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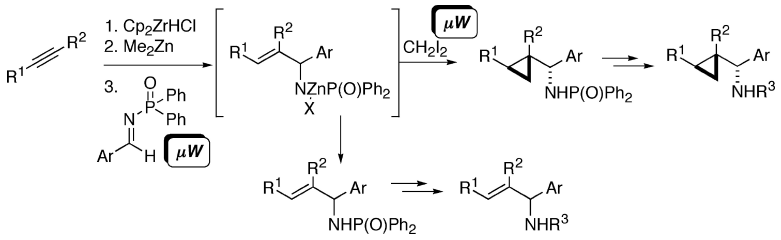

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Microwave-Assisted "Libraries from Libraries" Approach toward the Synthesis of Allyl- and *C*-Cyclopropylalkylamides

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Cascade reactions of internal and terminal alkynes, zirconocene hydrochloride, dimethylzinc, and phosphinoyl imines (prepared in one step from aldehydes and diphenylphosphinoyl amide) lead to allylic phosphinoyl amides after aqueous workup. Microwave acceleration allows the completion of this one-pot reaction sequence in 10 min. These allylic amides can be converted into a variety of derivatives, including carbamates and sulfonamides, or reacted prior to workup with diiodomethane to give novel *C*-cyclopropylalkylamides. A solution-phase "libraries from libraries" approach was used to generate an intermediate 20-member library which was subsequently expanded to a 100-member library by a series of N-functionalizations. The biological activity was evaluated in an assay for competitive binding to the estrogen receptor (ERα), revealing three potent lead compounds of a new structural type.

Introduction

The impact of combinatorial chemistry as a method for the generation of large numbers of compounds for high-throughput screening (HTS) remains undisputed.[1] From its origins in Merrifield peptide synthesis,[2] combinatorial library synthesis of organic molecules has continued to evolve in distinct stages. The current methods for library generation include parallel[3] and solid-phase synthesis or a combination of both,[4] split-and-mix synthesis,[5] and libraries derived from biological sources,[6] as well as diversity-oriented synthesis.[7] In contrast to synthesizing every possible compound accessible by a given combination of synthetic methodology and building blocks, the current focus of library generation lies in optimizing structural diversity and ADMET[8] properties and in accessing individually characterized compounds in milligram quantities.

The need for generating structurally and functionally novel compounds continually drives forward the search for new technologies that enhance combinatorial library generation. The synthetic strategy known as the "libraries from libraries" concept, introduced by Houghten in the mid 1990s,[9] offers a way to rapidly increase diversity in a library and multiply the number of screening samples. The physical properties of libraries derived from this process are typically very different from the scaffolds from which they originate. Combining this strategy with the technical advantages of microwave reaction acceleration[10] provides rapid access to interesting screening samples.

We initiated this study with the goal to expand the efficiency of our recently reported methodology for allylic amide and *C*-cyclopropylalkylamide synthesis[11] by microwave irradiation and to prepare chemical libraries by further compound functionalization using parallel solution-phase chemistry. Our motivation for this project was derived from our discovery of a new antiestrogen in a preliminary biological screen of allylic, homoallylic, and cyclopropyl amides obtained by classical solution-phase synthesis.[11] Specifically, *C*-cyclopropylalkylamide **1** was found to have antiestrogenic activity at ERα comparable to tamoxifen (**2**, Figure 1).[12] Moreover, **1** inhibited 17β-estradiol (E2)-induced proliferation of ERα-positive MCF-7 human breast cancer cells and exhibited minimal cytotoxicity to ERα-negative cells at high micromolar concentrations.

We envisioned that a focused library of analogues of **1** would provide interesting structure−activity relationship (SAR) data and allow us to analyze and improve the antiestrogenic activity of this new scaffold. Our goal was to prepare 20 allylic amides and *C*-cyclopropylalkylamides and expand this collection into a 100-member library by means of parallel N-acylation, -carbamoylation, and -sulfonation. Our one-pot, multicomponent preparation of phosphinoyl amides from alkenylzirconocenes, diphenylphosphinoylimines, dimethylzinc, and diiodomethane provided an attractive entry to the first-generation library intermediates from commercially available or readily synthesized starting materials (Scheme 1).[11] With toluene as the reaction solvent, the allylic amide **5** is formed in situ from imine **4** and the alkenyl zinc reagent derived from hydrozirconation of alkyne **3** followed

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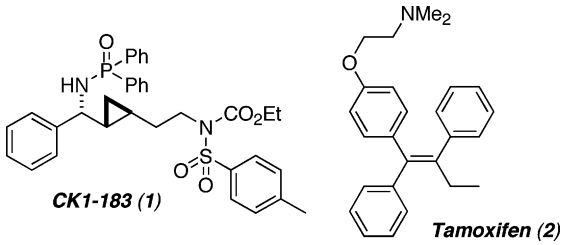
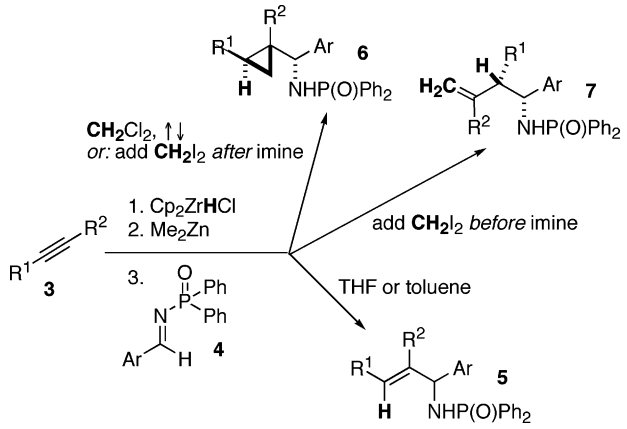


Figure 1. Both the clinically used tamoxifen (**2**) and the novel *C*-cyclopropylalkylamide **1** demonstrate similar antiestrogenic effects at ERα and selective antiproliferative activity.

Scheme 1. Divergent Multicomponent Reaction (DMCR) of Alkynes, Zirconocene Hydrochloride, Dimethylzinc, and Diphenylphosphinoylimines



by transmetalation to dimethylzinc.[13] In contrast, in dichloromethane or in the presence of CH_2I_2, *C*-cyclopropylalkylamide **6** or homoallylic amide **7** are formed, depending on the order of reagent addition.

Results and Discussion

The original protocol shown in Scheme 1 required long reaction times, often exceeding 12 h, since both hydrozirconation[14] and imine addition steps are slow even at room temperature. Therefore, these reaction conditions represented a serious detriment to adapting this process to parallel library synthesis. In contrast, microwave irradiation greatly accelerated the conversion, reducing reaction times from hours to minutes.[15] Several steps in this cascade synthesis, that is, hydrozirconation,[16] organometallic imine addition, and Simmons−Smith-type directed cyclopropanation, were enhanced in the microwave. Accordingly, the targeted 20-member library of allylic amides and *C*-cyclopropylalkylamides became readily accessible. In a typical example, 100 W microwave irradiation of a mixture of 4-octyne (Scheme 2, **3a**, $R^1{=}R^2{=}C_3H_7$) and zirconocene hydrochloride in toluene at 100 °C for 60 s provided a clear yellow solution of alkenyl zirconcocene. After cooling the 10-mL microwave vial to −78 °C, 1 equiv of imine **4a** [Ar=(*p*-MeO_2C)C_6H_4] and 1.6 equiv of dimethylzinc were added, and, after 5 min, microwave irradiation was resumed at 150 W and 100 °C for 120 s. The resulting dark solution of **8a** was subjected to an aqueous quench to give the allylic phosphinoyl amide **5a** in 76% yield. Alternatively, when CH_2Cl_2 was used as a solvent, intermediate **8a** was cooled to 0 °C, treated with 5 equiv of CH_2I_2, and irradiated in the microwave at 300 W and 60 °C for 30 min. A quench with MeOH was followed by serial automated chromatography using a CombiFlash Companion (ISCO) to remove any remaining allylic amide, and the desired *C*-cyclopropylalkylamide **6a** was obtained in 61% yield. After mild acidic cleavage of the phosphinoyl protective group, further derivatization by N-acylation, N-carbamoylation, and N-sulfonation provided derivatives **9**−**14** and completed the libraries-from-libraries approach.[17]

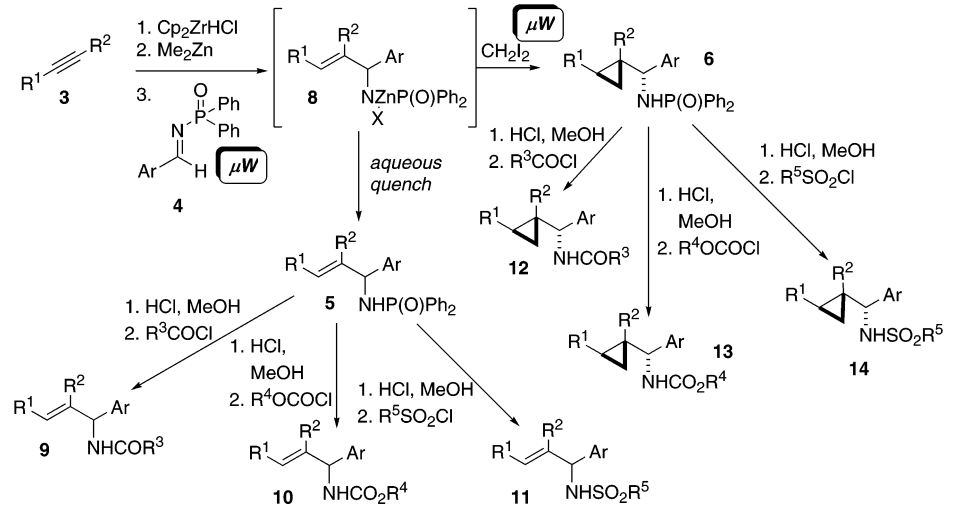
These reaction conditions were optimized for general scope using a representative set of building blocks and allowing sufficient reaction time to accommodate less reactive substrates. One advantage of the use of microwave irradiation is that these trial runs, which are necessary prior to any library production, require significantly less time than conventional procedures.

We selected a matrix of three alkynes **3** and seven phosphinoyl imines **4** to prepare the desired 20 phosphinoyl amides **5** and **6**. Two alkynes (4-octyne, **3a**, and 1-hexyne, **3b**) were commercially available, and prop-1-ynyl cyclohexane **3c** (R^1 = *c*-C_6H_{11}, R^2 = Me) was prepared in two steps from cyclohexylcarboxaldehyde using the Corey−Fuchs protocol.[18] Seven imines **4** were individually prepared in one step from commercially available aldehydes and diphenylphosphinamide **15** according to literature procedures (Table 1).[11a,19−21] Dropwise addition of $TiCl_4$ to a solution of aldehyde **15** and triethylamine in CH_2Cl_2 at 0 °C provided imines **4a**−**4g** in 47−71% yield.[22] Purification was carried out by crystallization from hexane/CH_2Cl_2; **4b** and **4e** were still contaminated with ca. 10% of unreacted aldehyde after crystallization and were used without further purification.

The three alkynes **3a**−**c** and seven imines **4a**−**g** were combined to give seven allylic amides **5a**−**g** and thirteen *C*-cyclopropylalkylamides **6a**−**m** (Table 2 and Figure 2). An automated Emrys Optimizer single-mode microwave reactor was used to perform the serial production on ca. 200-mg scale. All library members were purified by chromatography with a CombiFlash Companion system and analyzed by reversed-phase HPLC with UV and MS detection as well as by ^{1}H NMR. Allylic amides **5a**−**g** were formed in an average yield of 55% and a mean purity of 97%, as determined by UV detection at 220 nm. The yields and purities of cyclopropanes **6a**−**m** were lower, on average 46% and 80%, respectively, mainly because of unreacted allylic amide side products that proved difficult to remove chromatographically. We found that sluggish cyclopropanations could be improved by adding additional diiodomethane (10 equiv) and dimethylzinc (6 equiv).[11a] Entries 9, 12, 15, 16, 18, and 19 showed improved yields using this experimental variation. If additional sample was required, the reaction was repeated using the automated microwave setup, and crude products were combined for purification by automated serial chromatography, therefore providing convenient access to significant quantities of first-generation library intermediates for further diversifications.

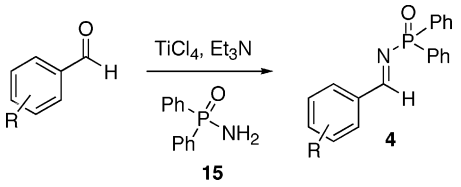
For the next stage of our library synthesis, solution-phase techniques in a Radley GreenHouse Carousel were used. In batches of 24 parallel reactions, the phosphinoyl group was removed by treatment with 2 M HCl in MeOH.[23] The

Scheme 2. Libraries-from-Libraries Approach for the Preparation of Potential Antiestrogens



R^1	R^2	Ar	R^3	R^4	R^5
H	*n*-C_4H_9	Ph	Ph	CH_2Ph	Ph
n-C_3H_7	*n*-C_3H_7	*p*-ClC_6H_4	CH_2Ph	$CH_2CH(CH_2)_2$	*rac*-camphorsulfonyl
c-C_6H_{11}	Me	*m*-ClC_6H_4	CH_2CH_2Ph	*i*-Bu	8-quinoline
		p-$CF_3C_6H_4$	*t*-Bu	*o*-$ClC_6H_4CH_2$	*p*-ClC_6H_4
		o-$CF_3C_6H_4$	*p*-PhC_6H_4	*p*-FC_6H_4	*p*-$CF_3C_6H_4$
		(*p*-CO_2Me)C_6H_4	*p*-$CF_3C_6H_4$	CH_2CCH	Me
		p-PhC_6H_4	(*p*-CO_2Me)C_6H_4		*p*-$MeOC_6H_4$
			2-furanyl		2-thiophene
			2-thiophene		*p*-PhC_6H_4
			3-pyridyl		

Table 1. Preparation of Phosphinoyl Imines **4**



entry	phosphinoyl imine	R	yield [%][a]
1	**4a**[11a]	*p*-CO_2Me	57
2	**4b**[19]	H	57
3	**4c**[19]	*p*-Ph	47
4	**4d**[21]	*p*-CF_3	71
5	**4e**	*m*-Cl	36
6	**4f**	*o*-CF_3	53
7	**4g**[19]	*p*-Cl	64

[a] Isolated yields.

reaction mixtures were monitored by TLC for the disappearance of starting material, and typically 3−12 h were required for deprotections to go to completion. The solutions were concentrated to dryness using a blowdown evaporator, CH_2Cl_2 was added, and the solution was repeatedly evaporated to dryness. Finally, a solution of **5** or **6** in CH_2Cl_2 was treated with approximately 2 equiv of 10 different acyl chlorides, 6 carbamoyl chlorides, and 9 sulfonyl chlorides, 3 equiv of DIPEA, and 10 mol % of DMAP. The acylating agents were selected to represent a set of aliphatic, aromatic, and electron-rich and -deficient substituted aromatic, halogenated, and heteroaromatic building blocks. The reaction mixtures were stirred at room temperature for 1 h and purified using an Optix 10 parallel chromatography system (ISCO). This protocol allowed for a rapid purification of 10 derivatives in 15 min using a step gradient of ethyl acetate/hexanes. Analyses of the final 100-member library by HPLC with UV detection at 210 and 220 nm, as well as online MS analysis, established that the desired products were formed in all cases. The average isolated yield was 51%, and the purity was >80% for 85 out of 100 samples at 220 nm. The average library purity of 44 allylic derivatives **9a**−**11m** and 56 cyclopropanes **12a**−**14g** was 91%. The library had 57 members with >90% purity. Structural and purity data for **9a**−**14g** are summarized in detail in the electronic supplementary information. Six derivatives (**9a**, **10h**, **11n**, **12a**, **13d**, **14a**) were also synthesized in a traditional fashion and fully characterized by ^1H and ^{13}C NMR, IR, and MS.

"Druglike" properties[24] for the 20-member first-generation and the 100-member second-generation libraries are summarized in Table 3. Average molecular weight and the number of hydrogen bond donors and acceptors are well within the recommended range for minimizing potential ADMET problems.[25] In contrast, lipophilicity in both libraries as expressed in *c*LogP values is considerably above the general range for marketed pharmaceuticals;[25] however, the second-generation library shows more than an order of magnitude improvement over the first-generation scaffolds.

Biological Evaluation

The biological activity of 70 library members with purities exceeding 85% as determined by HPLC with 220-nm UV detection was evaluated using a commercially available in vitro fluorescence polarization-based homogeneous ERα competition assay (Panvera).[12,26] Recombinant human ERα complexed with fluorescently labeled 17β-estradiol (ES2) was distributed to all wells of a 384-well flat and black-

Table 2. Preparation of First-Generation Library; Structures Are Shown in Figure 2

entry	product	yield [%][a]	LC purity [%][b]	MS [*m*/*z*][c]	entry	product	yield [%][a]	LC purity [%][b]	MS [*m*/*z*][c]
1	**5a**	76	100	475.2	11	**6d**	32[g]	80	478.5
2	**5b**	10[d]	96	498.4	12	**6e**	18[f,i]	73	462.4
3	**5c**	40[d]	93	506.3	13	**6f**	33[f]	92	466.4
4	**5d**	58[h]	91	390.3	14	**6g**	49[f]	80	404.3
5	**5e**	68	100	485.0	15	**6h**	73[d,i]	50	502.3
6	**5f**	65	100	494.2	16	**6i**	80[d,i]	78	520.2
7	**5g**	68	100	418.3	17	**6j**	63	92	432.2
8	**6a**	75	100	489.0	18	**6k**	34[d,i]	95	480.4
9	**6b**	30[f,i]	92	472.3	19	**6l**	31[e,i]	67	472.4
10	**6c**	45[f]	85	466.3	20	**6m**	33[h]	78	508.4

[a] Isolated yields of purified products on the basis of aldimine. [b] Purity determined by HPLC peak area integration at 210 or 220 nm. [c] LCMS analysis. [d] Average of two reactions. [e] Average of three reactions. [f] Average of four reactions. [g] Average of five reactions. [h] Average of six reactions. [i] Additional Me_2Zn (6 equiv) and CH_2I_2 (10 equiv) were added to the reaction mixture.

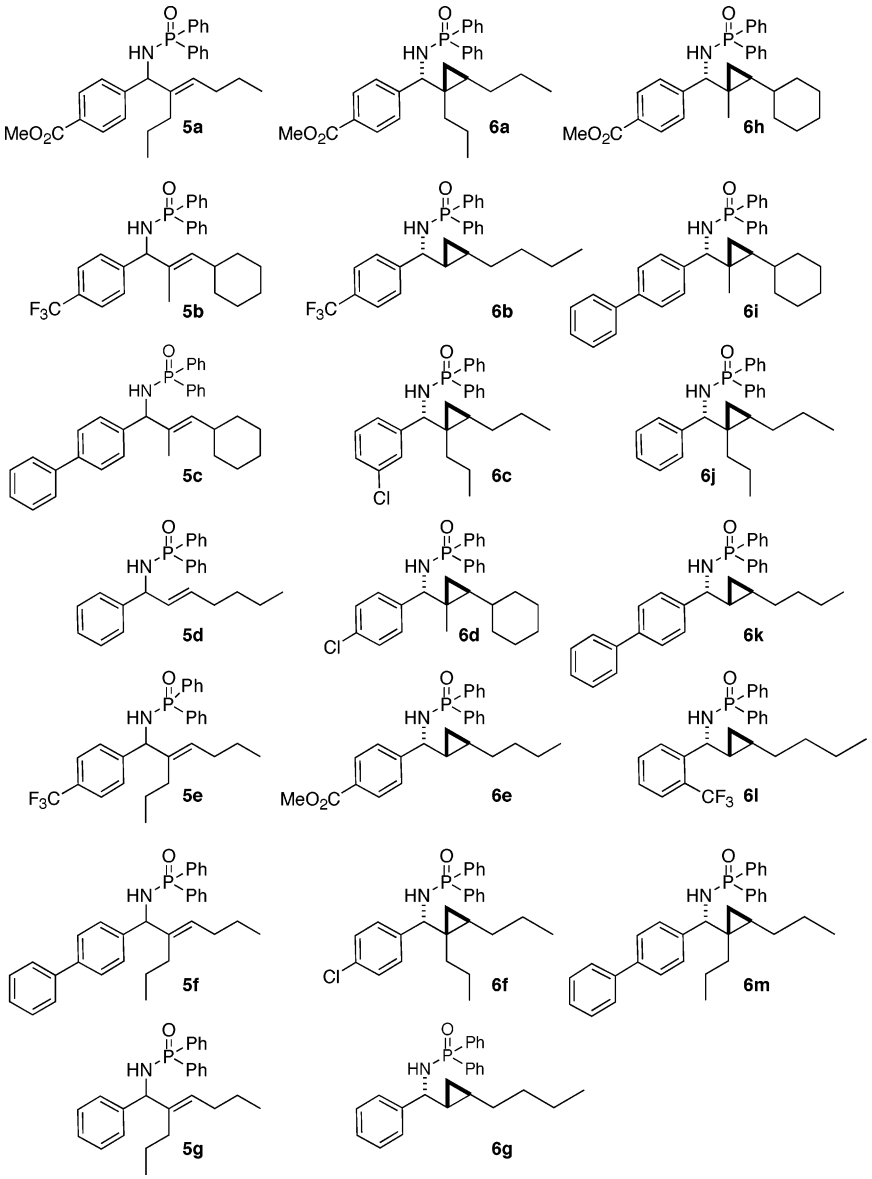


Figure 2. Structures of first-generation library components. All samples are racemic.

bottom plate, and then serial dilutions of test compounds were added. After 2 h, the fluorescence polarization was measured. ES2 remaining bound to ERα protein gave high fluorescence polarization. In the presence of a competing ligand, the fluorescence polarization decreased. The assay was performed at 40 μL total volume, in duplicates at three concentrations for each tested compound (5, 1, and 0.2 μM), and 17β-estradiol (E2, 1 μM) was used as a standard competitor. The data shown in Figure 3 represent the percent of competition (%I), calculated on the basis of the following formula: $\%\, I = [(mP_0 - mP)/(mP_0 - mP_{100})] \times 100$, where mP_0 is the fluorescence polarization (mP) value for 0% competition as referred to the high polarization of ES2 complexed to ERα (ER/ES2 complex); mP_{100} is the mP value

Table 3. Lipinski's Rule of Five[24] Average Physicochemical Characteristics for First- and Second-Generation Libraries

library	MW[a]	HBAcc[a]	HBDon[a]	*c*LogP[a]
20-member	470.6	1.20	1.00	8.52
100-member	400.4	1.32	1.01	7.13

[a] Average values; HBAcc = hydrogen bond acceptors; HBDon = hydrogen bond donors; *c*LogP = calculated log of octanol−water partition coefficient.

for 100% competition, as referred to the low polarization in the presence of 1 μM E2; and mP is the fluorescence polarization in the presence of test compounds.

The ERα competition screen identified 11 hits according to the following criteria: (1) the library member gave 50% competition at 0.2 μM and (2) the percent competition increased as the concentration of test compound increased. The hits that showed concentration dependence in the ERα competitor assay are shown in Figure 4. Data represent the averaged percent competition from a single screen done in duplicate with raloxifene (RAL) and tamoxifen (TAM) as positive controls.

The original hit **1** was previously shown to be a weak displacing agent in the ERα competitor assay.[12] Compounds **12g**, **12i**, and **14g**, in contrast, showed comparable or better activity in the ERα competitor assay than raloxifene. Like compound **1**, **12g**, **12i**, and **14g** inhibited the E2-induced proliferation of MCF-7 cells[27] by 50% at low micromolar concentrations [GI_{50}'s: 2.7 ± 0.8 μM (**12g**), 3.7 ± 2.8 μM (**12i**), and 5.7 ± 2.0 μM (**14g**)].

Conclusions

We have developed an expeditious divergent multicomponent reaction (DMCR) method, combining the advantages of microwave reaction acceleration and combinatorial technologies with a libraries-from-libraries concept to prepare 20 allylic amides and *C*-cyclopropylalkylamides and create an expanded 100-member library. An earlier, structurally novel hit in an antiestrogenic nuclear receptor (ERα) assay served as a lead structure for this targeted array. The library building blocks consisted of 3 alkynes, 7 phosphinoylimines, 10 acid chlorides, 6 carbamoyl chlorides, and 9 sulfonyl chlorides. Seventy high-purity library members were screened for their ability to compete with fluorescently labeled 17β-estradiol for binding to human ERα. Eleven hits were identified from the screen and three compounds exhibited affinity for ERα and antagonized estradiol induced proliferation of human breast cancer cells. QikProp[28] analysis of these three compounds, **12g**, **12i**, and **14g**, showed that their ADMET properties fall within the 95% range of similar values for known drugs (see Supporting Information). Exceptions are the *c*LogP and aqueous solubility values for **14g** and the aqueous solubility for **12g**. Most significantly, these compounds confirm that an alkene-containing substructure reminiscent of antiestrogens such as tamoxifen is not a critical requirement for biological activity at the ER. The cyclopropane ring is likely to demonstrate reduced in vivo metabolism compared to alkenes and therefore represents an attractive new scaffold for the development of ERα targeting agents.

Experimental Section

General. All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame-dried under vacuum prior to use. Toluene was purified by filtration through activated alumina. CH_2Cl_2 was distilled over calcium hydride. EtOAc was distilled prior to use. Acetyl chloride (AcCl), benzoyl chloride (PhCOCl), diisopropylethylamine [$(i\text{-Pr})_2$NEt], (dimethylamino)pyridine (DMAP), phenyl chloroformate ($ClCO_2Ph$), and benzenesulfonyl chloride ($PhSO_2$-Cl) were purchased from Aldrich or Acros and used without further purification. Me_2Zn (2.0 M in toluene) was purchased from the Aldrich Chemical Co. Cp_2ZrHCl was prepared according to a modification of a literature protocol.[29] CH_2I_2 was purchased from Acros and used without further purification. Unless stated otherwise, solvents or reagents were used as received. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates (particle size 0.040−0.055 mm, 230−400 mesh), and visualization was accomplished with a 254-nm UV light and by staining with Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.20 g of $Ce(SO_4)_2$ in 100 mL of 3.5 N H_2SO_4). NMR spectra were recorded in $CDCl_3$ at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 °C unless stated otherwise. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration, and coupling constants. HPLC/UV and -MS spectra were obtained using a ThermoFinnigan LC/autosampler/PDA detector coupled to a ThermoFinnigan octopole ion trap using a reversed-phase C_{18} column (acetonitrile/water/methanol 7:2:1, 1 mL/min) with UV detection at 210/220 nm and an APCI probe (positive ion detection mode). Individual sequential microwave reactions were run using an Emrys Optimizer microwave reactor from Biotage. Emrys Optimizer microwave reactor settings for allylic amide synthesis: Set hold time = 60 s; the reaction mixture was heated to set temperature over approximately 60−80 s and held at constant temperature for 60 s; T = 100 °C, power = 100 W (hydrozirconation) or 150 W (aldimine addition), pressure = 10 psi, time = 120 s, constant hold time "on", cooling "off". Emrys Optimizer settings for cyclopropanations: T = 100 °C, power = 300 W for 5 min and T = 60 °C, power = 300 W for 30 min. Parallel solution-phase reactions were conducted in a 24-vial Radley's GreenHouse carousel followed by evaporation with a blowdown evaporator using nitrogen at 40 °C. The allylic amide and *C*-cyclopropylalkylamide 20-member intermediate library was purified by automated serial chromatography with a CombiFlash Companion (ISCO). Each product was eluted with a hexanes/EtOAc gradient (0−100% EtOAc) over 14 column volumes on a 40-g Redisep column. The 100-member library was purified using a multichannel Optix 10 (ISCO) using 10 4-g normal-phase Redisep columns (ISCO). All derivatives were dried using a Christ Alpha RVC evaporator at 40 °C/0.1 mbar for 4 h.

General Procedure for Serial Microwave-Assisted Sequential Synthesis of Allylic Amides and *C*-Cyclopropylamides. Methyl (*E*)-4-[1-(Diphenylphosphinyl)amino-2-propylhex-2-enyl]benzoate (5a). A 10-mL microwave tube was flame-dried, charged with argon, and equipped with

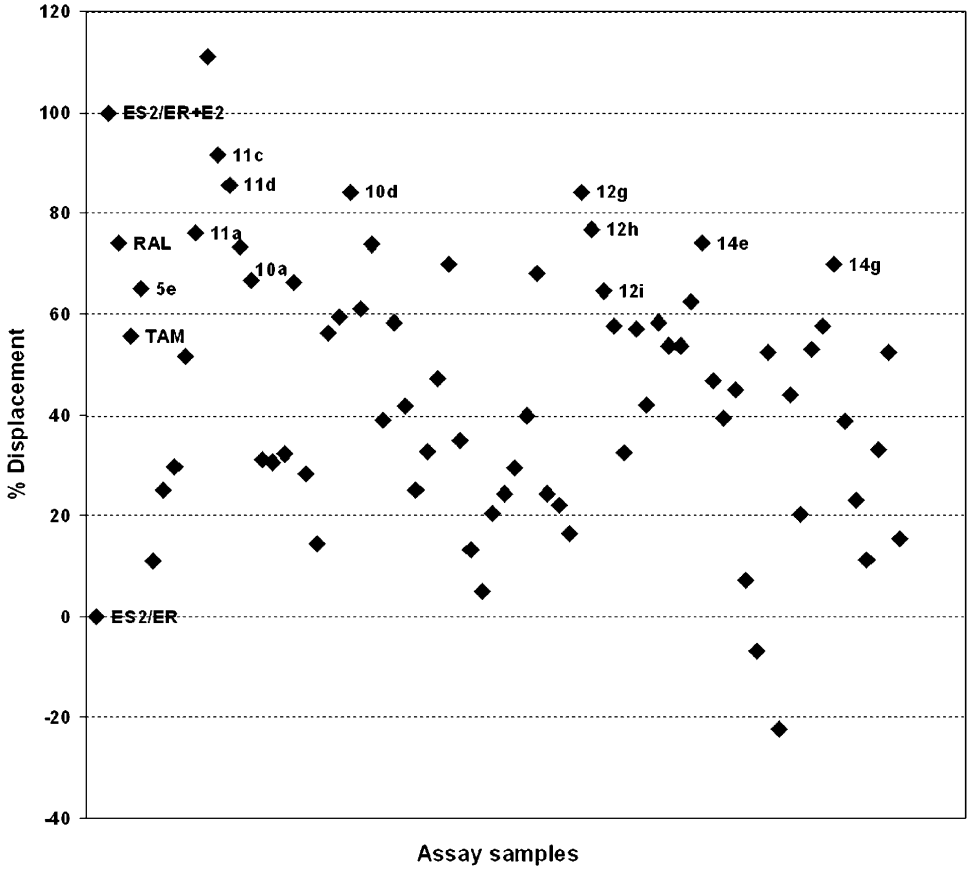


Figure 3. Results of ERα competitor assay screening of 70 high-purity library members at 1 μM. Raloxifene (RAL) and tamoxifen (TAM) were used as positive controls. All values were normalized to 1 μM 17β-estradiol (E2) as 100% competition (ES2/ER+E2). The library members that were identified as hits are noted with their compound numbers.

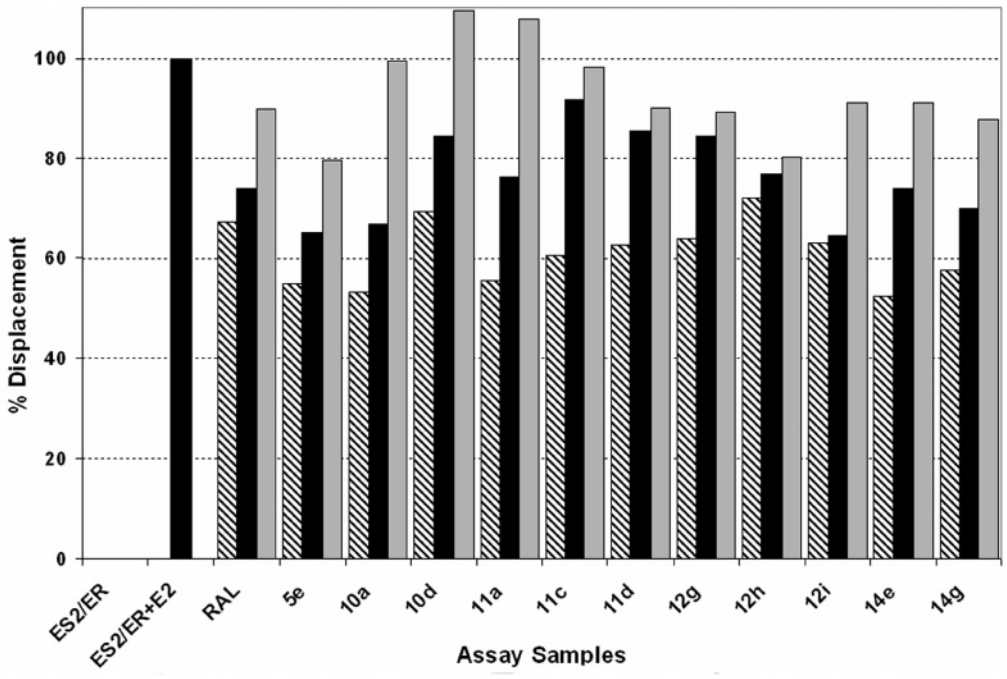


Figure 4. Concentration-dependent displacement of fluorescently labeled estradiol by 11 library members identified as hits in Figure 3. Hatched bar, 0.2 μM. Filled black bar, 1.0 μM. Gray bar, 5.0 μM.

a magnetic stirrer and a rubber septum. The tube was cooled to room temperature before reagents were added. A suspension of $Cp_2Zr(H)Cl$ (0.21 g, 0.80 mmol, 1.5 equiv) in dry toluene (1.6 mL) was treated with 4-octyne (0.13 mL, 0.87 mmol, 1.7 equiv). The reaction mixture was heated in a single-mode microwave reactor (100 °C, 100 W) for 60 s. The microwave tube was removed from the microwave reactor, placed in an acetone dry ice bath (−78 °C), and treated with neat **4a** (0.19 g, 0.52 mmol, 1.0 equiv) followed by a 2 M solution of Me_2Zn in toluene (0.40 mL, 0.80 mmol,

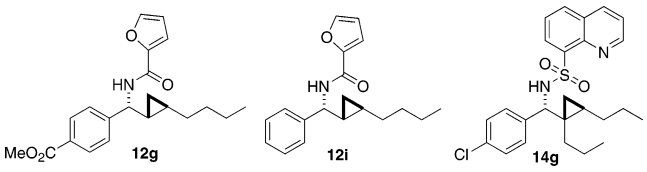


Figure 5. Structures of library members that exhibited signficant affinity for ERα and antagonized estradiol-induced proliferation of human breast cancer cells.

1.6 equiv). The reaction mixture was again heated in the microwave (100 °C, 150 W) for 120 s and cooled to room temperature. The reaction progress was monitored by TLC analysis (R_f = 0.41 (4:1 EtOAc/hexanes, UV, Vaughn stain). The solution was cooled to room temperature, quenched with 1 M NH_4Cl (0.5 mL), and diluted with EtOAc (50 mL) and 1 M $NaHCO_3$ (1 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with water (2 × 20 mL) and brine (1 × 10 mL) and dried ($MgSO_4$). The organic extract was purified by chromatography on deactivated SiO_2 (9:1, EtOAc/hexanes containing 1% Et_3N) to give **5a** (0.18 g, 76%) as a colorless solid: R_f = 0.41 (4:1, EtOAc/hexanes); mp 91.9−92.3 °C (EtOAc/hexanes); IR (KBr) 3181, 2957, 2930, 2869, 1722, 1610, 1436, 1281, 1185, 1107, 1123, 1019 cm^{-1}; ^1H NMR δ 7.97−7.77 (m, 6 H), 7.50−7.35 (m, 8 H), 5.50 (t, 1 H, J = 7.2 Hz), 4.76 (t, 1 H, J = 10.6 Hz), 3.90 (s, 3 H), 3.28 (dd, 1 H, J = 10.3, 6.3 Hz), 2.14−2.02 (m, 2 H), 1.75−1.70 (m, 1 H), 1.45−1.37 (m, 2 H), 1.17−1.09 (m, 2 H), 0.93 (t, 3 H, J = 7.3 Hz), 0.74 (t, 3 H, J = 7.3 Hz); ^{13}C NMR δ 167.21, 148.28, 140.24, 140.18, 133.71, 133.61, 132.72, 132.59, 132.41, 132.28, 132.16, 131.89, 130.02, 129.29, 128.77, 128.61, 128.78, 78.70, 59.51, 52.29, 43.09, 37.16, 31.40, 30.15, 23.23, 22.34, 14.46, 14.23; MS (EI) *m*/*z* (intensity) 475 (M^+, 59), 446 (16), 432 (14), 364 (63), 274 (45), 218 (53), 201 (100); HRMS (EI) *m*/*z* calcd for $C_{29}H_{34}NO_3P$ 475.2276, found 475.2283.

Methyl (*R)-4-{(Diphenylphosphinylamino)-[(1*R**,2*R**)-1,2-dipropylcyclopropyl]methyl}benzoate (6a).** A 10-mL microwave tube was flame-dried, equipped with a rubber septum, and purged with N_2 upon cooling to room temperature. The tube was charged with Cp_2ZrHCl (0.54 g, 2.1 mmol) and the solid was suspended in CH_2Cl_2 (3.0 mL). Upon addition of octyne (0.31 mL, 2.1 mmol), the reaction mixture was stirred for 20 min. The 4-octyne was added immediately after the CH_2Cl_2 to avoid decomposition of the Cp_2ZrHCl. The yellow-orange solution was cooled to −78 °C, treated sequentially with a solution of **4a** (0.25 g, 0.70 mmol) in dry CH_2Cl_2 (0.50 mL) and Me_2Zn (1.0 mL, 2.1 mmol, 2.0 M in toluene), and warmed to 0 °C. The reaction mixture was heated in the microwave (300 W, 100 °C) for 5 min and cooled to 0 °C. After treatment with CH_2I_2 (0.28 mL, 3.5 mmol), the mixture was heated in the microwave (300 W, 60 °C) for 30 min. The solution was cooled to 0 °C, quenched with MeOH (ca. 0.50 mL), diluted with EtOAc (10 mL, 50 mL for washing), filtered through SiO_2, and concentrated. The residue was purified by chromatography on SiO_2 (ISCO) to afford **6a** (0.21 g, 61%) as a colorless foam: R_f 0.6 (1:4 hexanes/EtOAc); mp 126.0−128.0 °C (hexanes/EtOAc); IR (KBr) 3195, 2956, 2930, 2871, 1722, 1610, 1437, 1277, 1183, 1108 cm^{-1}; ^1H NMR δ 7.94 (d, 2 H, J = 8.2 Hz), 7.83 (dd, 2 H, J = 11.8, 6.9 Hz), 7.68 (dd, 2 H, J = 11.7, 7.3 Hz), 7.53−7.38 (m, 4 H), 7.31−7.21 (m, 4 H), 4.19 (t, 1 H, J = 10.4 Hz), 3.92 (s, 3 H), 3.24 (dd, 1 H, J = 9.7, 6.8 Hz), 1.59−1.23 (m, 6 H), 1.16−1.03 (m, 3 H), 0.87 (t, 3 H, J = 7.3 Hz), 0.79 (t, 3 H, J = 7.2 Hz), 0.70−0.61 (m, 1 H), 0.01 (t, J = 5.0 Hz, 1 H); ^{13}C NMR δ 166.94, 147.81, 147.77, 132.43, 132.31, 131.94, 131.81, 131.71, 131.68, 129.37, 128.83, 128.55, 128.38, 128.27, 128.10, 127.23, 58.91, 51.98, 32.36, 31.06, 29.57, 29.51, 23.12, 21.91, 20.57, 15.09, 14.45, 14.09; MS (EI) *m*/*z* (intensity) 489 (M^+, 5), 364 (53), 298 (55), 288 (28), 218 (48), 201 (100); HRMS (EI) *m*/*z* calcd for $C_{30}H_{36}NO_3P$ 489.2433, found 489.2426.

General Procedure for the Conventional Synthesis of Second-Generation Library Members. Methyl (*E*)-4-[1-(Benzamido)-2-propylhex-2-enyl]benzoate (9a). General Protocol A. A 50-mL round-bottom flask containing MeOH (5.0 mL) was cooled in an ice bath and treated with AcCl (0.71 mL, 10 mmol). The colorless solution was stirred at 0 °C for 15 min, warmed to room temperature, and stirred for a further 5 min. The resulting solution of 2 N HCl in MeOH was treated with **5a** (48 mg, 0.10 mmol), stirred at room temperature for 12 h, and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (5.0 mL) and concentrated to dryness, and the residue was dissolved in CH_2Cl_2 (1.0 mL) and treated with PhCOCl (27 μL, 0.23 mmol), (*i*-Pr)$_2$NEt (60 μL, 0.34 mmol) and DMAP (2.0 mg, 0.016 mmol). The reaction mixture was stirred at room temperature for 1 h, concentrated to ∼0.50 mL, and purified by column chromatography on SiO_2 (4:1, hexanes/EtOAc) to afford **9a** (32 mg, 84%) as a colorless oil: R_f = 0.4 (4:1 hexanes/EtOAc); IR (neat) 3571, 3311, 2959, 2869, 1725, 1637, 1525, 1277, 1107 cm^{-1}; ^1H NMR δ 8.01 (d, 2 H, J = 8.4 Hz), 7.80 (d, 2 H, J = 8.4 Hz), 7.55−7.38 (m, 5 H), 6.42 (d, 1 H, J = 8.0 Hz), 5.81 (d, 1 H, J = 8.1 Hz), 5.33 (t, 1 H, J = 7.1 Hz), 3.91 (s, 3 H), 2.18−1.92 (m, 4 H), 1.53−1.31 (m, 4 H), 0.92 (t, 3 H, J = 7.3 Hz), 0.89 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 166.83, 166.40, 146.27, 138.81, 134.38, 131.63, 129.84, 129.26, 129.10, 128.65, 127.34, 126.93, 57.84, 52.02, 31.77, 29.82, 22.82, 22.14, 14.20, 13.83; MS (EI) *m*/*z* 379 (M^+, 46), 336 (59), 322 (56), 105 (100), 77 (48); HRMS (EI) *m*/*z* calcd for $C_{24}H_{29}NO_3$ 379.2147, found 379.2143.

Methyl (*E*)-4-(1-Phenoxycarbonylamino-2-propylhex-2-enyl)benzoate (10h). According to the General Protocol A, **5a** (44 mg, 0.090 mmol), $ClCO_2Ph$ (26 μL, 0.21 mmol), (*i*-Pr)$_2$NEt (55 μL, 0.32 mmol), and DMAP (2 mg, 0.02 mmol) afforded **10h** (33 mg, 90%) as a colorless oil: R_f = 0.6 (4:1, hexanes/EtOAc); IR (neat) 3336, 2957, 2869, 1723, 1524, 1490, 1281, 1207, 1112, 1018 cm^{-1}; ^1H NMR δ 8.03 (d, 2 H, J = 8.3 Hz), 7.46−7.12 (m, 7 H), 5.40−5.36 (m, 3 H), 3.93 (s, 3 H), 2.14−2.04 (m, 3 H), 1.96−1.86 (m, 1 H), 1.46−1.34 (m, 4 H), 0.92 (t, 3 H, J = 7.3 Hz), 0.91 (t, 3 H, J = 7.3 Hz); ^{13}C NMR δ 166.77, 145.99, 138.44, 129.85 (2 C), 129.51, 129.38, 129.22 (2 C), 127.20 (2 C), 125.31, 121.45 (2 C), 120.86, 52.03, 31.43, 29.75, 22.78, 22.05, 14.14, 13.80; MS (EI) *m*/*z* 395 (M^+, 2), 364 (8), 301 (23), 259 (100), 227 (22), 214 (45), 170 (24), 141 (34), 128 (34), 94 (95), 77 (63); HRMS (EI) *m*/*z* calcd for $C_{24}H_{29}NO_4$ 395.2097, found 395.2101.

Methyl (*E*)-4-(1-Benzenesulfonylamino-2-propylhex-2-enyl)benzoate (11n). According to the General Protocol A, **5a (**43 mg, 0.09 mmol), $PhSO_2Cl$ (26 μL, 0.20 mmol), (i-Pr)$_2$NEt (53 μL, 0.30 mmol), and DMAP (2.0 mg, 0.020 mmol) afforded **11n** (29 mg, 77%) as a colorless oil: R_f = 0.4 (4:1, hexanes/EtOAc); IR (neat) 3285, 2957, 2873, 1723, 1447, 1442, 1329, 1280, 1163, 1110 cm^{-1}; ^{1}H NMR δ 7.85 (d, 2 H, J = 8.4 Hz), 7.74 (d, 2 H, J = 8.1 Hz), 7.52−7.46 (m, 1 H), 7.41−7.35 (m, 2 H), 7.17 (d, 2 H, J = 8.3 Hz), 5.19−5.12 (m, 2 H), 4.96 (d, 1 H, J = 7.7 Hz), 3.90 (s, 3 H), 1.92−1.70 (m, 4 H), 1.30−1.12 (m, 4 H), 0.81 (t, 3 H, J = 7.3 Hz), 0.77 (t, 3 H, J = 7.3 Hz); ^{13}C NMR δ 166.70, 144.98, 140.53, 137.74, 132.42, 130.08, 129.57, 129.24, 128.76, 127.25, 127.09, 61.76, 52.02, 30.88, 29.70, 22.54, 21.94, 14.06, 13.75; MS (EI) m/z 415 (M$^+$, 1), 384 (1), 372 (1), 340 (1), 304 (16), 274 (19), 258 (17), 141 (31), 132 (20), 77 (100); HRMS (EI) m/z calcd for $C_{23}H_{29}NO_4S$ 415.1817, found 415.1819.

Methyl (*R)-4-{(Benzamido)-[(1*R**,2*R**)-1,2-dipropylcyclopropyl]methyl}benzoate (12a).** According to the General Protocol A, **6a** (50 mg, 0.10 mmol), PhCOCl (24 μL, 0.20 mmol), (i-Pr)$_2$NEt (53 μL, 0.31 mmol), and DMAP (1.0 mg, 0.01 mmol) afforded **12a** (40 mg, 100%) as a colorless oil: R_f 0.3 (4:1, hexanes/EtOAc); IR (neat) 3303, 2955, 2930, 2871, 1725, 1635, 1528, 1280, 1110 cm^{-1}; ^{1}H NMR δ 8.01−7.74 (m, 2 H), 7.81−7.78 (m, 1 H), 7.56−7.43 (m, 3 H), 7.39 (d, 2 H, J = 8.2 Hz), 6.52 (d, 1 H, J = 7.8 Hz), 5.19 (d, 1 H, J = 7.9 Hz), 3.91 (s, 3 H), 1.56−1.33 (m, 6 H), 1.27−1.16 (m, 2 H), 0.91 (t, 3 H, J = 7.1 Hz), 0.84 (t, 3 H, J = 6.9 Hz), 0.80−0.71 (m, 2 H), 0.14 (t, 1 H, J = 4.9 Hz); ^{13}C NMR δ 166.86, 166.67, 145.76, 134.33, 131.63, 129.64, 129.03, 128.66, 126.98, 126.85, 58.02, 52.02, 32.92, 30.94, 27.76, 23.14, 21.69, 20.82, 15.65, 14.59, 14.08; MS (EI) m/z (intensity) 393 (M$^+$, 8), 350 (18), 322 (27), 202 (52), 105 (100); HRMS (EI) m/z calcd for $C_{25}H_{31}NO_3$ 393.2304, found 393.2314.

***O*-(Phenyl)-*N*-{(*R**)-[(1*R**,2*R**)-1,2-dipropylcyclopropyl]-[4-(methoxycarbonyl)phenyl]methyl}carbamate (13d).** According to the General Protocol A, **6a** (50 mg, 0.10 mmol), $ClCO_2Ph$ (26 μL, 0.20 mmol), (i-Pr)$_2$NEt (53 μL, 0.31 mmol), and DMAP (1.0 mg, 0.010 mmol) afforded **13d** (39 mg, 94%) as a colorless solid: R_f 0.5 (4:1, hexanes/EtOAc); mp 140.0−141.5 °C (hexanes/EtOAc); IR (neat) 3317, 3005, 2955, 2933, 2871, 1713, 1611, 1520, 1491, 1468, 1456, 1433, 1282, 1204, 1116 cm^{-1}; ^{1}H NMR δ 8.03 (d, 2 H, J = 8.2 Hz), 7.38 (2 H, d, J = 8.3 Hz), 7.38−7.32 (m, 2 H), 7.21−7.11 (m, 3 H), 5.46 (d, 1 H, J = 8.1 Hz), 4.83 (d, 1 H, J = 8.1 Hz), 3.93 (s, 3 H), 1.65−1.10 (m, 8 H), 0.93 (t, 3 H, J = 7.2 Hz), 0.85 (t, 3 H, J = 6.8 Hz), 0.78−0.62 (m, 2 H), 0.11 (t, 1 H, J = 4.8 Hz); ^{13}C NMR δ 166.84, 154.00, 150.88, 129.64, 129.21, 129.14, 126.94, 125.28, 121.42, 59.33, 52.08, 32.66, 30.87, 27.71, 23.09, 21.54, 20.62, 15.19, 14.52, 14.08; MS (EI) m/z (intensity) 409 (M$^+$, 3), 284 (58), 273 (54), 218 (100), 191 (47), 94 (81); HRMS (EI) m/z calcd for $C_{25}H_{31}NO_4$ 409.2253, found 409.2271.

Methyl (*R)-4-{(Benzenesulfonylamino)-[(1*R**,2*R**)-1,2-dipropylcyclopropyl]methyl}benzoate (14a).** According to the General Protocol A, **6a** (50 mg, 0.10 mmol), $PhSO_2Cl$ (26 μL, 0.20 mmol), (i-Pr)$_2$NEt (53 μL, 0.31 mmol), and DMAP (1.0 mg, 0.01 mmol) afforded **14a** (43 mg, 98%) as a colorless oil: R_f 0.3 (4:1, hexanes/EtOAc); IR (neat) 3281, 2956, 2871, 1724, 1612, 1448, 1436, 1327, 1281, 1163, 1111 cm^{-1}; ^{1}H NMR δ 7.80 (d, 2 H, J = 8.4 Hz), 7.71−7.67 (m, 2 H), 7.49−7.44 (m, 1 H), 7.37−7.31 (m, 2 H), 7.08 (d, 2 H, J = 8.2 Hz), 5.32 (d, 1 H, J = 7.3 Hz), 4.32 (d, 1 H, J = 7.3 Hz), 3.89 (s, 3 H), 1.42−1.12 (m, 7 H), 1.09−0.95 (m, 3 H), 0.82 (t, 3 H, J = 7.2 Hz), 0.72 (t, 3 H, J = 7.0 Hz), 0.46−0.36 (m, 1 H), −0.02 (t, 1 H, J = 5.4 Hz); ^{13}C NMR δ 166.75, 144.48, 140.14, 132.44, 129.29, 128.95, 128.76, 127.06, 126.97, 61.68, 52.06, 32.32, 30.72, 28.48, 22.98, 21.60, 20.39, 14.99, 14.36, 14.00; MS (EI) m/z (intensity) 429 (M$^+$, 11), 304 (100), 272 (45), 229 (46), 212 (61), 141 (55), 132 (42),; HRMS (EI) m/z calcd for $C_{24}H_{31}NO_4S$ 429.1974, found 429.1955.

General Procedure for the Parallel Generation of the 100-Member Library. A 250-mL round-bottom flask containing MeOH (100 mL) was cooled in an ice bath and treated with AcCl (14 mL). The colorless solution was stirred in the ice bath for 15 min, then warmed to room temperature, and stirred for a further 5 min. Five milliliters of this 2 N HCl solution was added to each of 24 10-mL Radley's vials followed by allylic amide (0.10 mmol) or *C*-cyclopropylalkylamide (0.10 mmol). The solutions were stirred at room temperature for 3−12 h and monitored by TLC (4:1, EtOAc/hexane). The solutions were concentrated to dryness with a blowdown evaporator using nitrogen at 40 °C for 2 h. Dichloromethane (5.0 mL) was added to each vessel followed by repeated parallel evaporation. Dichloromethane (1.0 mL) was added to each tube followed by the appropriate acyl chloride (0.20 mmol), carbamoyl chloride (0.20 mmol) or sulfonyl chloride (0.20 mmol), DIPEA (0.30 mmol), and DMAP (0.010 mmol). The reaction mixtures were stirred for 1 h at room temperature and purified in parallel using an Optix 10 Combi Flash instrument on 10 × 4 g normal-phase RediSep silica columns (0−100%, EtOAc/hexanes).

***P*,*P*-Diphenylphosphinamide (15).**[19] A solution of diphenylphosphinic chloride (7.8 g, 33 mmol) in CH_2Cl_2 (100 mL) in a flame-dried three-neck round-bottom flask fitted with a septum, low-temperature condensor and a low-temperature thermometer was cooled to −78 °C with dry ice and acetone. The condensor was filled with a mixture of dry ice and acetone. Addition of ammonia gas was monitored by the number of drops of condensed liquid ammonia dropping into the flask. After each drop, a rise in internal temperature was observed. The solution was allowed to cool back to −78 °C before addition of the next portion of ammonia, for a total of 1 mL of liquid ammonia per gram of diphenylphosphinic chloride. The reaction mixture was allowed to warm to room temperature overnight and filtered. The residue was washed twice with CH_2Cl_2 (50 mL), and the combined filtrates were evaporated to dryness under reduced pressure. Recrystallization of the solid residue under inert atmosphere from toluene (90 mL) gave **15** (5.0 g, 70%) as a colorless, crystalline solid: mp 160−162 °C (toluene**)**; MS (EI) m/z 217 (M$^+$).

Methyl 4-[(Diphenylphosphinylimino)methyl]benzoate (4a).[11a] A three-neck round-bottom flask was equipped with a pressure-equalized dropping funnel, flame-dried, and

purged with nitrogen. Diphenylphosphinamide **15** (1.2 g, 5.6 mmol, 1.0 equiv), methyl 4-formylbenzoate (1.0 g, 6.1 mmol, 1.1 equiv), triethylamine (2.3 mL, 17 mmol, 3.0 equiv), and CH_2Cl_2 (24 mL) were added and the flask was cooled to 0 °C. Titanium tetrachloride (0.37 mL, 3.4 mmol, 0.60 equiv) was added into the dropping funnel and diluted with CH_2Cl_2 (5.0 mL). The titanium chloride solution was added dropwise into the flask over a period of 30 min. The reaction mixture was stirred for another 30 min at 0 °C, warmed to room temperature, stirred for 3 h, poured into anhydrous ether (150 mL), and filtered through a pad of a 1:1 mixture of Florisil and Celite. The solution was evaporated under reduced pressure to give a yellow foam. Precipitation from CH_2Cl_2 (5.0 mL) and hexanes (0.1 L) yielded **4a** (0.58 g, 31%): mp 144−146 °C (CH_2Cl_2/hexanes); ^{1}H NMR δ 9.38 (d, 1 H, J = 31.6 Hz), 8.13−8.15 (m, 2 H), 8.07−8.09 (m, 2 H), 7.94−7.96 (m, 4 H), 7.48−7.51 (m, 6 H), 3.96 (s, 3H).

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Supporting Information Available. Selected experimental protocols and spectroscopic data. HPLC/MS or ^{1}H NMR data for the intermediate 20-member library. HPLC-MS data for all 100 library members. List of purities determined by HPLC with UV detection at 220 nm, isolated weights, and yields of the 100-member library. *c*LogP profile for 20-member library. Hydrogen bond acceptor, *c*LogP, and molecular weight profiles for the 100-member library. QikProp analyses of **12g**, **12i**, and **14g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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