8.4 Hz), 116.4 (d, J = 20.6 Hz), 21.8; LRMS (APCI) calcd. for $C_{14}H_{13}FNO_2S$ [MH^+] 278.1, found 278.2.



C34

2-[(4-Methoxybenzylidene)sulfamoyl]benzoic Acid Methyl Ester (C34). Following the literature procedure,[8] 4-methoxybenzaldehyde (20.4 g, 150 mmol) was reacted with methyl 2-(aminosulfonyl)benzoate (30.1 g, 140.0 mmol) in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) to afford **C34** as a white solid after crystallization from hexanes/EtOAc. Yield: 16.8 g (50.6 mmol, 36%). M.p. 90–96 °C; IR (film) ν 2954, 2842, 1736, 1591, 1558, 1513, 1427, 1263, 1158, 1115, 1059, 1023, 954, 810, 772, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.28–8.26 (m, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.68–7.62 (m, 3H), 6.99 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 167.4, 165.5, 136.8, 134.0, 133.2, 132.8, 131.0, 130.4, 129.4, 125.2, 114.8, 55.7, 53.1; LRMS (APCI) calcd. for $C_{16}H_{16}NO_5S$ [MH^+] 334.1, found 334.3.

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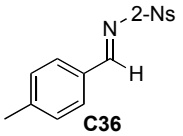
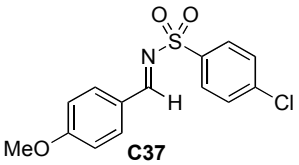


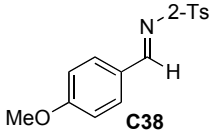
C36

***N*-(4-Methylbenzylidene)-2-nitrobenzenesulfonamide (C36)**. Following the literature procedure,[8] *p*-tolualdehyde (10.4 g, 86.8 mmol) was reacted with 2-nitrobenzenesulfonamide (14.6 g, 72.3 mmol) in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) to afford **C36** as a white solid after crystallization from hexanes/EtOAc. Yield: 16.7 g (54.9 mmol, 76%). M.p. 144–148 °C; IR (film) ν 1639, 1593, 1542, 1366, 1330, 1232, 1161, 1124, 1057, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.41–8.39 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.81–7.77 (m, 3H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 146.3, 133.6, 132.3, 131.7, 131.6, 131.5, 129.9, 129.7, 127.9, 124.1, 21.3; LRMS (APCI) calcd. for $C_{14}H_{13}N_2O_4S$ [MH^+] 305.1, found 305.2.



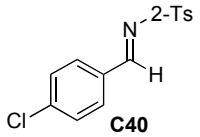
C37

4-Chloro-*N*-(4-methoxybenzylidene)-benzenesulfonamide (C37). Following the literature procedure,[8] 4-methoxybenzaldehyde (21.4 g, 157 mmol) was reacted with 4-chlorobenzenesulfonamide (28.7 g, 150.0 mmol) in the presence of $BF_3{\cdot}OEt_2$ (5 mol%) to afford **C37** as a white solid after crystallization from hexanes/EtOAc. Yield: 34.4 g (111.1 mmol, 74%). M.p. 100–102 °C; IR (film) ν 1644, 1591, 1562, 1513, 1426, 1319, 1264, 1156, 1088, 1014, 806, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 165.6, 139.9, 137.4, 134.0, 129.3, 128.3, 125.0, 114.8, 55.7; LRMS (APCI) calcd. for $C_{14}H_{13}NClO_3S$ [MH^+] 310.0, found 310.3.



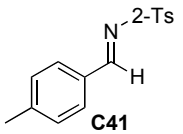
C38

***N*-(4-Methoxybenzylidene)-2-methylbenzenesulfonamide (C38)**. Following the literature procedure,[8] 4-methoxybenzaldehyde (4.3 g, 31.4 mmol) was reacted with *o*-toluenesulfonamide (5.1 g, 30.0 mmol) in the presence of $BF_3{\cdot}OEt_2$ (5 mol%) to afford **C38** as a white solid after crystallization from hexanes/EtOAc. Yield: 5.3 g (18.3 mmol, 61%). M.p. 90–93 °C; IR (film) ν 1591, 1561, 1513, 1425, 1314, 1263, 1157, 1131, 1062, 1024, 811, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.42 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.03–6.99 (m, 1H), 6.95–6.89 (m, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 3.11 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (100 MHz) δ 169.7, 165.4, 138.7, 133.7, 133.4, 132.4, 129.1, 126.3, 125.3, 114.8, 55.7, 20.7; LRMS (APCI) calcd. for $C_{15}H_{16}NO_3S$ [MH^+] 290.1, found 290.2.



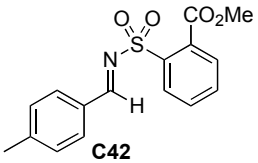
C40

***N*-(4-Chlorobenzylidene)-2-methylbenzenesulfonamide (C40)**. Following the literature procedure,[8] 4-chlorobenzaldehyde (24.3 g, 173 mmol) was reacted with *o*-toluenesulfonamide (25.7 g, 150 mmol) in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) to afford **C40** as a white solid after crystallization from hexanes/EtOAc. Yield: 37.4 g (127.3 mmol, 85%). M.p. 118–120 °C; IR (film) ν 1608, 1562, 1318, 1161, 1062, 791, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.52–7.49 (m, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.37–7.35 (m, 2H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 141.6, 138.9, 136.3, 133.8, 132.5, 132.4, 130.9, 129.7, 129.3, 126.4, 20.7; LRMS (APCI) calcd. for $C_{14}H_{13}NO_2ClS$ [MH^+] 294.0, found 294.1.



C41

2-Methyl-*N*-(4-methylbenzylidene)benzenesulfonamide (C41). Following the literature procedure,[8] *p*-tolualdehyde (12 mL, 100 mmol) was reacted with *o*-toluenesulfonamide (15.4 g, 90 mmol) in the presence of $BF_3{\cdot}OEt_2$ (9 mol%) to afford **C41** as a white solid after crystallization from hexanes/EtOAc. Yield: 20.4 g (74.6 mmol, 83%). M.p. 103–106 °C; IR (film) ν 1596, 1562, 1314, 1159, 1131, 1062, 870, 810, 797, 758, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.50–7.48 (m, 1H), 7.35–7.32 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.74 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 146.5, 138.8, 136.8, 133.5, 132.4, 131.5, 130.0, 129.9, 129.2, 126.3, 22.0, 20.7; LRMS (APCI) calcd. for $C_{15}H_{16}NO_2S$ [MH^+] 274.1, found 274.3.

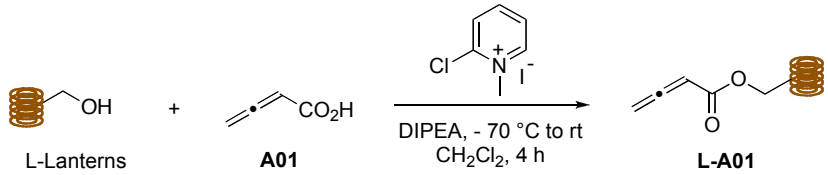


C42

2-[(4-Methylbenzylidene)sulfamoyl]benzoic Acid Methyl Ester (C42). Following the literature procedure,[8] *p*-tolualdehyde (15.6 g, 130 mmol) was reacted with methyl 2-(aminosulfonyl)benzoate (25.8 g, 120 mmol) in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) to afford **C42** as a white solid after crystallization from hexanes/EtOAc. Yield: 20.8 g (65.6 mmol, 55%). M.p. 109–112 °C; IR (film) ν 1736, 1645, 1595, 1562, 1433, 1324, 1294, 1161, 1117, 1059, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.29–8.27 (m, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.69–7.65 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.90 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 167.3, 146.6, 136.5, 133.3, 132.9, 131.6, 131.1, 130.6, 130.0, 129.8, 129.5, 53.1, 22.0; LRMS (APCI) calcd. for $C_{16}H_{16}NO_4S$ [MH^+] 318.1, found 318.1.

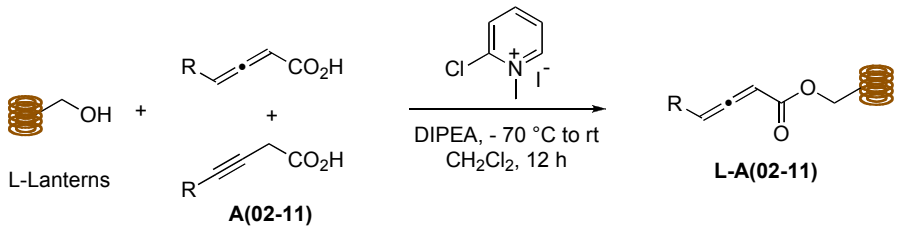
Resin Loading With 4-Substituted 2,3-Butadienoic Acids

Resin Loading With 2,3-Butadienoic Acid (A01)



General Procedure. An oven-dried vial was charged with lanterns (15 μmol/lantern), 2,3-butadienoic acid (10 equiv), and 2-chloro-1-methylpyridinium iodide (10 equiv). After two evacuation/backfill cycles with Ar, the solids were dissolved in dry CH_2Cl_2 (0.5 mL/lantern). After 30 min, the vial was cooled to –70 °C and diisopropylethylamine (Hünig's base, 20 equiv) was added under an Ar atmosphere. After 1 h, the cooling bath was removed; the vials were then flushed with Ar, capped, and shaken at room temperature for 4 h. The brown solution was removed and the light-yellow lanterns were washed as follows: THF × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, DCM × 5, THF × 5, DCM × 5, THF × 5, DCM × 5. (Note: Lanterns were soaked for at least 15 min before changing the solvents.)

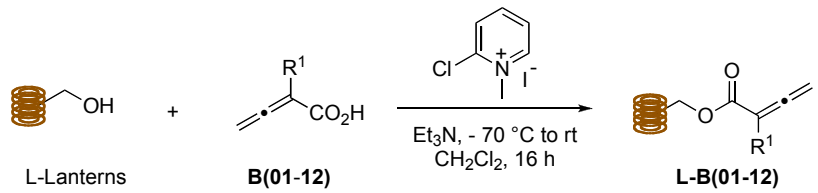
Resin Loading With 4-Substituted 2,3-Butadienoic Acids A(02–11)



General Procedure. An oven-dried vial was charged with a mixture of 4-substituted-2,3-butadienoic acid (**A02–A11**) and tautomeric 3-alkynoic acid (10 equiv), 2-chloro-1-methylpyridinium iodide (10 equiv), and lanterns (15 μmol/lantern). After two evacuation/backfill cycles with Ar, the solids were dissolved in dry CH_2Cl_2 (0.5

mL/lantern). After 30 min, the vial was cooled to −78 °C and DIPEA (20 equiv) was added under an Ar atmosphere. After 1 h, the cooling bath was removed; the vials were then flushed with Ar, capped, and shaken at room temperature for 12 h. The brown solution was removed and the light-yellow lanterns were washed as follows: THF × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, DCM × 5, THF × 5, DCM × 5, THF × 5, DCM × 5. (Note: Lanterns were soaked for at least 15 min before changing solvents.)

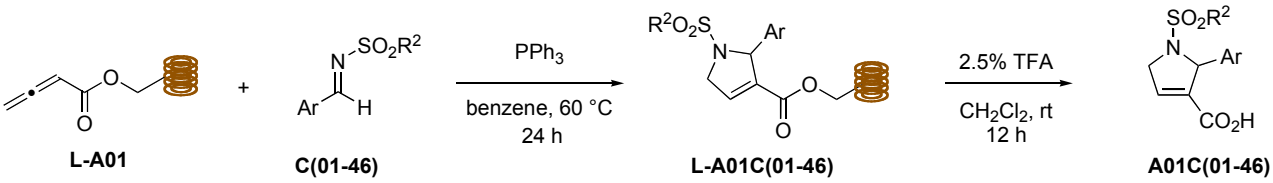
Resin Loading With 2-Substituted 2,3-Butadienoic Acids B(01–12)



General Procedure. An oven-dried flask or vial was loaded with the desired number of lanterns (L-series; 15 μmol loading capacity per lantern), 2-chloro-1-methylpyridinium iodide (10 equiv, 0.15 mmol/lantern), and the butadienoic acid (10 equiv, 0.15 mmol/lantern). The flask was charged with Ar and CH_2Cl_2 (0.5 mL/Lantern) was added. After soaking for 30 min, the suspension was cooled to −70 °C and triethylamine (20 equiv, 0.3 mmol/lantern) was added. The flask was swirled manually to ensure mixing and then the cooling bath was removed. While being warmed to room temperature, the flask was swirled manually from time to time; at ca. −5 °C the solution began to turn red/brown. At room temperature, the flask was capped and swirled or shaken gently for 16 h. The colored lanterns were then washed as follows (ca. 1 mL solvent/lantern; at room temperature, the lanterns were at least soaked for a couple of minutes unless otherwise stated): CH_2Cl_2 (7×), toluene (2×), THF (3×), DMF (3×), THF (3×), DMF for 16 h (1×), DMF (2×), THF (3×), toluene (3×), CH_2Cl_2 (3×). The loaded lanterns were dried in the air or used directly in the next step. The lantern-bound allenoate **L-B01** was stable for several months at –18 °C and **L-B05** for several weeks at –18 °C.

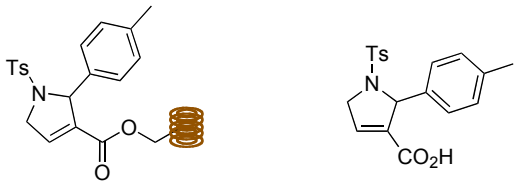
Solid Phase [3 + 2] Annulations with *N*-Sulfonylimines

[3 + 2] Cycloaddition of Lantern-Bound 2,3-Butadienoate L-A01



General Procedure. Lantern-bound 2,3-butadienoate **L-A01** was washed under an Ar flow with dry THF (1 mL/lantern, 5 times) and dry benzene (1 mL/lantern, 5 times). A solution of *N*-sulfonylimine (5 equiv) in benzene (0.5 mL/lantern) was then added followed by triphenylphosphine (0.5 equiv) in benzene (0.5 mL/lantern). The mixture was agitated manually and heated at 60 °C for 24 h. The reaction solution was then removed and the brown lanterns washed as follows: toluene, DCM × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, toluene, THF × 5, and then left in toluene overnight at 60 °C. Further washing with toluene × 5, THF × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, toluene, THF × 5, DCM × 5, THF × 5, DCM × 5, THF × 5, DCM × 5, and then left in DCM for 1 h. The annulation products were cleaved through treatment with TFA/DCM (2.5%, 1 mL/lantern) to yield the crude carboxylic acid product **A01C(01–46)**.

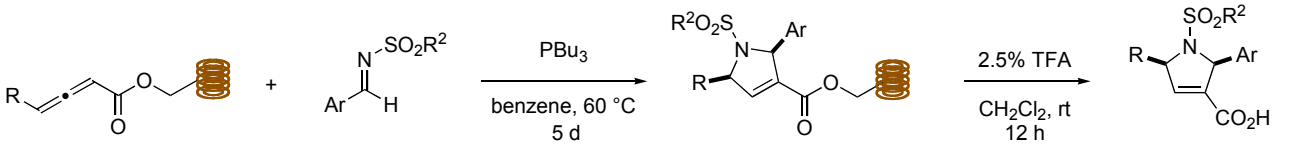
The spectroscopic data of a representative product **A01C02** are listed below.



L-A01C(01-46) A01C02

1-(4-Toluenesulfonyl)-2-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylic Acid (A01C02). According to the general procedure, **L-A01C02** was formed. Three lanterns were then treated with 2.5% TFA/DCM (3 mL) to yield a crude product (15.6 mg, 97% yield), which was purified by flash column chromatography (SiO_2; hexane/EtOAc, 4/1 with 2% AcOH) to afford **A01C02** as an off-white solid (14.7 mg, 91%). IR (neat) ν 3408, 2964, 2926, 2875, 1697, 1645, 1455, 1343, 1162, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 9.5 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 1.5 Hz, 1H), 5.67 (d, *J* = 6.0 Hz, 1H), 4.52–4.48 (dd, *J* = 2.0, 18.0 Hz, 1H), 4.41–4.36 (dd, *J* = 1.5, 6.0 Hz, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 2.06–1.99 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 143.3, 138.0, 137.9, 136.2, 135.6, 135.3, 129.5, 129.1, 127.7, 127.1, 68.5, 54.9, 21.5, 21.2; HRMS (EI) calcd. for $C_{19}H_{19}NO_4S$ [M^+] 357.1031, found 357.1035.

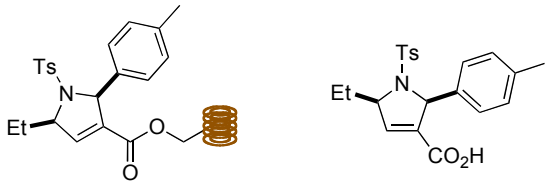
[3 + 2] Cycloaddition of Lantern-Bound 4-Substituted 2,3-Butadienoates



L-A(02-11) C(01-46) L-A(02-11)C(01-46) A(02-11)C(01-46)

General Procedure. Lantern-bound 4-substituted-2,3-butadienoate **L-A(02–11)** was washed under Ar flow with dry THF (1 mL/lantern, 5 times) and dry benzene (1 mL/lantern, 5 times). A solution of 5 equiv of *N*-tosylimine in benzene (0.5 mL for each lantern) was then added followed by 0.5 equiv of tributylphosphine. The mixture was agitated manually and heated at 60 °C for 5 days. The reaction solution was then removed and the light-yellow lanterns were washed as follows: toluene, DCM × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, toluene, THF × 5, and then left in toluene overnight at 60 °C. Further washing with toluene × 5, THF × 5, DMF × 5, THF × 5, DMF × 5, THF × 5, and then left in DMF at 60 °C for 4 h; THF × 5, DMF × 5, THF × 5, DMF, NH_4Cl/H_2O, THF/H_2O, DCM × 5, toluene, THF × 5, DCM × 5, THF × 5, DCM × 5, THF × 5, DCM × 5, and then left in DCM for 1 h. (Note: Lanterns were soaked for at least 15 min before changing solvents.) The annulation products were cleaved by treatment with TFA/DCM 2.5% (1 mL/lantern) to yield the crude carboxylic acid products **A(02–11)C(01–46)**.

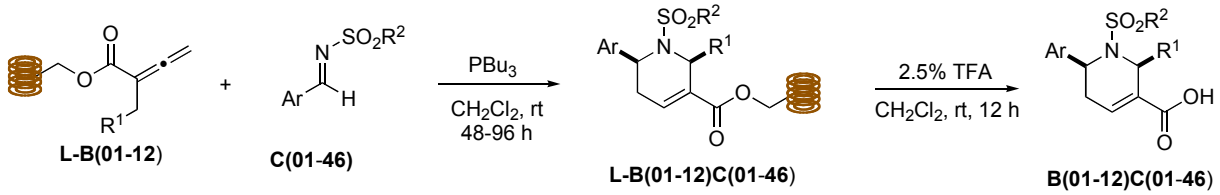
The spectroscopic data of the representative product **A05C02** are listed below.



L-A05C02 A05C02

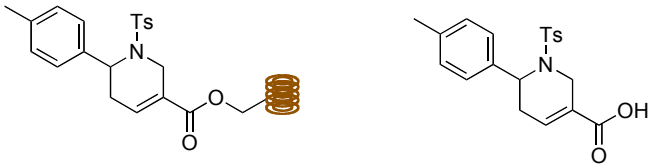
5-Ethyl-1-(4-toluenesulfonyl)-2-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylic Acid (A05C02). According to the general procedure, performed on a 0.045-mmol scale, **L-A05C02** was formed. Three lanterns were then treated with 2.5% TFA/DCM (3 mL) to yield a crude product (16.8 mg, 97% yield), which was purified by flash chromatography (SiO_2; hexane/EtOAc, 4:1 with 2% AcOH) to afford **A05C02** as an off-white solid (15.9 mg, 92% yield over three steps). IR (neat) ν 3408, 2964, 2926, 2875, 1697, 1645, 1455, 1343, 1162, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 4H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.87 (s, 1H), 5.65 (s, 1H), 4.60–4.56 (m, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 2.16–2.02 (m, 1H), 1.85–1.65 (m, 1H), 1.05 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 143.7, 142.5, 137.9, 136.7, 135.2, 133.2, 129.6, 129.1, 127.9, 127.5, 120.0, 68.9, 29.9, 21.5, 21.2, 10.4; HRMS (EI) calcd. for $C_{21}H_{23}NO_4S$ [M^+] 385.1348, found 385.1354.

Solid Phase [4 + 2] Annulations with *N*-Sulfonylimines

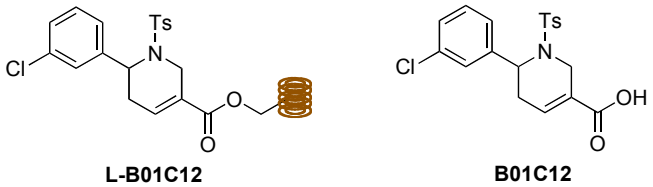


General Procedure. The lantern-bound allenoates **L-B(01–12)** were placed in an oven-dried vial or flask, charged with Ar, and washed with distilled, dry CH_2Cl_2 (3×). The solvent was evaporated and the *N*-sulfonylimine (5 equiv) was added as a solid. CH_2Cl_2 (0.5 mL/lantern) was added. After the imine had dissolved, PBu_3 (0.5 equiv) was added. The vial or flask was removed from the Ar line, capped, and then gently shaken or swirled at room temperature for 48 h (R^1 = H) or 96 h (R^1 = aryl). The lanterns were washed as follows (ca. 1 mL solvent/lantern; the lanterns were soaked at least for a couple of minutes at room temperature unless otherwise stated): CH_2Cl_2 (5×), toluene (2×), THF (3×), DMF (3×), THF (3×), 20% Bu_3N in THF at 60 °C for 16 h (1×), THF (3×), 50% H_2O in THF (3×), THF (3×), 20% HOAc in THF for 1h (1×), THF (3×), 50% H_2O in THF (3×), THF (3×), DMF (3×), THF (3×), 20% Bu_3N in THF at 60 °C for 16 h (1×), THF (3×), 50% H_2O in THF (3×), THF (3×), 20% HOAc in THF for 1h (1×), THF (3×), 50% H_2O in THF (2×), 2.5 M aqueous NH_4Cl:THF (1:1) for 1 h (1×), 50% H_2O in THF (3×), THF (3×), DMF (3×), THF (3×), toluene (2×), CH_2Cl_2 (3×), toluene for 16 h (1×), CH_2Cl_2 (3×). The loaded lanterns were dried in the air or used directly in the next step. After washing, the products **L-B(01–12)C(01–46)** were cleaved from the lantern by adding a solution of 2.5% TFA in CH_2Cl_2 (1 mL) and leaving the mixture to stand for 12 h in a small vial. Removal of the lantern, rinsing it with CH_2Cl_2, and concentration afforded the product as a crude oil. Small amounts of remaining TFA were removed by co-evaporation with $CHCl_3$ and blow-drying using a gentle flow of air.

The spectroscopic data of the representative products **B01C02**, **B01C12**, and **B02C02** are listed below.

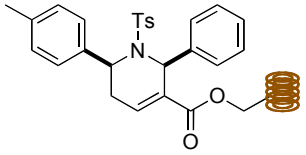


1-(4-Toluenesulfonyl)-6-(*p*-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid (B01C02). According to the general procedure, lantern-bound 2-methyl-buta-2,3-dienoate **L-B01** (80 L-lanterns, 1.20 mmol) was reacted with 4-methyl-*N*-(4-methylbenzylidene)-benzenesulfonamide **C02** (1.64 g, 6 mmol) in the presence of *n*-Bu_3P (150 μL, 0.6 mmol). After washing, the product was cleaved from one lantern by adding a solution of 2.5% TFA in CH_2Cl_2 (1 mL) and letting it stand for 12 h. Cleavage afforded **B01C02** as a yellowish oil; crude yield: 6.2 mg (0.0167 mmol, 111%); yield after flash column chromatography: 5.25 mg (0.0142 mmol, 94%). IR (film) ν 3032, 2930, 1694, 1340, 1160, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.16–7.07 (m, 5H), 5.33 (d, *J* = 6.6 Hz, 1H), 4.43 (d, *J* = 18.6 Hz, 1H), 3.45–3.38 (m, 1H), 2.67–2.55 (m, 2H), 2.41 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 143.6, 139.7, 137.7, 137.2, 134.8, 129.8, 129.3, 127.1, 127.0, 126.7, 51.8, 39.1, 27.2, 21.5, 21.0; HRMS (EI) calcd. for $C_{20}H_{21}NO_4S$ [M^+] 371.1191, found 371.1184.

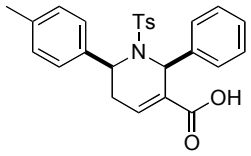


6-(3-Chlorophenyl)-1-(4-toluenesulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid (B01C12). According to the general procedure, lantern-bound 2-methylbuta-2,3-dienoate **L-B01** (6 L-lanterns, 0.09 mmol) was reacted with *N*-(3-chlorobenzylidene)-4-methylbenzenesulfonamide **C12** (0.132 g, 0.45 mmol) in the presence of *n*-Bu_3P (12 μL, 0.045 mmol). After washing, the product was cleaved from one lantern by adding a solution of 2.5% TFA in CH_2Cl_2 (1 mL) and letting the mixture stand for 12 h. Cleavage afforded **B01C12** as a yellowish oil; crude yield: 5.9 mg

(0.015 mmol, 100%); yield after flash column chromatography: 5.8 mg (99%). R_f 0.22 (hexanes/EtOAc, 2:1 + 2% HOAc); IR (film) ν 2925, 1692, 1596, 1433, 1338, 1289, 1160, 1101, 960, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.39–7.32 (m, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.23–7.12 (m, 2H), 5.33 (d, *J* = 6.4 Hz, 1H), 4.49 (d, *J* = 18.8 Hz, 1H), 3.44 (d, *J* = 18.7 Hz, 1H), 2.70–2.53 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 169.2, 143.9, 140.0, 138.8, 137.0, 134.6, 130.0, 129.9, 128.2, 127.4, 127.0, 126.9, 125.3, 51.7, 39.3, 27.2, 21.6; HRMS (EI) calcd. for $C_{19}H_{18}ClNO_4S$ [M^+] 391.0645, found 391.0646.



L-B02C02

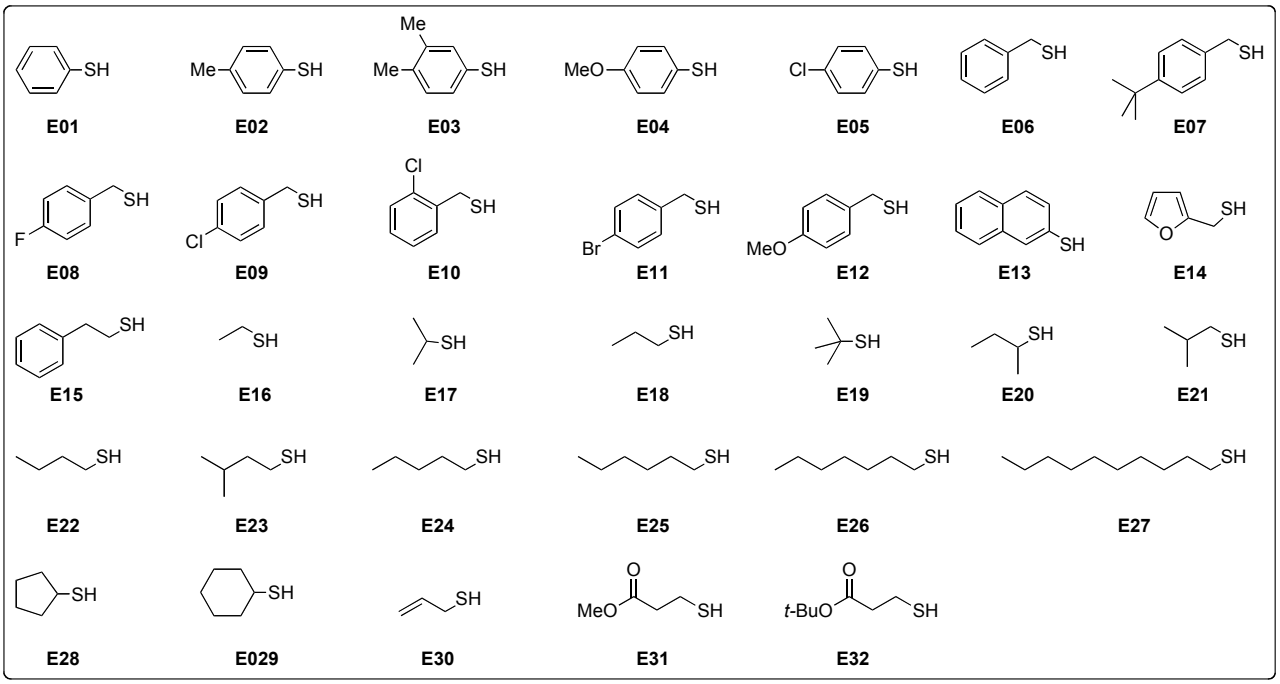


B02C02

2-Phenyl-1-(4-toluenesulfonyl)-6-(*p*-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid (B02C02). Following the general procedure, lantern-bound 2-benzylbuta-2,3-dienoate **L-B02** (31 L-Lanterns, 0.465 mmol) was reacted with *N*-(4-methylbenzylidene)-4-methylbenzenesulfonamide **C02** (0.64 g, 2.33 mmol) in the presence of *n*-Bu_3P (58 μL, 0.235 mmol). Cleavage afforded **B02C02** as a yellowish oil; crude yield: 7.0 mg (0.0156 mmol, 104%); yield after flash column chromatography: 6.1 mg (91%). IR (film) ν 2923, 1690, 1341, 1284, 1161, 1090, 730, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.99–6.91 (m, 6H), 6.83 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.11 (s, 1H), 5.11 (m, 1H), 2.70–2.63 (m, 1H), 2.42 (s, 3H), 2.25–2.17 (m, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 143.7, 140.8, 138.1, 137.2, 136.8, 135.2, 130.1, 129.9, 128.4, 127.7, 127.6 (2x), 127.2, 126.5, 54.1, 52.5, 26.4, 21.6, 20.8; HRMS (EI) calcd. for $C_{26}H_{25}NO_4S$ [M^+] 447.1504, found 447.1506.

Solid Phase Thiol Addition to the Dihydropyrrole Scaffold

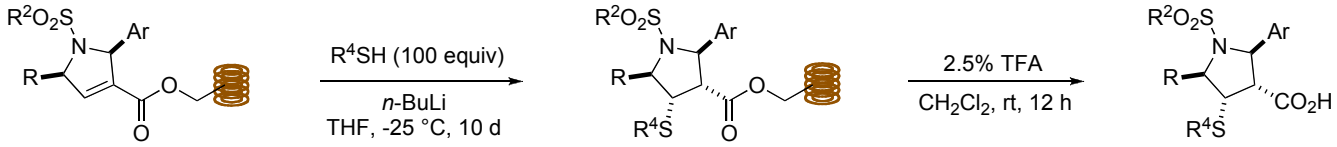
Chart 4. Thiol building blocks **E(01–32)**



For each of the selected thiols, the reaction conditions were optimized. The conditions used for the library synthesis are listed below.

Conditions A: For thiols **E01**, **E06**, **E07**, **E16**, **E25**, **E30**, **E32**, **E02**, **E04**, **E17**, **E18**, **E19**, **E20**, **E21**, **E22**, **E23**, **E24**, **E28**, and **E29** with the imine building blocks **C01**, **C03**, **C09**, **C10**, **C24**, and **C27**; 100 equiv thiol, 10 equiv *n*-BuLi, THF, –25 °C, 10 d.

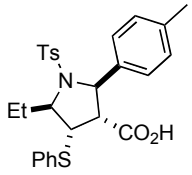
Conditions B: For thiols **E02**, **E04**, **E17**, **E18**, **E19**, **E20**, **E21**, **E22**, **E23**, **E24**, **E28**, and **E29** with the rest of the imines: 100 equiv thiol, 6 equiv *n*-BuLi, THF, –25 °C, 10 d.



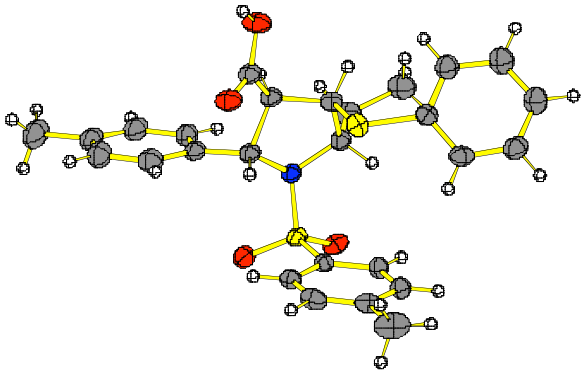
L-A(05-11)C(01-46) **L-A(05-11)C(01-46)E(01-32)** **A(05-11)C(01-46)E(01-32)**

General Procedure. The lantern-bound dihydropyrrole **L-A(05–11)C(01–46)** was placed in an oven-dried vial or flask and charged with Ar. The lantern(s) were washed five times with freshly distilled THF and then soaked in THF (0.5 mL/lantern) for 30 min. The thiol (100 equiv, in solid or liquid form) was then added. The vial or flask was placed in a cooling bath at –70 °C and *n*-BuLi (6 or 10 equiv) was added via syringe. The mixture was left to warm to room temperature over 30 min, the Ar line was removed, and the vial was capped and placed in a freezer at –25 °C for 10 days. The lanterns were then washed as follows: THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), DMF (5×), CH_2Cl_2 (3×), toluene (1× and overnight), THF (5×), 50% H_2O in THF (1×), 2.5 M aqueous NH_4Cl:THF (1:1) for 1 h (1×), 50% H_2O in THF (3×), THF (5×), DMF (3×), DMF (1× and overnight), THF (3×), CH_2Cl_2 (3×), toluene (3×), THF (3×), CH_2Cl_2 (3×), toluene (3×), CH_2Cl_2 (3×). The lanterns were soaked in CH_2Cl_2 for 30 min and then a solution of 2.5% TFA in CH_2Cl_2 (ca. 1 mL per lantern) was added to cleave the compound. After 12 h, the lantern was removed, rinsed with CH_2Cl_2, and concentrated to afford the crude product **A(05–11)C(01–46)E(01–32)**.

The spectroscopic data of the representative product **A05C02E01** are listed below. Crystallographic data for **A05C02E01** and **B01C02E01** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 631680 and 631681. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).



A05C02E01



5-Ethyl-4-phenylsulfanyl-1-(4-toluenesulfonyl)-2-(*p*-tolyl)-pyrrolidine-3-carboxylic Acid (A05C02E01). Following the procedure described above, **L-A05C02** was reacted with benzenethiol (0.045 mmol scale, conditions A). Upon TFA-mediated cleavage, the product **A05C02E01** was obtained as an off-white solid (13.2 mg, 89% yield over four steps). IR (neat) ν 3544, 3165, 3002, 2944, 1726, 1634, 1444, 1375, 1164, 819, 750, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 5.0 Hz, 2H), 7.33–7.30 (m, 5H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.00 (d, *J* = 10.0 Hz, 1H), 3.95 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.69 (d, *J* = 6.0 Hz, 1H), 3.47 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.46 (s, 3H), 2.36 (s, 3H), 2.14–2.09 (m, 1H), 1.80–1.74 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 143.4, 137.4, 137.2, 134.6, 133.1 132.3, 129.3, 129.1, 128.9, 128.2, 128.0, 127.8, 127.0, 69.7, 64.0, 56.0, 51.9, 29.7, 21.5, 21.0, 10.6; HRMS (EI) calcd. for $C_{27}H_{29}NO_4S_2$ [M^+] 495.1523, found 495.1538.

Solid Phase Thiol Addition to the Tetrahydropyridine Scaffold

For each of the selected thiols, the reaction conditions were optimized. The conditions used for the library synthesis are listed below.

Conditions A: For **E01**, **E02**, **E04**, and **E05**; 100 equiv thiol, 1 equiv *n*-BuLi, 1 equiv [12]crown-4, THF, 60 °C, 4 d.

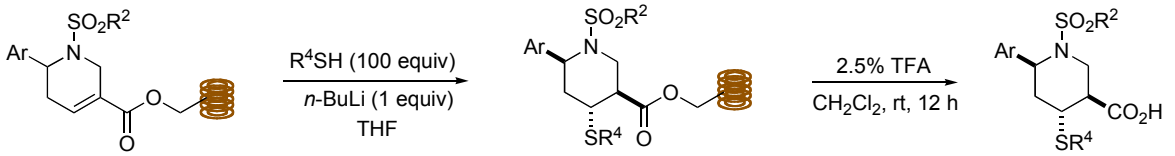
Conditions B: For **E06** and **E09**; 100 equiv thiol, 1 equiv *n*-BuLi, THF, rt, 4 d.

Conditions C: For **E15**, **E16**, **E18**, and **E30**; 100 equiv thiol, 1 equiv *n*-BuLi, THF, 40 °C, 2 d.

Conditions D: For **E22**; 100 equiv thiol, 1 equiv *n*-BuLi, THF, 40 °C, 4 d.

Conditions E: For **E07**, **E21**, and **E24**; 100 equiv thiol, 1 equiv *n*-BuLi, THF, 40 °C, 8 d.

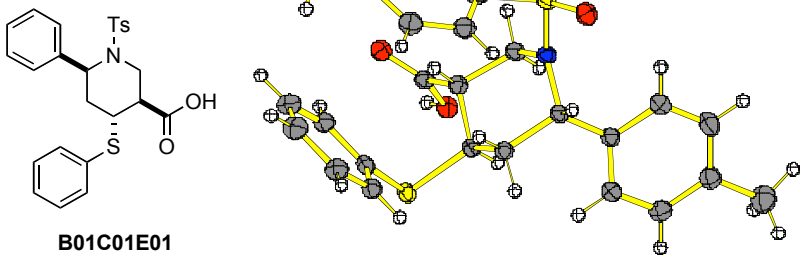
Conditions F: For **E23**, **E25**, and **E28**; 100 equiv thiol, 1 equiv *n*-BuLi, THF, 60 °C, 2 d.



L-B01C(01-46) **L-B01C(01-46)E(01-32)** **B01C(01-46)E(01-32)**

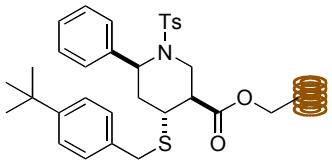
General Procedure. The lantern-bound 6-aryl-*N*-sulfonyl-1,2,5,6-tetrahydropyridine-3-carboxylate **L-B01C(01–46)** was placed in an oven-dried vial or flask and charged with Ar. The lantern(s) were washed three times with freshly distilled THF and then soaked in THF (0.5 mL/lantern). The thiol (100 equiv) was added to the soaked lanterns as a liquid or as a solid. In the case of aromatic thiols, [12]crown-4 (1 equiv) was added. The vial or flask was placed in a cooling bath at −70 °C and *n*-BuLi (1 equiv) was added via syringe. The mixture was left to warm to room temperature over 30 min, the Ar line was removed, and then the vial was capped and placed aside for the indicated time and at the indicated temperature. It was not necessary to shake or swirl this mixture during the reaction. After the reaction was complete, the lanterns were washed as follows: THF (5×), DMF (3×), THF (3×), CH_2Cl_2 (3×), toluene (1× and overnight), THF (3×), 50% H_2O in THF (1×), 2.5 M aqueous NH_4Cl:THF (1:1) for 1 h (1×), 50% H_2O in THF (3×), THF (3×), DMF (2×), DMF (1× and overnight), THF (3×), CH_2Cl_2 (3×), toluene (3×), THF (3×), CH_2Cl_2 (3×), toluene (3×), CH_2Cl_2 (3×). After washing, the product was cleaved from a lantern by adding a solution of 2.5% TFA in CH_2Cl_2 (1 mL) and then letting the mixture stand for 12 h in a 4-mL vial. Removal of the lantern, rinsing it with CH_2Cl_2, and concentration afforded the product as a crude oil. Small amounts of remaining TFA were removed by co-evaporation with $CHCl_3$ and blow-drying using a gentle flow of air.
Note: Because the thioethers are sensitive, extensive contact with basic media should be avoided to prevent β-elimination.

The spectroscopic data of the representative products **B01C01E01** and **B01C01E07** are listed below. The ORTEP drawing below is that of the piperidine derivative **B01C02E01** presenting a 6-tolyl substituent.

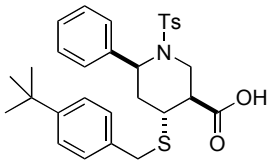


B01C01E01

6-Phenyl-4-phenylsulfanyl-1-(4-toluenesulfonyl)-piperidine-3-carboxylic Acid (B01C01E01). According to the general procedure, lantern-bound 6-phenyl-1-(4-toluenesulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate **L-B01C01** (1 lantern, 0.015 mmol) was reacted with benzenethiol **E01** (154 μL, 1.5 mmol) and *n*-BuLi (10 μL, 0.015 mmol) in the presence of [12]crown-4 (2.4 μL, 0.015 mmol). The reaction mixture was heated at 60 °C for 4 days (conditions A). Cleavage afforded **B01C01E01** as a slightly yellow-colored oil. Crude yield: 5.4 mg (0.0115 mmol, 77%). IR (film) ν 3429, 2925, 1708, 1448, 1339, 1157, 1091, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.38–7.19 (m, 12H), 5.29 (br d, *J* = 5.1 Hz, 1H), 4.14–4.09 (m, 1H), 3.15–3.06 (m, 2H), 2.55 (d, *J* = 13.5 Hz, 1H), 2.44 (s, 3H), 2.39–2.32 (s, 1H), 1.60–1.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 143.6, 137.5, 136.8, 135.1, 130.3, 130.0, 129.0, 128.9, 128.5, 127.5, 126.8, 126.4, 55.2, 46.7, 43.6, 41.6, 32.8, 21.7; HRMS (EI) calcd. for $C_{25}H_{25}NO_4S_2$ [M^+] 467.1225, found 467.1214.



L-B01C01E07



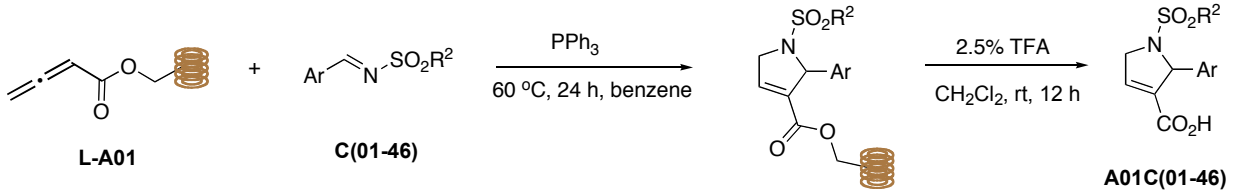
B01C01E07

4-(4-*tert*-Butylbenzylsulfanyl)-6-phenyl-1-(4-toluenesulfonyl)-piperidine-3-carboxylic Acid (B01C01E07). According to the general procedure, lantern-bound 6-phenyl-1-(4-toluenesulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate **L-B01C01** (1 lantern, 0.015 mmol) was reacted with 4-*tert*-butylbenzylmercaptan **E07** (0.28 mL, 1.5 mmol) in the presence of *n*-BuLi (10 μL, 0.015 mmol) as a base for 8 days at 40 °C (conditions E). Cleavage afforded **B01C01E07** as a slightly yellow-colored oil. Crude yield: 7.9 mg (0.0143 mmol, 95%). IR (film) ν 2962, 1709, 1449, 1340, 1158, 1092, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.35–7.31 (m, 4H), 7.25–7.20 (m, 3H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 5.24 (br d, *J* = 4.8 Hz, 1H), 4.09–4.05 (m, 1H), 3.63 (s, 2H), 3.00–2.95 (m, 1H), 3.81–3.73 (m, 1H), 2.44 (s, 3H), 2.36–2.33 (m, 2H), 1.73–1.64 (m, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 150.1, 143.7, 137.6, 136.8, 134.6, 130.0, 128.7, 128.5, 127.2, 126.9, 126.4, 125.4, 55.1, 47.4, 43.5, 38.2, 35.2, 34.4, 33.6, 31.2, 21.4; HRMS (EI) calcd. for $C_{30}H_{35}NO_4S_2$ [M^+] 537.2007, found 537.1965.

Screening for the Selection of Building Blocks Used in the Library Synthesis

Building Block Screening for the [3 + 2] Annulation

Screening Imines Using Resin-Bound Allenoate L-A01: Imines were reacted with allenoate **L-A01** according to the general procedure described previously. The data from the spectroscopic analyses (^1H NMR and LCMS spectra; see Supporting Information, Part C, for copies of spectra and chromatograms) of the cleaved annulation products **A01C(01–46)** are summarized in Table 3. Based on this screen, 30 imines (of 46) were chosen for inclusion in the library synthesis.



L-A01 C(01-46) L-A01C(01-46) A01C(01-46)

Table 3. Unsubstituted Lantern-Bound Allenoate + Imine Screening.

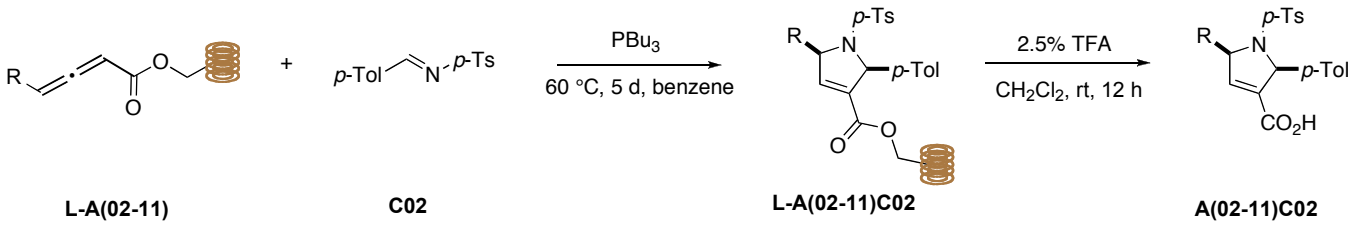
entry	product Ar	product R^2	product no.	yield[a] (%)	calcd. [M]	LCMS[b] observed $[M + Na]^+$	LCMS[b] retention time (min)	LCMS[b] purity (%)	incl.
1	Ph	*p*-tolyl	**A01C01**	95	343.09	366.0	3.609	89	√
2	4-MeC_6H_4	*p*-tolyl	**A01C02**	97	357.10	380.0	3.744	93	√
3	4-EtC_6H_4	*p*-tolyl	**A01C03**	72	371.12	394.0	3.983	99	√
4	4-$OMeC_6H_4$	*p*-tolyl	**A01C04**	46	373.10	N/A	N/A	N/A	no

5	4-OEtC_6H_4	*p*-tolyl	**A01C05**	60	387.11	N/A	N/A	N/A	no
6	piperonal	*p*-tolyl	**A01C06**	69	387.08	410.0	3.625	99	√
7	4-$Me_2NC_6H_4$	*p*-tolyl	**A01C07**	49	386.13	N/A	N/A	N/A	no
8	4-$Et_2NC_6H_4$	*p*-tolyl	**A01C08**	51	414.16	N/A	N/A	N/A	no
9	4-CNC_6H_4	*p*-tolyl	**A01C09**	99	368.08	391.0	3.627	99	√
10	2-FC_6H_4	*p*-tolyl	**A01C10**	99	361.08	384.0	3.701	99	√
11	4-ClC_6H_4	*p*-tolyl	**A01C11**	99	377.05	400.0	3.885	99	√
12	3-ClC_6H_4	*p*-tolyl	**A01C12**	99	377.05	400.0	3.867	87	√
13	3,4-ClC_6H_4	*p*-tolyl	**A01C13**	95	411.01	434.9	4.035	100	√
14	4-BrC_6H_4	*p*-tolyl	**A01C14**	89	421.00	445.9	3.928	98	√
15	3-BrC_6H_4	*p*-tolyl	**A01C15**	95	421.00	445.9	3.904	97	√
16	1-naphthyl	*p*-tolyl	**A01C16**	63	393.10	416.0	3.907	96	√
17	2-furyl	*p*-tolyl	**A01C17**	68	333.07	N/A	N/A	N/A	no
18	Ph	*p*-NO_2Ph	**A01C18**	95	374.06	397.0	3.680	99	√
19	Ph	Me	**A01C19**	110	267.06	290.0	2.874	84	√
20	3,4-$OMeC_6H_4$	*p*-tolyl	**A01C20**	45	403.11	N/A	N/A	N/A	no
21	2-thiophenyl	*p*-tolyl	**A01C21**	67	349.04	N/A	N/A	N/A	no
22	4-Me-2-furyl	*p*-tolyl	**A01C22**	46	347.08	N/A	N/A	N/A	no
23	4-FC_6H_4	*p*-tolyl	**A01C23**	90	361.08	384.0	3.738	99	√
24	4-*i*-PrC_6H_4	*p*-tolyl	**A01C24**	65	385.13	408.1	4.116	98	√
25	3,4,5-$OMeC_6H_4$	*p*-tolyl	**A01C25**	57	433.12	N/A	N/A	N/A	no
26	3-FC_6H_4	*p*-tolyl	**A01C26**	79	361.08	384.0	3.736	94	√
27	4-ClC_6H_4	*p*-ClPh	**A01C27**	75	396.99	421.9	3.981	93	√
28	4-ClC_6H_4	Me	**A01C28**	86	301.02	323.9	3.198	88	√
29	4-ClC_6H_4	Ph	**A01C29**	97	363.03	386.0	3.738	96	√
30	4-MeC_6H_4	*p*-ClPh	**A01C30**	100	377.05	400.0	3.943	98	√
31	4-ClC_6H_4	*o*-CO_2MePh	**A01C31**	112	421.04	444.0	3.716	100	√
32	1-Methyl-pyrrolyl	*p*-tolyl	**A01C32**	24	346.10	N/A	N/A	N/A	no
33	3-MeC_6H_4	*p*-tolyl	**A01C33**	87	357.10	380.0	3.798	99	√
34	4-$OMeC_6H_4$	*o*-CO_2MePh	**A01C34**	78	417.09	N/A	N/A	N/A	no
35	4-$OMeC_6H_4$	Ph	**A01C35**	63	359.08	N/A	N/A	N/A	no
36	4-MeC_6H_4	*o*-NO_2Ph	**A01C36**	142	388.07	411.0	3.741	95	√
37	4-$OMeC_6H_4$	*p*-ClPh	**A01C37**	68	393.04	N/A	N/A	N/A	no
38	4-$OMeC_6H_4$	*o*-tolyl	**A01C38**	34	373.10	N/A	N/A	N/A	no
39	3-$OMeC_6H_4$	*p*-tolyl	**A01C39**	41	373.10	N/A	N/A	N/A	no
40	4-ClC_6H_4	*o*-tolyl	**A01C40**	104	377.05	400.0	3.897	100	√
41	4-MeC_6H_4	*o*-tolyl	**A01C41**	80	357.10	380.0	3.852	90	√
42	4-MeC_6H_4	*o*-CO_2MePh	**A01C42**	50	401.09	424.0	3.659	84	√
43	4-MeC_6H_4	Ph	**A01C43**	97	343.09	366.0	3.681	94	√
44	4-MeC_6H_4	*p*-NO_2Ph	**A01C44**	81	388.07	411.0	3.801	96	√
45	4-MeC_6H_4	*m*-NO_2Ph	**A01C45**	68	388.07	N/A	N/A	N/A	no
46	4-MeC_6H_4	Me	**A01C46**	48	281.07	304.0	3.017	86	√

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.

Screening γ-Substituted Allenoic Acids Using *N*-Tosyltolualdimine C02: Allenoic acids were loaded and reacted with imine **C02** according to the general procedure on pages S18 and S19. The data from the spectroscopic analyses (^{1}H NMR and LCMS spectra; see Supporting Information, Part C, for copies of spectra and chromatograms) of the

cleaved annulation products **A(02–11)C02** are summarized in Table 4. Based on these results, all of the γ-substituted allenoic acids were chosen for inclusion in the library synthesis.



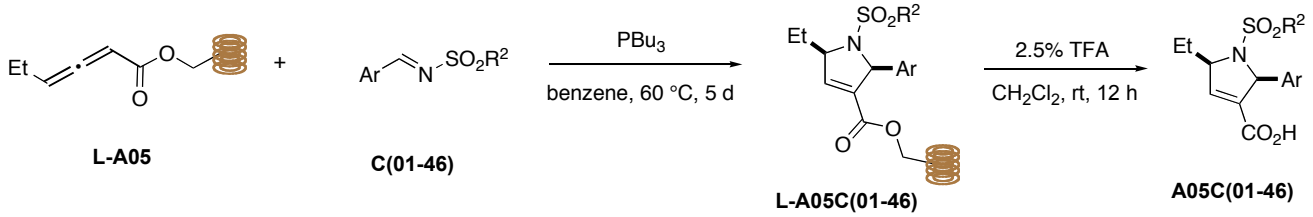
L-A(02-11) **C02** **L-A(02-11)C02** **A(02-11)C02**

Table 4. γ-Substituted Allenoic Acid Screening.

	product		NMR				LCMS[b]			
entry	R	no.	conv. (%)	yield (%)[a]	dr	calcd. [M]	observed $[M + Na]^+$	retention time (min)	purity (%)	incl.
1	Me	**A02C02**	>99	100	92:8	371.12	394.1	3.871	80	√
2	*t*-Bu	**A03C02**	>99	80	99:1	413.17	436.1	4.383	100	√
3	Ph	**A04C02**	>99	50	99:1	433.13	456.1	4.146	87	√
4	Et	**A05C02**	>99	99	95:5	385.13	408.1	4.090	89	√
5	*i*-Pr	**A06C02**	>99	92	99:1	399.15	422.1	4.158	83	√
6	*n*-Pr	**A07C02**	>99	102	99:1	399.15	422.1	4.176	72	√
7	*n*-Bu	**A08C02**	>99	77	99:1	413.17	436.1	4.425	89	√
8	*n*-pentyl	**A09C02**	>99	66	99:1	427.18	450.1	4.516	74	√
9	*n*-hexyl	**A10C02**	>99	85	83:17	441.20	464.1	4.683	49	√
10	cyp-Me	**A11C02**	>99	70	92:8	439.18	462.1	4.547	87	√

[a] Crude yield after cleavage.
[b] Short 6 min method, purity observed at λ 210 nm.

Screening Imines Using Resin-Bound Allenoate L-A05: Imines were reacted with allenoate **L-A05** according to the general procedure in page S20. The analytical data (^{1}H NMR and LCMS spectra; see Supporting Information, Part C, for copies of spectra and chromatograms) of the cleaved annulation products **A05C(01–46)** are summarized in Table 5. Based on this screen, 21 imines (of 46) were chosen for inclusion in the library synthesis.



L-A05 **C(01-46)** **L-A05C(01-46)** **A05C(01-46)**

Table 5. Imine Screening in the [3 + 2] Annulation Using **L-A05**.

	product			NMR				LCMS[b]			
entry	Ar	R^2	no.	conv. (%)	yield[a] (%)	dr	calcd. [M]	obs. $[M + Na]^+$	ret. time (min)	purity (%)	incl.
1	Ph	*p*-tolyl	**A05C01**	>99	99	99:9	371.12	394.1	3.890	66	√[c]
2	4-MeC_6H_4	*p*-tolyl	**A05C02**	>99	99	95:5	385.13	408.1	4.090	89	√
3	4-EtC_6H_4	*p*-tolyl	**A05C03**	>99	100	98:2	399.15	422.1	4.237	83	√
4	4-$MeOC_6H_4$	*p*-tolyl	**A05C04**	>99	75	mess	401.13	N/A	N/A	N/A	no
5	4-$EtOC_6H_4$	*p*-tolyl	**A05C05**	>99	64	mess	415.15	N/A	N/A	N/A	no
6	piperonal	*p*-tolyl	**A05C06**	>99	87	>91:1	415.11	438.0	3.919	100	√
7	4-$Me_2NC_6H_4$	*p*-tolyl	**A05C07**	trace	58	mess	414.16	N/A	N/A	N/A	no
8	4-$Et_2NC_6H_4$	*p*-tolyl	**A05C08**	trace	63	mess	442.19	N/A	N/A	N/A	no

9	4-NCC_6H_4	*p*-tolyl	**A05C09**	>99	40	97:3	396.11	419.0	3.921	100	√
10	2-FC_6H_4	*p*-tolyl	**A05C10**	>99	106	100:0	389.11	412.0	3.969	71	√
11	4-ClC_6H_4	*p*-tolyl	**A05C11**	>99	66	96:4	405.08	406.1[d]	4.132	95	√
12	3-ClC_6H_4	*p*-tolyl	**A05C12**	>99	53	93:7	405.08	428.0	4.159	79	√
13	3,4-ClC_6H_4	*p*-tolyl	**A05C13**	>99	85	94:6	439.04	440.0[d]	4.306	85	√
14	4-BrC_6H_4	*p*-tolyl	**A05C14**	>99	98	93:7	449.03	474.0*	4.217	87	√
15	3-BrC_6H_4	*p*-tolyl	**A05C15**	>99	70	mess	449.03	472.2	4.201	66	no
16	1-naphthyl	*p*-tolyl	**A05C16**	>99	79	100:0	421.13	444.0	4.173	95	√
17	2-furyl	*p*-tolyl	**A05C17**	no rxn	56	mess	361.10	N/A	N/A	N/A	no
18	Ph	*p*-NO_2Ph	**A05C18**	mess	68	mess	402.09	N/A	N/A	N/A	no
19	Ph	Me	**A05C19**	>99	140	100:0	295.09	318.0	3.327	57	√[c]
20	3,4-$MeOC_6H_4$	*p*-tolyl	**A05C20**	>99	65		431.14	454.0	3.767	80	√
21	2-thiophenyl	*p*-tolyl	**A05C21**	mess	64	mess	377.08	N/A	N/A	N/A	no
22	4-Me-2-furyl	*p*-tolyl	**A05C22**	no rxn	67	-	375.11	N/A	N/A	N/A	no
23	4-FC_6H_4	*p*-tolyl	**A05C23**	>99	89	92:8	389.11	412.0	4.026	92	√
24	4-*i*-PrC_6H_4	*p*-tolyl	**A05C24**	>99	92	94:6	413.17	436.1	4.378	88	√
25	3,4,5-$MeOC_6H_4$	*p*-tolyl	**A05C25**	mess	38	mess	461.15	N/A	N/A	N/A	no
26	3-FC_6H_4	*p*-tolyl	**A05C26**	>99	60	96:4	389.11	412.0	4.028	78	√
27	4-ClC_6H_4	*p*-ClPh	**A05C27**	>99	81	98:2	425.03	447.9	4.268	75	√
28	4-ClC_6H_4	Me	**A05C28**	mess	95	mess	329.05	N/A	N/A	N/A	no
29	4-ClC_6H_4	Ph	**A05C29**	>99	91		391.06	414.0	4.045	86	√
30	4-MeC_6H_4	*p*-ClPh	**A05C30**	>99	79	93:7	405.08	428.0	4.220	78	√
31	4-ClC_6H_4	*o*-CO_2MePh	**A05C31**	mess	71	mess	449.07	472.0	3.998	54	no
32	1-Methyl-pyrrolyl	*p*-tolyl	**A05C32**	no rxn	23	-	374.13	N/A	N/A	N/A	no
33	3-MeC_6H_4	*p*-tolyl	**A05C33**	>99	92	92:8	385.13	408.1	4.092	91	√
34	4-$MeOC_6H_4$	*o*-CO_2MePh	**A05C34**	mess	nd	mess	445.12	N/A	N/A	N/A	no
35	4-$MeOC_6H_4$	Ph	**A05C35**	mess	nd	mess	387.11	N/A	N/A	N/A	no
36	4-MeC_6H_4	*o*-NO_2Ph	**A05C36**	mess	nd	mess	416.10	N/A	N/A	N/A	no
37	4-$MeOC_6H_4$	*p*-ClPh	**A05C37**	mess	nd	mess	421.08	N/A	N/A	N/A	no
38	4-$MeOC_6H_4$	*o*-tolyl	**A05C38**	mess	nd	mess	401.13	N/A	N/A	N/A	no
39	3-$MeOC_6H_4$	*p*-tolyl	**A05C39**	mess	nd	mess	401.13	N/A	N/A	N/A	no
40	4-ClC_6H_4	*o*-tolyl	**A05C40**	>99	108		405.08	406.1[d]	4.181	67	√[c]
41	4-MeC_6H_4	*o*-tolyl	**A05C41**	>99	105	100:0	385.13	386.1[d]	4.113	55	√[c]
42	4-MeC_6H_4	*o*-CO_2MePh	**A05C42**	mess	nd	mess	429.12	N/A	N/A	N/A	no
43	4-MeC_6H_4	Ph	**A05C43**	>99	100		371.12	394.1	3.883	70	no
44	4-MeC_6H_4	*p*-NO_2Ph	**A05C44**	mess	nd	mess	416.10	N/A	N/A	N/A	no
45	4-MeC_6H_4	*m*-NO_2Ph	**A05C45**	mess	nd	mess	416.10	N/A	N/A	N/A	no
46	4-MeC_6H_4	Me	**A05C46**	>99	97		309.10	332.1	3.388	57	no

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.
[c] Selection based on ^{1}H NMR spectrum.
[d] $[M + H]^+$

Building Block Screening for the [4 + 2] Annulation

Screening Imines Using Resin-Bound Allenoate L-B01. Imines **C(01–46)** were reacted with allenoate **L-B01** according to the general procedure described previously. The analytical data (^{1}H NMR and LCMS spectra; see Supporting Information, Part D, for copies of spectra and chromatograms) of the cleaved annulation products **B01C(01–46)** are summarized in Table 6. Based on these results, 25 imines (of 46) were chosen for inclusion in the library synthesis.

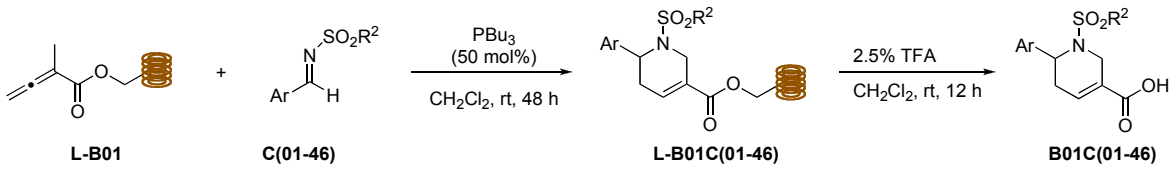


Table 6. Screening Imines **C(01–46)** Using Resin-Bound Allenoate **L-B01**.

		product					LCMS[b]			
entry	imine	Ar	SO_2R^2	no.	yield[a] (%)	calcd. [M]	retention time (min)	observed $[M + Na]^+$	purity (%)	incl.
1	C01	Ph	Ts	**B01C01**	108	357.10	3.91	380.0	85	√
2	C02	4-MeC_6H_4	Ts	**B01C02**	102	371.12	4.02	394.0	99	√
3	C03	4-EtC_6H_4	Ts	**B01C03**	118	385.13	4.18	408.1	99	√
4	C04	4-$MeOC_6H_4$	Ts	**B01C04**	95	387.11	3.82	410.1	68	√
5	C05	4-$EtOC_6H_4$	Ts	**B01C05**	80	401.13	4.09	424.0	99	√
6	C06	piperonyl	Ts	**B01C06**	95	401.09	3.82	424.0	90	√
7	C07	4-$Me_2NC_6H_4$	Ts	**B01C07**	68	400.15	3.38	401.1[c]	73	no
8	C08	4-$Et_2NC_6H_4$	Ts	**B01C08**	62	428.18	nd	nd	nd	no
9	C09	4-NCC_6H_4	Ts	**B01C09**	82	382.10	3.74	405.0	50	no
10	C10	2-FC_6H_4	Ts	**B01C10**	100	375.09	3.85	398.0	95	√
11	C11	4-ClC_6H_4	Ts	**B01C11**	87	391.06	4.10	414.0	82	no
12	C12	3-ClC_6H_4	Ts	**B01C12**	100	391.06	3.99	414.0	80	√
13	C13	3,4-di-ClC_6H_4	Ts	**B01C13**	99	425.03	4.25	448.0	75	no
14	C14	4-BrC_6H_4	Ts	**B01C14**	84	435.01	4.13	460.0	77	no
15	C15	3-BrC_6H_4	Ts	**B01C15**	90	435.01	4.10	457.9	77	no
16	C16	1-naphthyl	Ts	**B01C16**	95	407.12	4.15	430.0	95	√
17	C17	2-furyl	Ts	**B01C17**	56	347.08	nd	nd	nd	no
18	C18	Ph	Ns	**B01C18**	50	388.07	nd	nd	nd	no
19	C19	Ph	Ms	**B01C19**	85	281.07	nd	nd	nd	no
20	C20	3,4-di-$MeOC_6H_4$	Ts	**B01C20**	83	417.12	3.66	440.0	91	√
21	C21	2-thiophene	Ts	**B01C21**	53	363.06	3.80	386.0	99	√
22	C22	5-methyl-2-furyl	Ts	**B01C22**	55	361.10	nd	nd	nd	no
23	C23	4-FC_6H_4	Ts	**B01C23**	89	375.09	3.91	398.0	82	no
24	C24	4-*i*-PrC_6H_4	Ts	**B01C24**	77	399.15	4.33	422.1	96	√
25	C25	3,4,5-tri-$MeOC_6H_4$	Ts	**B01C25**	61	447.14	3.67	470.0	80	√
26	C26	3-FC_6H_4	Ts	**B01C26**	103	375.09	3.90	398.0	78	no
27	C27	4-ClC_6H_4	4ClBs	**B01C27**	103	411.01	nd	nd	nd	no
28	C28	4-ClC_6H_4	Ms	**B01C28**	122	315.03	nd	nd	nd	no
29	C29	4-ClC_6H_4	Bs	**B01C29**	115	377.05	nd	nd	nd	no
30	C30	4-MeC_6H_4	4ClBs	**B01C30**	102	391.06	4.10	414.0	87	√
31	C31	4-ClC_6H_4	2MCBs	**B01C31**	67	435.05	3.90	458.0	85	no
32	C32	1-Me-2-pyrrole	Ts	**B01C32**	31	360.11	nd	nd	nd	no
33	C33	3-MeC_6H_4	Ts	**B01C33**	99	371.12	4.04	394.0	77	√
34	C34	4-$MeOC_6H_4$	2MCBs	**B01C34**	68	431.10	3.69	454.0	87	√
35	C35	4-$MeOC_6H_4$	Bs	**B01C35**	93	373.10	3.69	396.0	94	√
36	C36	4-MeC_6H_4	2Ns	**B01C36**	61	402.09	3.89	403.1[c]	95	√
37	C37	4-$MeOC_6H_4$	4ClBs	**B01C37**	103	407.06	3.93	430.0	92	√
38	C38	4-$MeOC_6H_4$	2Ts	**B01C38**	105	387.11	3.89	410.0	84	√
39	C39	3-$MeOC_6H_4$	Ts	**B01C39**	57	387.11	3.84	410.1	87	√

40	C40	4-ClC_6H_4	2Ts	**B01C40**	92	391.06	4.12	414.0	98	√
41	C41	4-MeC_6H_4	2Ts	**B01C41**	83	371.12	4.07	394.1	90	√
42	C42	4-MeC_6H_4	2MCBs	**B01C42**	90	415.11	3.86	438.0	93	√
43	C43	4-MeC_6H_4	Bs	**B01C43**	75	357.10	3.91	380.0	90	√
44	C44	4-MeC_6H_4	4Ns	**B01C44**	70	402.09	nd	nd	nd	no
45	C45	4-MeC_6H_4	3Ns	**B01C45**	51	402.09	nd	nd	nd	no
46	C46	4-MeC_6H_4	Ms	**B01C46**	97	295.09	3.39	318.0	55	no

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.
[c] $[M + H^+]$.

Screening α-Substituted Allenoic Acids Using *N*-Tosyltolualdimine (C02): Allenoic acids **B(02–12)** were loaded and reacted with imine **C02** according to the general procedures. The data from spectroscopic analyses (^{1}H NMR and LCMS spectra; see Supporting Information, Part D, for copies of spectra and chromatograms) of the cleaved annulation products **B(02–12)C02** are summarized in Table 7. Based on this screen, all of the α-substituted allenoic acids were chosen for inclusion in the library synthesis.

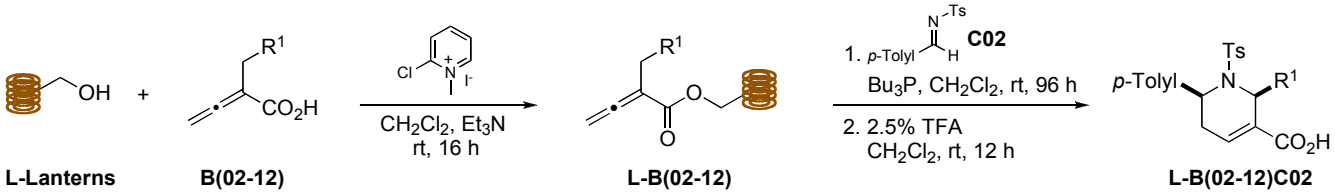


Table 7. Screen Data for Allenoic Acids **B(02–12)**

		product		NMR			LCMS[b]			
entry	allenoic acid	R^1	no.	d.r.	yield[a] (%)	calcd. [M]	retention time (min)	observed $[M + Na]^+$	purity (%)	incl.
1	B02	Ph	**B02C02**	93:7	104	447.15	4.36	470.1	85	√
2	B03	2-F-C_6H_4	**B03C02**	99:1	110	465.14	4.33	488.1	95	√
3	B04	3-F-C_6H_4	**B04C02**	95:5	93	465.14	4.39	488.0	98	√
4	B05	3-Cl-C_6H_4	**B05C02**	96:4	104	481.11	4.52	504.0	95	√
5	B06	3-Br-C_6H_4	**B06C02**	96:4	113	525.06	4.56	548.0	93	√
6	B07	3-Me-C_6H_4	**B07C02**	95:5	92	461.17	4.48	484.1	95	√
7	B08	4-F-C_6H_4	**B08C02**	94:6	100	465.14	4.40	488.1	98	√
8	B09	4-Cl-C_6H_4	**B09C02**	95:5	112	481.11	4.55	504.0	93	√
9	B10	4-Br-C_6H_4	**B10C02**	96:4	110	525.06	4.59	548.0	89	√
10	B11	4-Me-C_6H_4	**B11C02**	95:5	111	461.17	4.49	484.1	91	√
11	B12	4-*t*-Bu-C_6H_4	**B12C02**	94:6	98	503.21	4.87	526.1	99	√

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.

Screening Imines Using Resin-Bound Allenoate L-B05: Imines **C(01–46)** were reacted with allenoate **L-B05** according to the general procedure on page S20. The analytical data (^{1}H NMR and LCMS spectra; see Supporting Information, Part D, for copies of spectra and chromatograms) of the cleaved annulation products **B05C(01–46)** are summarized in Table 8. Based on these results, 31 imines (of 46) were chosen for inclusion in the library synthesis.

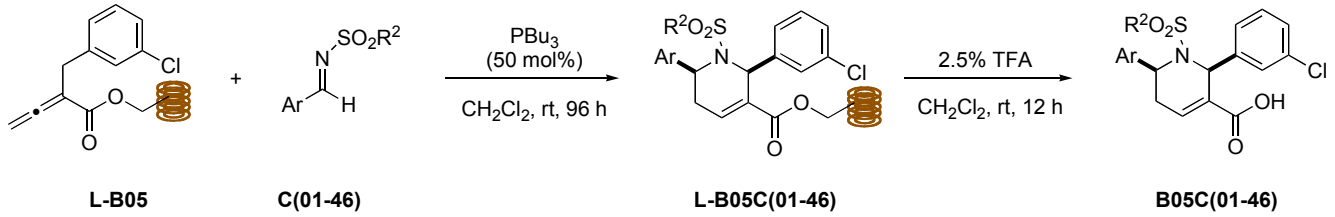


Table 8. Screening Imines Using Allenoate **L-B05**.

entry	imine	product			NMR			LCMS[b]			incl.
		Ar	R^2	no.	d.r.	yield[a] (%)	calcd. [M]	retention time (min)	observed $[M + Na]^+$	purity (%)	
1	C01	Ph	Ts	**B05C01**	98:2	63	467.10	4.36	468.1[c]	86	√
2	C02	4-MeC_6H_4	Ts	**B05C02**	96:4	59	481.11	4.49	504.0	98	√
3	C03	4-EtC_6H_4	Ts	**B05C03**	96:4	149	495.13	4.69	518.0	86	√
4	C04	4-$MeOC_6H_4$	Ts	**B05C04**	96:4	54	497.11	4.29	520.0	99	√
5	C05	4-$EtOC_6H_4$	Ts	**B05C05**	96:4	52	511.12	4.40	534.0	98	√
6	C06	piperonyl	Ts	**B05C06**	92:8	61	511.09	4.17	534.0	98	√
7	C07	4-$Me_2NC_6H_4$	Ts	**B05C07**	99:1	52	510.14	3.80	511.1[c]	37	no
8	C08	4-$Et_2NC_6H_4$	Ts	**B05C08**	nd	nd	538.17	nd	nd	nd	no
9	C09	4-NCC_6H_4	Ts	**B05C09**	94:6	76	492.09	4.12	515.0	99	√
10	C10	2-FC_6H_4	Ts	**B05C10**	94:6	84	485.09	4.24	508.0	98	√
11	C11	4-ClC_6H_4	Ts	**B05C11**	96:4	76	501.06	4.50	524.0	97	√
12	C12	3-ClC_6H_4	Ts	**B05C12**	96:4	81	501.06	4.46	524.0	98	√
13	C13	3,4-di-ClC_6H_4	Ts	**B05C13**	95:5	75	535.02	4.61	553.3	99	√
14	C14	4-BrC_6H_4	Ts	**B05C14**	95:5	66	545.01	4.60	568.0	99	no
15	C15	3-BrC_6H_4	Ts	**B05C15**	97:3	62	545.01	4.50	569.9	99	√
16	C16	1-naphthyl	Ts	**B05C16**	nd	53	517.11	4.59	540.0	73	no
17	C17	2-furyl	Ts	**B05C17**	nd	nd	457.08	nd	nd	nd	no
18	C18	Ph	Ns	**B05C18**	68:32	59	498.07	nd	nd	nd	no
19	C19	Ph	Ms	**B05C19**	98:2	68	391.06	3.78	414.0	97	√
20	C20	3,4-di-$MeOC_6H_4$	Ts	**B05C20**	97:3	58	527.12	4.00	550.0	99	√
21	C21	2-thiophene	Ts	**B05C21**	99:1	59	473.05	4.22	496.0	95	√
22	C22	5-methyl-2-furyl	Ts	**B05C22**	nd	nd	471.09	nd	nd	nd	no
23	C23	4-FC_6H_4	Ts	**B05C23**	97:3	78	485.09	4.32	508.0	95	√
24	C24	4-*i*-PrC_6H_4	Ts	**B05C24**	98:2	65	509.14	4.76	532.1	98	√
25	C25	3,4,5-tri-$MeOC_6H_4$	Ts	**B05C25**	nd	43	557.13	4.07	580.0	52	no
26	C26	3-FC_6H_4	Ts	**B05C26**	99:1	81	485.09	4.31	508.0	97	√
27	C27	4-ClC_6H_4	4ClBs	**B05C27**	93:7	68	521.00	4.55	544.0	99	√
28	C28	4-ClC_6H_4	Ms	**B05C28**	99:1	63	425.03	3.96	448.0	94	√
29	C29	4-ClC_6H_4	Bs	**B05C29**	88:12	60	487.04	4.45	510.0	85	no
30	C30	4-MeC_6H_4	4ClBs	**B05C30**	95:5	86	501.06	4.56	524.0	97	√
31	C31	4-ClC_6H_4	2MCBs	**B05C31**	99:1	98	545.05	4.38	568.0	41	no
32	C32	1-Me-2-pyrrole	Ts	**B05C32**	nd	nd	470.11	nd	nd	nd	no
33	C33	3-MeC_6H_4	Ts	**B05C33**	98:2	82	481.11	4.47	504.0	95	√
34	C34	4-$MeOC_6H_4$	2MCBs	**B05C34**	93:7	62	541.10	4.14	564.0	88	no
35	C35	4-$MeOC_6H_4$	Bs	**B05C35**	96:4	65	483.09	4.11	506.0	98	√
36	C36	4-MeC_6H_4	2Ns	**B05C36**	nd	57	512.08	nd	nd	nd	no
37	C37	4-$MeOC_6H_4$	4ClBs	**B05C37**	93:7	80	517.05	4.32	540.0	97	√
38	C38	4-$MeOC_6H_4$	2Ts	**B05C38**	94:6	63	497.11	4.25	520.0	99	√
39	C39	3-$MeOC_6H_4$	Ts	**B05C39**	99:1	75	497.11	4.26	520.0	94	√
40	C40	4-ClC_6H_4	2Ts	**B05C40**	95:5	92	501.06	4.51	524.0	99	√
41	C41	4-MeC_6H_4	2Ts	**B05C41**	97:3	86	481.11	4.51	504.0	95	√
42	C42	4-MeC_6H_4	2MCBs	**B05C42**	97:3	99	525.10	4.31	548.0	96	√
43	C43	4-MeC_6H_4	Bs	**B05C43**	98:2	103	467.10	4.37	490.0	99	√
44	C44	4-MeC_6H_4	4Ns	**B05C44**	81:19	105	512.08	nd	nd	33	no
45	C45	4-MeC_6H_4	3Ns	**B05C45**	80:20	91	512.08	nd	nd	nd	no
46	C46	4-MeC_6H_4	Ms	**B05C46**	98:2	79	405.08	3.94	428.0	96	√

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.
[c] $[M + H]^+$.

Building Block Screening for the Thiol 1,4-Addition to the Dihydropyrrole Scaffolds

Screening γ-Substituted Allenoic Acids Using *N*-Tosyltolualdimine and Benzenethiol/*p*-Toluenethiol. The lantern-bound dihydropyrroles **L-A(02–11)02** derived from allenoic acids **A(02–11)** were reacted with thiol **E01** or **E02** according to the general procedure. The data from analyses (^{1}H NMR and LCMS spectra; see Supporting Information, Part C, for copies of spectra and chromatograms) of the cleaved Michael addition products **A(02–11)C02E01/02** are summarized in Table 9. Based on this screening result, seven allenoic acids (of 10) were chosen for inclusion in the library synthesis of pyrrolidines.

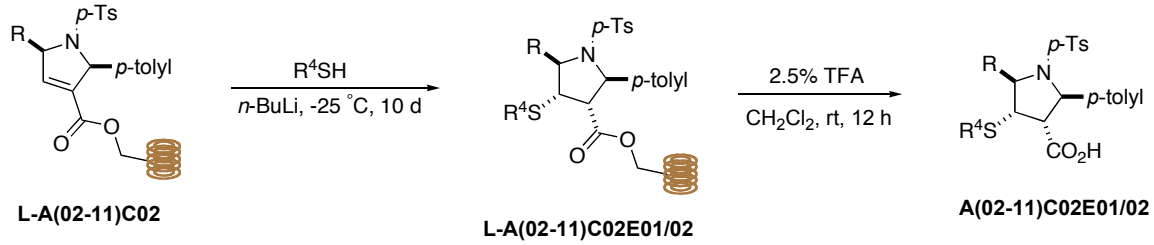


Table 9. Screening Allenoic Acids **A(02–11)** for the Thiol Addition to the Dihydropyrrole Scaffolds.

	product			NMR				LCMS[b]			
entry	R	R^4	no.	conv. (%)	yield (%)[a]	dr	calcd. [M]	observed $[M + Na]^+$	retention time (min)	purity (%)	incl.
1	Me	Ph	**A02C02E01**	>90	92	1:0.21:0.14	481.14	nd	nd	nd	no
2	*t*-Bu	Ph	**A03C02E01**	0	sm	nd	523.19	nd	nd	nd	no
3	Ph	Ph	**A04C02E01**	>80	59	1 : 0.20	543.15	nd	nd	nd	no
4	Et	*p*-tolyl	**A05C02E02**	99	91	1 : 0.10	509.17	532.1	4.617	81	√
5	*i*-Pr	*p*-tolyl	**A06C02E02**	98	88	1 : 0.03	523.19	546.1	4.661	56	√[c]
6	*n*-Pr	*p*-tolyl	**A07C02E02**	>98	87	1 : 0.11	523.19	546.1	4.678	66	√[c]
7	*n*-Bu	*p*-tolyl	**A08C02E02**	97	79	1 : 0.07	537.20	560.1	4.849	86	√
8	*n*-pentyl	*p*-tolyl	**A09C02E02**	93	61	1 : 0.11	551.22	574.0	4.994	73	√
9	*n*-hexyl	*p*-tolyl	**A10C02E02**	96	64	1 : 0.10	565.23	588.1	5.140	78	√
10	cyp-Me	*p*-tolyl	**A11C02E02**	96	86	1 : 0.08	563.22	586.1	4.999	76	√

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.
[c] Selection based on ^{1}H NMR spectrum.

Screening Imines Using Resin-Bound Allenoate L-A05 and *p*-Toluenethiol E02. The lantern-bound dihydropyrroles **L-A05C(01–46)** were reacted with thiol **E02** according to the procedure on page S23. The analytical data (^{1}H NMR and LCMS spectra; see Supporting Information, Part C, for copies of spectra and chromatograms) of the cleaved 1,4-addition products **A05C(01–46)E02** are summarized in Table 10. Based on these results, 25 imines (of 46) were chosen for inclusion in the library synthesis.

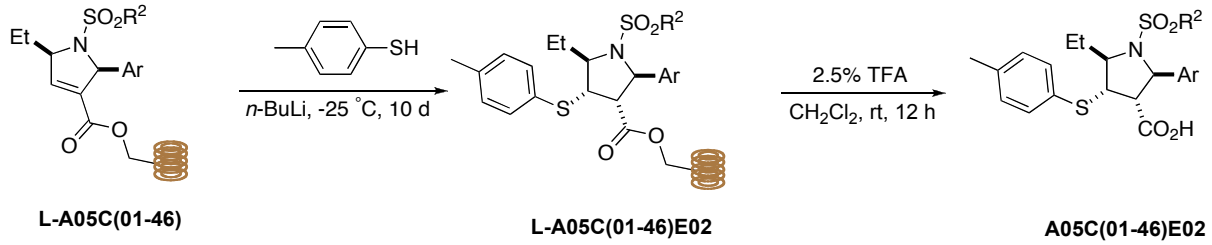


Table 10. Imine Screening for the 5-Ethyldihydropyrrole Scaffold With *p*-Toluenethiol.

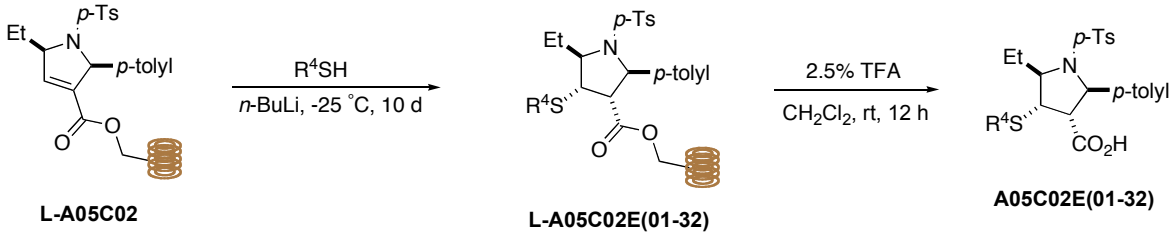
	Product			NMR				LCMS[b]			
entry	Ar	R^2	no.	conv. (%)	yield (%)[a]	dr	calcd. [M]	obs. $[M + Na]^+$	ret time (min)	purity (%)	incl.
1	Ph	*p*-tolyl	**A05C01E02**	99	85	100:0	495.15	518.1	4.511	48	√[c]

2	4-MeC_6H_4	*p*-tolyl	**A05C02E02**	96	94	95:5	509.17	532.1	4.617	81	√
3	4-EtC_6H_4	*p*-tolyl	**A05C03E02**	98	75	99:1	523.19	546.1	4.730	69	√[c]
4	4-$MeOC_6H_4$	*p*-tolyl	**A05C04E02**	99	60	100:0	525.16	548.1	4.447	60	√[c]
5	4-$EtOC_6H_4$	*p*-tolyl	**A05C05E02**	99	65	100:0	539.18	539.3[d]	4.429	76	√
6	piperonal	*p*-tolyl	**A05C06E02**	93	80	90:10	539.14	562.1	4.451	60	√[c]
7	4-$Me_2NC_6H_4$	*p*-tolyl	**A05C07E02**	nd	mess	nd	538.20	nd	nd	nd	no
8	4-$Et_2NC_6H_4$	*p*-tolyl	**A05C08E02**	nd	mess	nd	566.23	nd	nd	nd	no
9	4-NCC_6H_4	*p*-tolyl	**A05C09E02**	91	67	91:9	520.15	543.1	4.448	57	√[c]
10	2-FC_6H_4	*p*-tolyl	**A05C10E02**	95	87	100:0	513.14	536.0	4.451	69	√[c]
11	4-ClC_6H_4	*p*-tolyl	**A05C11E02**	95	86	91:9	529.11	552.0	4.654	92	√
12	3-ClC_6H_4	*p*-tolyl	**A05C12E02**	95	74	91:9	529.11	552.0	4.655	44	√[c]
13	3,4-$Cl_2C_6H_3$	*p*-tolyl	**A05C13E02**	90	79	91:9	563.08	586.0	4.785	87	√
14	4-BrC_6H_4	*p*-tolyl	**A05C14E02**	94	97	91:9	573.06	598.0	4.685	90	√
15	3-BrC_6H_4	*p*-tolyl	**A05C15E02**	nd	mess	nd	573.06	nd	nd	nd	no
16	1-naphthyl	*p*-tolyl	**A05C16E02**	97	101	100:0	545.17	568.1	4.691	78	√
17	2-furyl	*p*-tolyl	**A05C17E02**	nd	nd	nd	485.13	nd	nd	nd	no
18	Ph	*p*-NO_2Ph	**A05C18E02**	nd	mess	N/A	526.12	nd	nd	nd	no
19	Ph	Me	**A05C19E02**	nd	mess	100:1	419.12	442.0	4.059	67	no
20	3,4-$MeOC_6H_4$	*p*-tolyl	**A05C20E02**	95	66	92:8	555.17	578.1	4.335	90	√
21	2-thiophenyl	*p*-tolyl	**A05C21E02**	90	71	89:11	501.11	524.0	4.436	69	√[c]
22	4-Me-2-furyl	*p*-tolyl	**A05C22E02**	nd	nd	nd	499.15	nd	nd	nd	no
23	4-FC_6H_4	*p*-tolyl	**A05C23E02**	98	83	92:8	513.14	514.2[e]	4.500	70	√
24	4-*i*-PrC_6H_4	*p*-tolyl	**A05C24E02**	93	88	93:7	537.20	537.4[d]	4.827	70	√
25	3,4,5-$MeOC_6H_4$	*p*-tolyl	**A05C25E02**	nd	mess	nd	585.19	608.1	4.301	42	no
26	3-FC_6H_4	*p*-tolyl	**A05C26E02**	99	75	93:7	513.14	537.3	4.549	52	√[c]
27	4-ClC_6H_4	*p*-ClPh	**A05C27E02**	91	79	90:10	549.06	572.0	4.740	43	√[c]
28	4-ClC_6H_4	Me	**A05C28E02**	N/A	mess	N/A	453.08	nd	nd	nd	no
29	4-ClC_6H_4	Ph	**A05C29E02**	94	90	100:0	515.10	539.0	4.560	68	√[c]
30	4-MeC_6H_4	*p*-ClPh	**A05C30E02**	98	86	100:0	529.11	553.3	4.710	54	√[c]
31	4-ClC_6H_4	*o*-CO_2MePh	**A05C31E02**	N/A	N/A	N/A	573.10	nd	nd	nd	no
32	1-methyl-pyrrolyl	*p*-tolyl	**A05C32E02**	nd	nd	nd	498.16	nd	nd	nd	no
33	3-MeC_6H_4	*p*-tolyl	**A05C33E02**	99	92	91:9	509.17	51e[d]	4.573	58	√[c]
34	4-$MeOC_6H_4$	*o*-CO_2MePh	**A05C34E02**	N/A	N/A	N/A	569.15	nd	nd	nd	no
35	4-$MeOC_6H_4$	Ph	**A05C35E02**	99	66	93:7	511.15	534.1	4.314	72	√
36	4-MeC_6H_4	*o*-NO_2Ph	**A05C36E02**	nd	mess	nd	540.14	nd	nd	nd	no
37	4-$MeOC_6H_4$	*p*-ClPh	**A05C37E02**	nd	mess	nd	545.11	nd	nd	nd	no
38	4-$MeOC_6H_4$	*o*-tolyl	**A05C38E02**	nd	mess	nd	525.16	nd	nd	nd	no
39	3-$MeOC_6H_4$	*p*-tolyl	**A05C39E02**	nd	mess	nd	525.16	nd	nd	nd	no
40	4-ClC_6H_4	*o*-tolyl	**A05C40E02**	98	106	93:7	529.11	530.0[e]	4.672	52	√[c]
41	4-MeC_6H_4	*o*-tolyl	**A05C41E02**	95	78	92:8	509.17	532.4	4.619	61	√[c]
42	4-MeC_6H_4	*o*-CO_2MePh	**A05C42E02**	nd	mess	N/A	553.16	nd	nd	nd	no
43	4-MeC_6H_4	Ph	**A05C43E02**	96	86	90:1	495.15	518.2	4.510	38	no
44	4-MeC_6H_4	*p*-NO_2Ph	**A05C44E02**	nd	mess	N/A	540.14	nd	nd	nd	no
45	4-MeC_6H_4	*m*-NO_2Ph	**A05C45E02**	nd	mess	N/A	540.14	nd	nd	nd	no
46	4-MeC_6H_4	Me	**A05C46E02**	85	77	93:7	433.14	456.0	4.192	55	no

[a] Crude yield after cleavage.

[b] Short 6-min method; purity observed at λ 210 nm.
[c] Selection based on ^{1}H NMR spectrum.
[d] $[M]^+$
[e] $[M + H]^+$

Screening Thiols Using Resin-Bound Dihydropyrrole L-A05C02. The thiols were reacted with dihydropyrrole **L-A05C02** according to the procedure on page S23. The data from the spectroscopic analyses (^{1}H NMR and LCMS spectra; see Supporting Information, Part C, for copies of spectra and chromatograms) of the cleaved pentasubstituted pyrrolidines **A05C02E(01–32)** are summarized in Table 11. Based on these results, 19 thiols (of 32) were chosen for inclusion in the library synthesis.



L-A05C02 **L-A05C02E(01-32)** **A05C02E(01-32)**

Table 11. Screening Thiols **E(01–32)** Using **L-A05C02**.

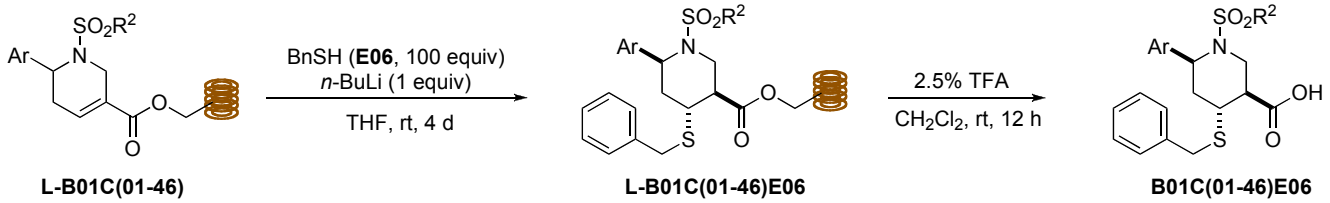
	product		NMR				LCMS[b]			
entry	R^4	no.	conv. (%)	yield (%)[a]	dr	calcd. [M]	obs. $[M + Na]^+$	ret time (min)	purity (%)	incl.
1	Ph	**A05C02E01**	99	95	93:7	495.15	518.1	4.429	56	√[c]
2	*p*-tolyl	**A05C02E02**	96	94	95:5	509.17	532.1	4.617	81	√
3	3,4-$(CH_3)_2C_6H_3$	**A05C02E03**	>99	97	90:10	523.19	N/A	N/A	N/A	no
4	4-$MeOC_6H_4$	**A05C02E04**	>99	115	100:0	525.16	526.2[d]	4.416	72	√
5	4-ClC_6H_4	**A05C02E05**	88	91	83:17	529.11	N/A	N/A	N/A	no
6	Bn	**A05C02E06**	>99	80	91:9	509.17	532.1	4.507	50	√[c]
7	4-*t*-butylbenzyl	**A05C02E07**	>99	87	92:8	565.23	588.1	4.960	32	√[c]
8	4-fluorobenzyl	**A05C02E08**	>99	109	70:30	527.16	N/A	N/A	N/A	no
9	4-chlorobenzyl	**A05C02E09**	>99	97	87:13	543.13	N/A	N/A	N/A	no
10	2-chlorobenzyl	**A05C02E10**	>99	102	81:19	543.13	N/A	N/A	N/A	no
11	4-bromobenzyl	**A05C02E11**	94	80	72:28	587.08	N/A	N/A	N/A	no
12	4-methoxybenzyl	**A05C02E12**	87	61	77:23	539.18	N/A	N/A	N/A	no
13	2-naphtyl	**A05C02E13**	44	81	82:18	545.17	N/A	N/A	N/A	no
14	2-furanyl	**A05C02E14**	>99	55	77:23	499.15	N/A	N/A	N/A	no
15	phenethyl	**A05C02E15**	95	94	85:15	523.19	N/A	N/A	N/A	no
16	Et	**A05C02E16**	>99	79	97:3	447.15	448.1[d]	4.233	72	√
17	*i*-propyl	**A05C02E17**	>99	82	100:0	461.17	484.1	4.559	92	√
18	*n*-propyl	**A05C02E18**	>99	87	100:0	461.17	484.1	4.420	86	√
19	*t*-butyl	**A05C02E19**	>99	95	100:0	475.19	498.1	4.496	90	√
20	*sec*-butyl	**A05C02E20**	>99	98	100:0	475.19	498.1	4.524	92	√
21	isobutyl	**A05C02E21**	>99	102	100:0	475.19	498.1	4.541	90	√
22	*n*-butyl	**A05C02E22**	>99	135	100:0	475.19	498.1	4.558	83	√
23	isoamyl	**A05C02E23**	>99	90	100:0	489.20	512.1	4.669	75	√
24	*n*-pentyl	**A05C02E24**	>99	88	91:9	489.20	512.1	4.693	68	√[c]
25	*n*-hexyl	**A05C02E25**	>99	116	88:12	503.22	526.1	4.841	69	√[c]
26	*n*-heptyl	**A05C02E26**	58	104	85:15	517.23	N/A	N/A	N/A	no
27	*n*-decyl	**A05C02E27**	<10	73	mess	559.28	N/A	N/A	N/A	no
28	cyclopentyl	**A05C02E28**	>99	100	100:0	487.19	510.1	4.567	74	√
29	cyclohexyl	**A05C02E29**	>99	98	100:0	501.20	524.0	4.673	66	√[c]

30	CH_2=$CHCH_2$	**A05C02E30**	>99	74	91:9	459.15	482.1	4.340	56	√[c]
31	$MeO_2CCH_2CH_2$	**A05C02E31**	>99	100	86:14	505.16	N/A	N/A	N/A	no
32	*t*-$BuO_2CCH_2CH_2$	**A05C02E32**	>99	94	91:9	547.21	570.1	4.575	41	√[c]

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.
[c] Selection based on ^{1}H NMR spectrum.
[d] $[M + H]^+$

Building Block Screening for the Thiol 1,4-Addition to the Tetrahydropyridine Scaffolds

Screening Imines by Reacting Resin-Bound Tetrahydropyridines L-B01C(01–46) With Benzyl Thiol (E06). A series of 46 resin-bound tetrahydropyridines **L-B01C(01–46)** were reacted with thiol **E06** according to the general procedure. The analytical data (^{1}H NMR and LCMS spectra; see Supporting Information, Part D, for copies of spectra and chromatograms) of the cleaved Michael addition products **B01C(01–46)E06** are summarized in Table 12. Based on these results, 21 imines (of 46) were chosen for inclusion in the library synthesis.



L-B01C(01-46) **L-B01C(01-46)E06** **B01C(01-46)E06**

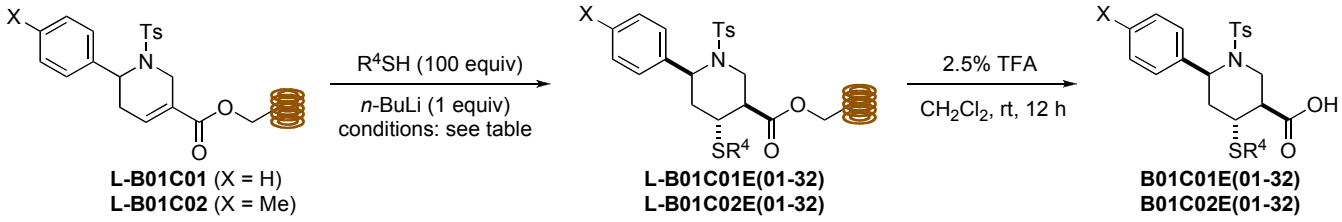
Table 12. Screening Imines for the Benzylthiol Addition Using Resin-Bound Tetrahydropyridine **B01C(01–46)**.

		product[a]					LCMS[c]			
entry	imine	Ar	R^2	no.	yield[b] (%)	calcd. [M]	retention time (min)	observed $[M + Na]^+$	purity (%)	incl.
1	C01	Ph	Ts	**B01C01E06**	80	481.14	4.43	504.0	84	√
2	C02	4-MeC_6H_4	Ts	**B01C02E06**	66	495.15	4.52	518.1	88	√
3	C03	4-EtC_6H_4	Ts	**B01C03E06**	82	509.17	4.65	532.1	89	√
4	C04	4-$MeOC_6H_4$	Ts	**B01C04E06**	84	511.15	4.35	534.1	99	√
5	C05	4-$EtOC_6H_4$	Ts	**B01C05E06**	77	525.16	4.51	548.0	86	√
6	C06	piperonyl	Ts	**B01C06E06**	76	525.13	4.33	526.1[d]	85	√
7	C07	4-$Me_2NC_6H_4$	Ts	**B01C07E06**	56	524.18	4.21	525.1[d]	33	no
8	C08	4-$Et_2NC_6H_4$	Ts	**B01C08E06**	51	552.21	nd	nd	nd	no
9	C09	4-NCC_6H_4	Ts	**B01C09E06**	47	506.13	nd	nd	nd	no
10	C10	2-FC_6H_4	Ts	**B01C10E06**	60	499.13	4.43	522.0	73	√
11	C11	4-ClC_6H_4	Ts	**B01C11E06**	84	515.10	4.60	538.0	88	√
12	C12	3-ClC_6H_4	Ts	**B01C12E06**	80	515.10	4.51	538.0	93	√
13	C13	3,4-di-ClC_6H_4	Ts	**B01C13E06**	51	549.06	4.71	572.0	54	no
14	C14	4-BrC_6H_4	Ts	**B01C14E06**	74	559.05	4.63	582.0	59	no
15	C15	3-BrC_6H_4	Ts	**B01C15E06**	83	559.05	4.59	582.0	70	√
16	C16	1-naphthyl	Ts	**B01C16E06**	80	531.15	nd	nd	nd	no
17	C17	2-furyl	Ts	**B01C17E06**	nd	471.12	nd	nd	nd	no
18	C18	Ph	Ns	**B01C18E06**	nd	512.11	nd	nd	nd	no
19	C19	Ph	Ms	**B01C19E06**	104	405.11	3.89	428.0	40	no
20	C20	3,4-di-$MeOC_6H_4$	Ts	**B01C20E06**	62	541.16	4.19	564.0	51	√[e]
21	C21	2-thiophene	Ts	**B01C21E06**	60	487.09	4.37	510.0	45	no
22	C22	5-methyl-2-furyl	Ts	**B01C22E06**	78	485.13	nd	nd	nd	no
23	C23	4-FC_6H_4	Ts	**B01C23E06**	76	499.13	4.44	522.0	59	no
24	C24	4-*i*-PrC_6H_4	Ts	**B01C24E06**	70	523.19	4.78	546.1	59	no
25	C25	3,4,5-tri-$MeOC_6H_4$	Ts	**B01C25E06**	45	571.17	4.17	594.1	73	√
26	C26	3-FC_6H_4	Ts	**B01C26E06**	77	499.13	4.42	522.0	51	no
27	C27	4-ClC_6H_4	4ClBs	**B01C27E06**	70	535.04	nd	nd	nd	no
28	C28	4-ClC_6H_4	Ms	**B01C28E06**	76	439.07	nd	nd	nd	no

29	C29	4-ClC_6H_4	Bs	**B01C29E06**	nd	501.08	4.48	524.0	46	no
30	C30	4-MeC_6H_4	4ClBs	**B01C30E06**	72	515.10	4.63	537.4	67	√[e]
31	C31	4-ClC_6H_4	2MCBs	**B01C31E06**	73	559.09	nd	nd	nd	no
32	C32	1-Me-2-pyrrole	Ts	**B01C32E06**	33	484.15	nd	nd	nd	no
33	C33	3-MeC_6H_4	Ts	**B01C33E06**	86	495.15	4.53	518.0	42	no
34	C34	4-$MeOC_6H_4$	2MCBs	**B01C34E06**	64	555.14	nd	nd	nd	no
35	C35	4-$MeOC_6H_4$	Bs	**B01C35E06**	72	497.13	4.26	520.0	92	√
36	C36	4-MeC_6H_4	2Ns	**B01C36E06**	51	526.12	nd	nd	nd	no
37	C37	4-$MeOC_6H_4$	4ClBs	**B01C37E06**	91	531.09	4.46	553.0	66	√[e]
38	C38	4-$MeOC_6H_4$	2Ts	**B01C38E06**	69	511.15	4.41	534.1	59	√[e]
39	C39	3-$MeOC_6H_4$	Ts	**B01C39E06**	69	511.15	4.36	534.1	81	√
40	C40	4-ClC_6H_4	2Ts	**B01C40E06**	70	515.10	4.62	516.1[d]	44	√[e]
41	C41	4-MeC_6H_4	2Ts	**B01C41E06**	71	495.15	4.58	518.0	79	√
42	C42	4-MeC_6H_4	2MCBs	**B01C42E06**	84	539.14	nd	nd	nd	no
43	C43	4-MeC_6H_4	Bs	**B01C43E06**	68	481.14	4.39	504.1	88	√
44	C44	4-MeC_6H_4	4Ns	**B01C44E06**	46	526.12	nd	nd	nd	no
45	C45	4-MeC_6H_4	3Ns	**B01C45E06**	28	526.12	nd	nd	nd	no
46	C46	4-MeC_6H_4	Ms	**B01C46E06**	73	419.12	3.96	442.0	51	√[e]

[a] All reactions exhibited conversions >95%. Products all exhibited a diastereoisomeric ratio of 90:10 or better.
[b] Crude yield after cleavage.
[c] Short 6-min method; purity observed at λ 210 nm.
[d] $[M + H]^+$
[e] Selection based on ^1H NMR spectrum only.

Screening Thiols Using Resin-Bound Tetrahydropyridine L-B01C01/02. The thiols were reacted with lantern-bound tetrahydropyridine **L-B01C01** or **L-B01C01** according to the procedure described on page S24. The analytical data (^1H NMR and LCMS spectra; see Supporting Information, Part D, for copies of spectra and chromatograms) of the cleaved tetrasubstituted piperidines **B01C01/02E(01–32)** are summarized in Table 13. Based on these results, 17 thiols (of 32) were chosen for inclusion in the library synthesis.



L-B01C01 (X = H)
L-B01C02 (X = Me)

L-B01C01E(01-32)
L-B01C02E(01-32)

B01C01E(01-32)
B01C02E(01-32)

Table 13. Thiol **E(01–32)** Screening Using Resin-Bound Tetrahydropyridine **B01C01** or **B01C02**.

		product		NMR				LCMS[b]			
entry	cond.	R^4	no.	conv.	d.r.	yield[a] (%)	calcd. [M]	retention time (min)	observed $[M + Na]^+$	purity (%)	incl.
1	A	Ph	**B01C02E01**	>98	96:4	60	481.14	4.50	504.0	95	√
2	A	*p*-tolyl	**B01C01E02**	>98	96:4	47	495.17	4.67	496.1[c]	91	√
3	A	3,4-di-MeC_6H_3	**B01C01E03**	>98	88:12	54	495.15	nd	nd	nd	no
4	A	4-$MeOC_6H_4$	**B01C02E04**	>98	93:7	42	511.15	4.49	534.1	87	√
5	A	4-ClC_6H_4	**B01C02E05**	>98	90:10	58	515.10	4.71	538.0	99	√
6	B	Bn	**B01C02E06**	99	93:7	89	495.15	4.51	518.1	96	√
7	E	4-*t*-butylbenzyl	**B01C02E07**	99	89:11	95	551.22	5.00	574.0	97	√
8	B	4-fluorobenzyl	**B01C01E08**	96	93:7	57	499.13	nd	nd	nd	no
9	B	4-chlorobenzyl	**B01C02E09**	>98	94:6	57	529.11	4.69	552.0	92	√
10	B	2-chlorobenzyl	**B01C01E10**	>98	93:7	58	515.10	nd	nd	nd	no
11	B	4-bromobenzyl	**B01C01E11**	>98	93:7	67	559.05	nd	nd	nd	no
12	B	4-methoxybenzyl	**B01C01E12**	95	92:8	64	511.15	nd	nd	nd	no

13	A	2-naphtyl	**B01C01E13**	>98	91:9	35	517.14	nd	nd	nd	no
14	B	2-furanyl	**B01C01E14**	>98	nd	23	471.12	nd	nd	nd	no
15	C	phenethyl	**B01C02E15**	>98	93:7	77	509.17	4.61	532.1	83	√
16	C	ethyl	**B01C02E16**	98	94:6	71	433.14	4.26	456.1	72	√
17	E	*i*-propyl	**B01C01E17**	70	89:11	74	433.14	nd	nd	nd	no
18	C	*n*-propyl	**B01C02E18**	96	95:5	76	447.15	4.42	470.1	55	√[d]
19	D	*t*-butyl	**B01C01E19**	0	nd	0	447.15	nd	nd	nd	no
20	D	2-butanyl	**B01C01E20**	81	88:12	10	447.15	nd	nd	nd	no
21	E	isobutyl	**B01C02E21**	97	93:7	71	461.17	4.55	484.1	99	√
22	D	*n*-butyl	**B01C02E22**	95	93:7	76	461.17	4.62	484.1	83	√
23	F	isoamyl	**B01C02E23**	>98	97:3	50	475.19	4.74	498.2	80	√
24	E	*n*-pentyl	**B01C02E24**	86	92:8	72	475.19	4.78	498.1	45	√[d]
25	F	*n*-hexyl	**B01C02E25**	95	95:5	59	489.20	4.92	512.1	88	√
26	D	*n*-heptyl	**B01C01E26**	74	nd	nd	489.20	nd	nd	nd	no
27	D	*n*-decyl	**B01C01E27**	69	nd	nd	531.25	nd	nd	nd	no
28	F	cyclopentyl	**B01C02E28**	96	96:4	66	473.17	4.77	496.1	87	√
29	F	cyclohexyl	**B01C02E29**	86	89:11	30	487.19	nd	nd	nd	no
30	C	allyl	**B01C02E30**	98	97:3	57	445.14	4.36	468.0	99	√
31	C	$MeO_2CCH_2CH_2$	**B01C02E31**	89	83:17	83	491.14	nd	nd	nd	no
32	C	*t*-$BuO_2CCH_2CH_2$	**B01C02E32**	95	89:11	69	533.19	nd	nd	nd	no

[a] Crude yield after cleavage.
[b] Short 6-min method; purity observed at λ 210 nm.
[c] $[M + H]^+$
[d] Selection based on ^1H NMR spectrum only.

Experimental Procedures for the Library Tagging and the Split-Pool Library Synthesis

Tagging of the Building Blocks. The individual lanterns were tagged with colored spindles and cogs to encode the building blocks used for each lantern. Tables 14–16 summarize the colors of the spindles and cogs used to encode the allenoic acid and imine building blocks. Because the thiol Michael addition was the last step of the synthesis, tagging for thiols was not necessary. The [3 + 2] and [4 + 2] annulation-based parts of the library were never pooled together. Consequently, there are overlaps of the colors of the spindles and cogs encoding the allenoic acids.

Table 14. Tagging for the γ-Substituted Allenoic Acids **A(02–11)**.

entry	R	allenoic acid	spindle
1	methyl	**A02**	black
2	*t*-butyl	**A03**	red[a]
3	phenyl	**A04**	none
4	ethyl	**A05**	red[a]
5	isopropyl	**A06**	yellow
6	*n*-propyl	**A07**	green
7	*n*-butyl	**A08**	blue
8	*n*-pentyl	**A09**	natural
9	*n*-hexyl	**A10**	brown
10	cyclopentylmethyl	**A11**	white

[a] The lanterns loaded with **A03** had only red spindles inserted (no cogs to encode imines) because the dihydropyrrole annulation products with **A03** were not pooled with the other annulation products for the thiol 1,4-addition. On the other hand, lanterns loaded with **A05** had red spindles and cogs that encode for imines.

Table 15. Tagging for the α-Substituted Allenoic Acid Building Blocks **B(02–12)**.

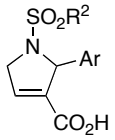
entry	R^1	allenoic acid	spindle	cog
1	Ph	**B02**	–	–
2	2-F-C_6H_4	**B03**	white	–

3	3-F-C_6H_4	**B04**	yellow	–
4	3-Cl-C_6H_4	**B05**	red	–
5	3-Br-C_6H_4	**B06**	blue	–
6	3-Me-C_6H_4	**B07**	green	–
7	4-F-C_6H_4	**B08**	brown	–
8	4-Cl-C_6H_4	**B09**	black	–
9	4-Br-C_6H_4	**B10**	natural	–
10	4-Me-C_6H_4	**B11**	white	red
11	4-*t*-Bu-C_6H_4	**B12**	white	blue

Table 16. Tagging for the Imines **C(01–46)** Used in the [3 + 2] and [4 + 2] Annulations.

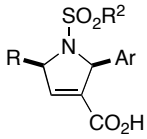
entry	Ar	R^2	imine	color of cog
1	Ph	*p*-tolyl	**C01**	red
2	4-MeC_6H_4	*p*-tolyl	**C02**	yellow
3	4-EtC_6H_4	*p*-tolyl	**C03**	blue
4	4-MeOC_6H_4	*p*-tolyl	**C04**	red/green
5	4-EtOC_6H_4	*p*-tolyl	**C05**	yellow/white
6	piperonal	*p*-tolyl	**C06**	green
7	4-$Me_2N$$C_6H_4$	*p*-tolyl	**C07**	–
8	4-$Et_2N$$C_6H_4$	*p*-tolyl	**C08**	–
9	4-NCC_6H_4	*p*-tolyl	**C09**	white
10	2-FC_6H_4	*p*-tolyl	**C10**	natural
11	4-ClC_6H_4	*p*-tolyl	**C11**	brown
12	3-ClC_6H_4	*p*-tolyl	**C12**	black
13	3,4-$Cl_2C_6H_3$	*p*-tolyl	**C13**	red/yellow
14	4-BrC_6H_4	*p*-tolyl	**C14**	yellow/blue
15	3-BrC_6H_4	*p*-tolyl	**C15**	blue/natural
16	1-naphthyl	*p*-tolyl	**C16**	blue/green
17	2-furyl	*p*-tolyl	**C17**	–
18	Ph	*p*-NO_2Ph	**C18**	–
19	Ph	Me	**C19**	green/white
20	3,4-$(MeO)_2C_6H_3$	*p*-tolyl	**C20**	white/natural
21	2-thiophenyl	*p*-tolyl	**C21**	green/brown
22	4-Me-2-furyl	*p*-tolyl	**C22**	–
23	4-FC_6H_4	*p*-tolyl	**C23**	natural/brown
24	4-*i*-PrC_6H_4	*p*-tolyl	**C24**	brown/black
25	3,4,5-$(MeO)_3C_6H_2$	*p*-tolyl	**C25**	white/black
26	3-FC_6H_4	*p*-tolyl	**C26**	black/red
27	4-ClC_6H_4	*p*-ClPh	**C27**	red/blue
28	4-ClC_6H_4	Me	**C28**	–
29	4-ClC_6H_4	*o*-CO_2MePh	**C29**	yellow/green
30	4-MeC_6H_4	*p*-ClPh	**C30**	blue/white
31	4-ClC_6H_4	*o*-MeOPh	**C31**	–
32	1-methylpyrrolyl	*p*-tolyl	**C32**	–
33	3-MeC_6H_4	*p*-tolyl	**C33**	green/natural
34	4-MeOC_6H_4	*o*-MePh	**C34**	black/blue
35	4-MeOC_6H_4	Ph	**C35**	red/white
36	4-MeC_6H_4	*o*-NO_2Ph	**C36**	yellow/natural
37	4-MeOC_6H_4	*p*-ClPh	**C37**	blue/brown

38	4-$MeOC_6H_4$	*o*-tolyl	**C38**	green/black
39	3-$MeOC_6H_4$	*p*-tolyl	**C39**	white/red
40	4-ClC_6H_4	*o*-tolyl	**C40**	white/brown
41	4-MeC_6H_4	*o*-tolyl	**C41**	natural/black
42	4-MeC_6H_4	*o*-MeOPh	**C42**	natural/yellow
43	4-MeC_6H_4	Ph	**C43**	brown/red
44	4-MeC_6H_4	*p*-NO_2Ph	**C44**	–
45	4-MeC_6H_4	*m*-NO_2Ph	**C45**	–
46	4-MeC_6H_4	Me	**C46**	black/yellow



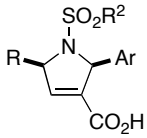
A01C(01-46)

Library Synthesis of 30 A01C(01–46). The thirty annulation products selected as indicated in Table 3 constituted the final members of the library.



A(02-04)C(01-46)

Library Synthesis of 63 A(02–04)C(01–46). As described in the general procedure for the loading of γ-subsituted allenoic acids, each acid was loaded as follows: 21 lanterns (0.315 mmol) were reacted with 2-chloro-1-methylpyridinium iodide (0.805 g, 3.15 mmol) and 4-substituted buta-2,3-dienoic acid (**A02**, 0.309 g, 3.15 mmol; **A03**, 0.442 g, 3.15 mmol, **A04**, 0.505 g, 3.15 mmol) in the presence of diisopropylethylamine (1.10 mL, 6.3 mmol). After washing, the lanterns were split into 21 vials (three lanterns per vial), corresponding to the 21 selected imines. Following the general procedure for annulation, these lanterns were reacted with the appropriate imine in the presence of PBu_3. When the reaction was complete, the lanterns were washed as described in the general procedure, cleaved, and arrayed into 96-well plates.



A(05-11)C(01-46)

Library Synthesis of 147 A(05–11)C(01–46)

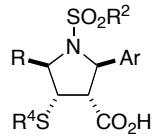
Loading of Acids. Following the general procedure for the loading of γ-substitued allenoic acids, 500 tagged lanterns (7.5 mmol) for each acid [**A05** (8.41 g); **A06** (9.46 g); **A07** (9.46 g); **A08** (10.51 g); **A09** (11.57 g); **A10** (12.62g); **A11** (12.47 g)] were placed into an oven-dried 500-mL round-bottom flask. The lanterns were washed with CH_2Cl_2 three times and subsequently rinsed with dry CH_2Cl_2 (1×). 2-Chloro-1-methylpyridinium iodide (19.16 g, 75 mmol) was added, followed by two evacuation/backfill cycles with Ar. A mixture of the 4-substituted 2,3-butadienoic acid and the tautomeric 3-alkynoic acid (75 mmol) was added into the corresponding flasks and dry CH_2Cl_2 (250 mL) was added to dissolve the solids. The lanterns were soaked in CH_2Cl_2 for 30 min. The flasks were then cooled to –78 °C and diisopropylethylamine (26.1 mL, 150 mmol) was added under an Ar atmosphere. After 1 h, the cooling bath was removed and the flasks were flushed with Ar and shaken at room temperature overnight.

Washing and Splitting. The brown solution was removed and the lanterns were washed as follows: THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), CH_2Cl_2 (5×), THF (5×), CH_2Cl_2 (5×), THF (5×), CH_2Cl_2 (5×). (Note: Lanterns were soaked for at least 15 min before changing solvents.) The lanterns were washed

further with THF (5×), CH_2Cl_2 (5×), and toluene (5×) and then they were split into 25 250-mL round-bottom flasks according to the color combination of their cogs.

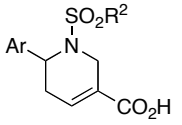
[3 + 2] Cycloaddition of Lantern-Bound 4-Substituted 2,3-Butadienoates L-A(05–11). For each of the 25 imines, 140 lantern-bound 4-substituted 2,3-butadienoates (15 μmol/lantern) in a 250-mL round-bottom flask were washed under Ar with dry THF (1 mL/lantern, 5 times) and dry benzene (1 mL/lantern, 5 times). The imine (5 equiv) was added followed by 0.5 equiv of tributylphosphine. The mixture was agitated manually and heated at 60 °C for 5 days. The reaction solution was then removed and the lanterns were washed as follows: toluene, CH_2Cl_2 (5×), THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), toluene, THF (5×), and then left in toluene overnight at 60 °C. Further washing with toluene (5×), THF (5×), DMF (5×), THF (5×), and then left in DMF at 60 °C for 4 h; THF (5×), DMF (5×), THF (5×), DMF, NH_4Cl/H_2O, THF/H_2O, CH_2Cl_2 (5×), toluene, THF (5×), CH_2Cl_2 (5×), THF (5×), CH_2Cl_2 (5×), THF (5×), CH_2Cl_2 (5×), and then left in CH_2Cl_2 for 1 h. (Note: Lanterns were soaked for at least 15 min before changing solvents.) A selection of 147 lanterns were set aside for the cleavage and arraying into 96-well plates.

Washing and Splitting. The lanterns used for the Michael addition were further washed as follows: THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), CH_2Cl_2 (5×), THF (5×), CH_2Cl_2 (5×), THF (5×), CH_2Cl_2 (5×). (Note: Lanterns were soaked for at least 15 min before changing solvents.) The lanterns were further washed with THF (5×), CH_2Cl_2 (5×), and toluene (5×), and were split into 19 250-mL and 12 100-mL round-bottom flasks according to the color combination of their spindles and cogs for the next split step. The lanterns that reacted with the seven thiols **E01**, **E06**, **E07**, **E16**, **E25**, **E30**, and **E32** (conditions **A** on page S22) were all combined in one flask. The lanterns that were treated with the 12 thiols **E02**, **E04**, **E17**, **E18**, **E19**, **E20**, **E21**, **E22**, **E23**, **E24**, **E28**, and **E29** were divided into a 250-mL flask (for annulation products formed with imines **C02**, **C04**, **C05**, **C06**, **C11**, **C12**, **C13**, **C14**, **C16**, **C20**, **C23**, **C25**, **C29**, **C30**, **C33**, **C35**, **C40**, **C41**; conditions **B**) and a 100-mL flask (for annulation products formed with imines **C01**, **C03**, **C09**, **C10**, **C24**, **C27**; conditions **A**).



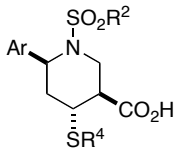
A(05-11)C(01-46)E(01-32)

Library Synthesis of 3,325 A(05–11)C(01–46)E(01–32). Lantern-bound dihydropyrroles **L-A(05–11)C(01–46)** (15 μmol/lantern) were washed under Ar with dry THF (1 mL/lantern, 5 times). The thiol (100 equiv) was added to the lanterns in THF (0.5 mL/lantern) followed by *n*-BuLi (6 or 10 equiv, 1.6 M in hexanes). The mixture was agitated manually at –25 °C for 10 days. The reaction solution was then removed and the lanterns were washed as follows: THF (5×), toluene, CH_2Cl_2 (5×), THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), DMF (5×), THF (5×), toluene, and THF (5×). Further washing with THF (5×), CH_2Cl_2 (5×), THF (5×), CH_2Cl_2 (5×) THF (5×), CH_2Cl_2 (5×), and then left in CH_2Cl_2 for at least 1 h. When the washing was complete, the lanterns were cleaved according to the general procedure and arrayed into 96-well plates.



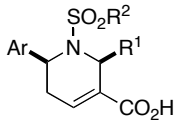
B01C(01-46)

Library Synthesis of 25 B01C(01–46). According to Table 16, 382 L-series lanterns were tagged (natural spindle was used for **B01**). Following the general procedure for the loading described earlier, these 382 lanterns (5.73 mmol) were reacted with 2-chloro-1-methylpyridinium iodide (14.7 g, 57.3 mmol) and 2-methyl-buta-2,3-dienoic acid (**B01**, 5.63 g, 57.3 mmol) in the presence of Et_3N (16.0 mL, 115 mmol). After washing, the lanterns were split into 28 vials, according to the selected imines with which they were to react. Following the general procedure for annulation, these lanterns were reacted with the appropriate imine in the presence of PBu_3 in CH_2Cl_2 at room temperature. After the reaction was complete and the washing performed, the 25 annulation products selected were set aside to be cleaved and arrayed into 96-well plates.



B01C(01-46)E(01-32)

Library Synthesis of 357 B01C(01–46)E(01–32). A set of 17 vials, corresponding to the 17 thiols to be used in the 1,4 addition, were dried and placed under Ar. No tagging was required for the thiols used. Into each of these vials, 21 lanterns of the different annulation products **B01C(01–46)** selected to undergo the 1,4-addition of thiols were pooled and reacted with the thiols according to the method outlined in the general procedure. Please note the different conditions (A–F) used for the different thiols. After the washing protocol was complete, the 357 lanterns, each containing a different product, were split and cleaved according to the general procedure and subsequently arrayed into 96-well plates.



B(02-12)C(01-46)

Library Synthesis of 341 B(02–12)C(01–46). According to Table 15, 31 lanterns were tagged for each of the 11 allenoic acids (total number of lanterns was 341). A set of 11 vials was dried, flushed with Ar, and charged with the 31 lanterns. The loading with each of the allenoic acids took place according to the general procedure. After washing, the lanterns were pooled and split again into 31 vials corresponding to the 31 imines selected for the annulation with these lantern-bound α-benzyl allenoates. Each vial contained a lantern for each allenoic acid (11 in total). For these series, no separate tagging occurred for the imines. The annulation was performed following the general procedure; after washing, the 341 lanterns, each containing a distinct annulation product, were split, cleaved, and arrayed into 96-well plates.

Global Cleavage and Arraying into 96-Well Plates as 10 mM DMSO Stock Solutions. The 4288 lanterns were inserted into 4288 vials and treated with 2.5% TFA in CH_2Cl_2 for 12 h. The lanterns were then removed and rinsed with CH_2Cl_2. The resulting solution was concentrated and further co-evaporated with $CHCl_3$ to effectively remove TFA. The cleaved compounds were weighed and redissolved in $CHCl_3$; a portion (2 μmol) of each compound was transferred to 54 96-well plates (80 compounds per well; two columns of wells in each plate were left empty to accommodate controls in subsequent assays) and the solvents were left to evaporate. The products were redissolved in DMSO and analyzed in the biochemical enzymatic assay for activity against GGTase I.

LCMS Data for Randomly Selected Library Products. Out of 4288 library compounds, 121 compounds were randomly selected and analyzed by LCMS for their identity and purity; 107 (of 121; 88%) compounds indicated the correct identity and 79 compounds (65%) demonstrated >70% purity (UV210).

Table 17. Random Selection of Library Products With the Corresponding LCMS Data.[a]

entry	product label	calcd [M]	retention time (min)	observed $[M + H]^+$	purity (%)
1	**A04C11**	453.08	4.252	454.0	100
2	**A03C11**	433.11	4.462	434.0	100
3	**A10C11**	461.14	4.795	462.0	100
4	**A03C13**	467.07	4.651	468.0	90
5	**A06C01**	385.15	4.041	408.1[b]	87
6	**A06C09**	410.13	4.042	411.1	84
7	**A08C11**	433.11	4.446	434.1	76
8	**A03C20**	459.17	4.003	460.1	70
9	**A07C09**	410.13	4.034	411.1	95
10	**A08C09**	424.15	3.731	446.1[b]	78
11	**A09C09**	438.16	4.377	439.1	76
12	**A07C13E01**	563.08	4.776	564.1	80
13	**A05C13E01**	549.06	4.646	550.1	82

14	**A05C14E01**	559.05	4.538	560.0	92
15	**A06C09E01**	520.15	4.384	521.2	82
16	**A06C11E01**	529.11	4.61	530.1	88
17	**A07C11E01**	529.11	4.627	530.1	90
18	**A07C14E01**	573.06	4.67	574.1	84
19	**A08C09E01**	534.16	4.564	535.2	79
20	**A08C13E01**	577.09	4.926	600.1[b]	90
21	**A09C11E01**	557.15	4.916	–	80
22	**A05C11E01**	515.1	4.488	–	75
23	**A06C09E04**	550.16	4.322	–	92
24	**A06C11E04**	559.13	4.591	560.1	74
25	**A06C14E04**	603.07	4.638	604.1	87
26	**A06C23E04**	543.15	4.474	544.2	82
27	**A05C16E18**	497.17	4.428	498.1	90
28	**A05C06E01**	525.13	4.345	526.1	80
29	**A05C14E02**	573.06	4.669	574.1	100
30	**A05C13E02**	563.08	4.787	–	92
31	**A05C09E01**	506.13	4.276	507.1	71
32	**A05C29E01**	501.08	4.525	–	85
33	**A09C11E19**	537.18	4.957	538.2	100
34	**A08C14E01**	587.08	4.815	588.1	66
35	**A05C11E04**	545.11	4.491	546.	71
36	**A06C13E01**	563.08	4.78	564.0	83
37	**A06C11E18**	495.13	4.617	496.1	70
38	**A06C09E28**	512.18	4.709	–	80
39	**A07C11E29**	535.16	4.489	535.2	77
40	**A07C03E28**	515.22	4.579	516.0	86
41	**A05C23E29**	505.18	4.548	506.2	84
42	**A06C09E29**	527.2	4.623	528.5	93
43	**A06C11E32**	581.17	4.731	604.0[b]	89
44	**A06C14E32**	625.12	4.771	648.0[b]	79
45	**A06C16E16**	497.17	4.424	498.2	81
46	**A05C14E16**	511.05	4.348	512.0	91
47	**A05C04E01**	463.15	4.081	464.1	77
48	**A06C09E17**	486.16	4.3	487.1	70
49	**A06C10E17**	479.16	4.335	480.1	73
50	**A05C05E01**	524.16	3.942	524.2	83
51	**A06C09E23**	514.2	4.602	515.2	83
52	**A08C09E20**	514.2	4.621	537.4[b]	63
53	**A05C11E20**	495.13	4.541	496.1	71
54	**A07C14E32**	625.12	4.488	625.4	76
55	**A07C03**	413.17	4.355	414.1	81
56	**A09C03**	441.2	4.695	442.2	82
57	**A10C03**	455.21	4.866	478.2[b]	84
58	**A03C01**	399.15	4.223	400.1	79
59	**A03C10**	417.14	4.17	418.0	87
60	**A03C12**	433.11	4.418	456.1[b]	83
61	**A03C26**	417.14	4.287	418.0	79
62	**A03C27**	453.06	4.558	454.0	77
63	**A03C30**	433.11	4.452	456.8[b]	93
64	**A03C41**	413.17	4.415	414.1	76
65	**A07C41E01**	509.17	4.588	510.1	48
66	**A06C14E01**	573.06	4.65	nd	51
67	**A07C23E01**	513.14	4.489	514.2	51
69	**A09C13E01**	591.11	–	–	–
70	**A09C14E01**	601.1	–	–	–
71	**A10C14E01**	615.11	–	–	–
72	**A05C21E22**	451.15	4.219	–	42
73	**A06C14E18**	539.08	4.586	563.0[b]	51
74	**A08C09E04**	564.18	4.509	565.2	61
75	**A09C11E25**	565.21	–	–	–

76	**A10C14E25**	623.17	–	–	–
77	**A08C14E25**	595.14	–	–	–
78	**A08C11E25**	551.19	–	–	–
79	**A07C11E25**	537.18	–	–	–
80	**A06C11E25**	537.18	–	–	–
81	**A05C14E30**	523.05	4.406	524.0	44
82	**A09C09E30**	512.18	4.389	535.2[b]	35
83	**A09C11E30**	521.15	–	–	–
84	**A10C11E30**	535.16	–	–	–
85	**A05C09E07**	576.21	4.426	599.3[b]	48
86	**A09C16E01**	573.2	–	–	–
87	**A09C09E01**	548.18	4.720	571.2[b]	59
88	**A09C20E01**	583.21	4.606	584.2	48
89	**A10C11E01**	571.16	–	–	–
90	**A10C09E01**	562.2	4.875	564.2	55
91	**A11C06E01**	579.17	4.72	580.2	52
92	**A11C09E01**	560.18	4.727	nd	53
93	**A11C13E01**	603.11	–	–	–
94	**A05C11E07**	585.18	–	–	–
95	**A09C11E16**	509.15	–	–	–
96	**A06C14E17**	539.08	4.575	540.0	65
97	**A05C09E16**	458.13	4.064	481.1[b]	39
98	**A05C09E17**	472.15	4.179	473.1	55
99	**A07C04E19**	505.2	4.467	nd	57
100	**A05C11E24**	509.15	4.719	510.1	54
101	**A05C09E21**	486.16	4.343	487.1	50
102	**A05C30E20**	495.13	4.585	496.0	59
103	**A09C35E19**	519.21	4.671	520.0	56
104	**A10C09E24**	556.24	–	–	–
105	**A10C14E23**	609.16	–	–	–
106	**A05C13E22**	529.09	4.716	530.0	38
107	**B01C04**	387.11	3.783	410.1[b]	90
108	**B02C09**	458.13	4.016	481.1[b]	93
109	**B04C39**	481.14	4.150	504.1[b]	91
110	**B06C05**	555.07	4.433	580.0[b]	98
111	**B07C10**	465.14	4.226	488.1[b]	99
112	**B08C43**	451.13	4.238	474.0[b]	98
113	**B10C26**	529.04	4.372	552.0[b]	97
114	**B11C21**	453.11	4.207	476.0[b]	69
115	**B12C09**	514.19	4.521	537.3[b]	99
116	**B01C01E06**	481.14	4.377	504.0[b]	78
117	**B01C01E18**	433.14	4.252	456.1[b]	56[c]
118	**B01C02E04**	511.15	4.462	534.1[b]	70
119	**B01C03E01**	495.15	4.623	518.1[b]	87
120	**B01C30E09**	549.06	4.747	572.0[b]	57
121	**B01C35E02**	497.13	4.323	520.1[b]	90

[a] Short 6-min method; purity observed at λ 210 nm.
[b] $[M + Na]^+$
[c] Major byproduct is the retro-Michael product, formed on the LCMS column. ^{1}H NMR spectra verified the correct identity of the compounds.

Bioassays Using 4,288 GGTI Analogs

Filter Binding Assays to Identify GGTIs With Improved Efficacy and Determination of IC_{50}. The percentage activities of GGTase-I for protein K-Ras4B or RhoA in the presence of the 4288 compounds were determined as follows: We first prepared the working solution that contained each compound in DMSO at a concentration of 1 mM. The working solution was added to the GGTase I reaction mixture so that the final concentration of the compound was 50 μM. The GGTase-I activity was assayed by incubating [^{3}H]GGPP with K-Ras4B or RhoA protein in the presence of GGTase-I and examining the radioactivity incorporated into the substrate protein by spotting onto a filter paper. After washing with trichloroacetic acid (TCA), ethanol, and acetone, the radioactivity retained on the

filter was determined using a scintillation counter. The GGTase-I activity in the presence of DMSO was taken as a 100% value and the activity in the presence of the compound is presented as a percentage activity relative to the 100% value. Compounds **22** and **23** were identified as the best inhibitors of GGTase I. The dose dependency of the inhibition of the two compounds **22** and **23** is shown in Figure S4. The IC_{50} values for the inhibition of GGTase-I using RhoA as a substrate were 0.5 and 0.3 μM for **22** and **23**, respectively.

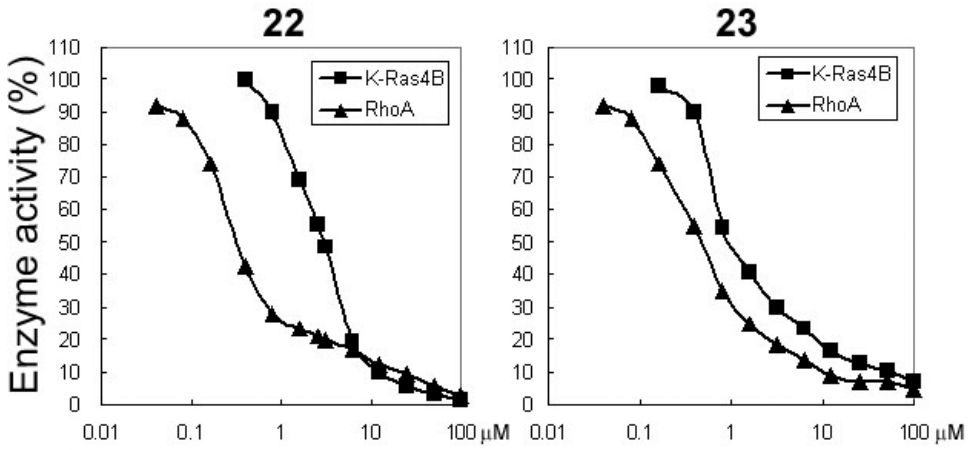


Figure S4. Dose dependency of GGTase-I activity in the presence of compounds **22** or **23**.

Measurement of Specificity. The specificity of the GGTase-I inhibition by **22** and **23** was examined. As is evident from Figure S5, no inhibition of FTase activity was caused by any of these compounds, even when the concentration was increased to 100 μM. The farnesyltransferase (FTase) inhibitor BMS225975, used as a control, inhibited FTase but did not inhibit GGTase-I. The GGTase-I inhibitor GGTI-298 inhibited GGTase-I, whereas little inhibition was observed with FTase.

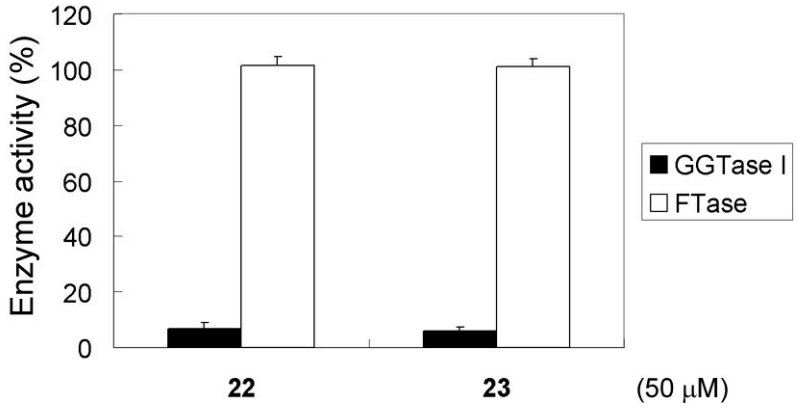


Figure S5. Effects of compounds **22** and **23** on the enzymatic activity of GGTase-I (black) and FTase (white). Data represent the mean ± S.D. of measurements from three independent experiments.

Protein Geranylgeranylation Assay. Human embryonic kidney-293 (HEK293) cells were transfected with pCDNA3-mycHARheb (M184L) mutant [11] using the Polyfect transfection reagent (Qiagen, Chatsworth, CA). Cells were cultured in DMEM plus 10% (v/v) fetal bovine serum overnight, and then DMSO, GGTI-298 (10 μM; Calbiochem, La Jolla, CA), GGTI-2166 (10 μM; obtained from Dr Said Sebti, University of South Florida),[12] and

[11] Gau, C. L.; Kato-Stankiewicz, J.; Jiang, C.; Miyamoto, S.; Guo, L.; Tamanoi, F. *Mol. Cancer Ther.* **2005**, *4*, 918.

[12] Sun, J.; Blaskovich, M. A.; Knowles, D.; Qian, Y.; Ohkanda, J.; Bailey, R. D.; Hamilton, A. D.; Sebti, S. M. *Cancer Res.* **1999**, *59*, 4919.

compound **22** or **23** (25 μM) were added. Incubation was continued for 48 h. The cells were harvested and lysed in lysis buffer (20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% NP-40, 1x Protease Inhibitor Cocktail). Lysates (10 μg) were electrophoresed on a 10% SDS-PAGE, transferred to nitrocellulose membranes and immunoblotted with anti-myc 9B11 antibody (Cell Signaling, Beverly, CA). The descriptors P and U in Figure S6 indicate the processed and unprocessed Rheb, respectively. Data are representative of two independent experiments.

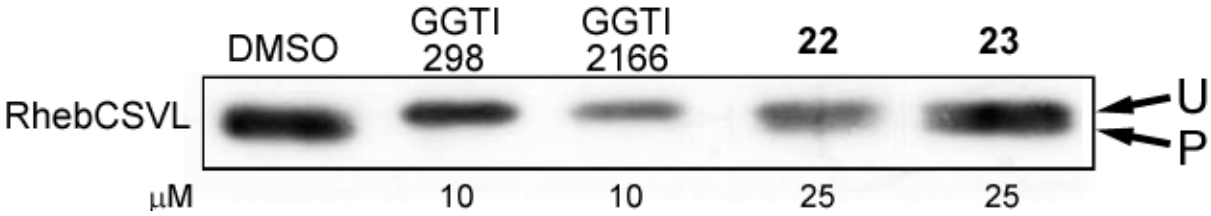


Figure S6. Effects of compounds **22** and **23** on Rheb-CVSL processing in HEK293 cells.

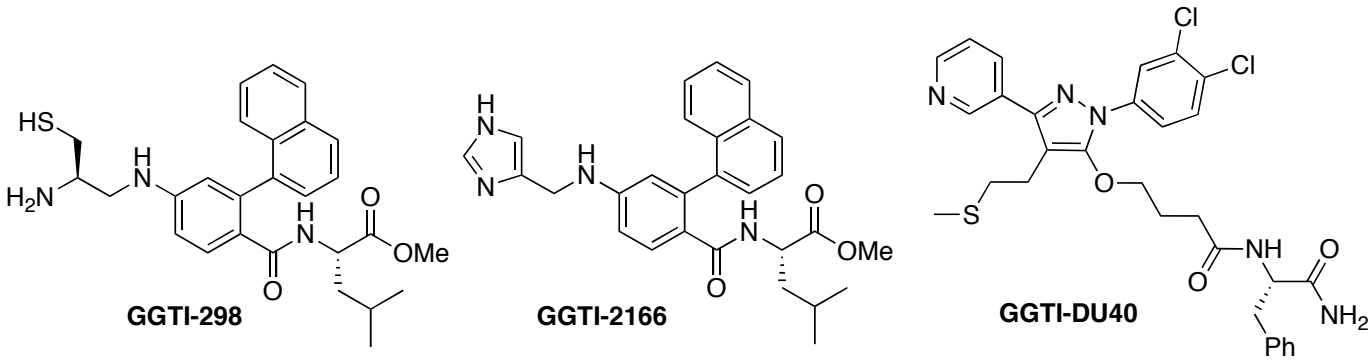


Figure S7. Structures of GGTI-298, GGTI-2166, and GGTI-DU40.