Diversity-Oriented Synthesis and Preliminary Biological Screening of Highly Substituted Five-Membered Lactones and Lactams Originating From an Allyboration of Aldehydes and Imines

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α-*exo*-Methylene-γ-lactones and α-*exo*-methylene-γ-lactams are key structural units in a wide variety of natural products. These substances exhibit a high degree of bioactivity against numerous biological targets that play important roles in several diseases. A library of functionalized γ-lactones and γ-lactams containing both unsaturated and saturated side chains at the α position of the ring was synthesized. The generation of this library first involves sequential allylation of aldehydes or imines with 2-alkoxycarbonyl allylboronates, followed by ring closure to give α-*exo*-methylene-γ-lactones or α-*exo*-methylene-γ-lactams, which are subjected to various transition metal catalyzed coupling reactions to introduce additional diversity. A subset of the library was screened for inhibition of homoserine transacetylase (HTA) from *Haemophilus influenzae* and showed promising initial activity profiles.

1. Introduction

The α-*exo*-methylene-γ-butyrolactone ring is a key structural motif in many natural products, most notably the sesquiterpene lactones (Figure 1). In 1985, it was estimated that approximately 10% of the known 30 000 natural products contained this α-*exo*-methylene-γ-butyrolactone functionality.[1] Because the number of natural products that contain a α-*exo*-methylene-γ-butyrolactone group has increased since then, more and more interest is being shown in these compounds because of their unique biological properties. In many cases, the high bioactivity of these compounds is caused by the presence of the electrophilic α-*exo*-methylene-γ-lactone or γ-lactam moiety, which can trap nucleophilic sites on enzyme targets. These natural products have shown to be quite useful as DNA polymerase inhibitors, nuclear vitamin D receptor inhibitors, cellular steroidal inhibitors, blockers of tumor necrosis factor-α production, as well as many other uses.[2] The wide inhibitory action of these natural products makes them potential drug candidates because of their cytotoxic, allergenic, anti-inflammatory, phytotoxic, and antimicrobial properties.[3] For example, the HCl salt of one α-*exo*-methylene-γ-lactone natural product, arglabin, has been used successfully in Kazakhstan for the treatment of breast, colon, ovarian, and lung cancers.[4]

As a result of the biological importance of these natural products, the synthesis of polysubstituted α-*exo*-methylene-γ-lactones has been of interest to synthetic chemists for several years. Several routes have been devised to access the α-*exo*-methylene-γ-lactone ring; however, they tend to be lengthy and cumbersome if the lactone contains any sort of substitution.[5] Studies in our group[6] and others[7] have shown that the allylboration of aldehydes using thermal or Brønsted acidic conditions is an expedient and very convenient approach to access a wide range of highly substituted α-*exo*-methylene-γ-lactones. With our facile route to this class of compounds, this article describes how this chemistry was exploited to synthesize numerous α-*exo*-methylene-γ-lactones containing a wide variety of substituents. Furthermore, it is known that α-*exo*-methylene-γ-lactams can be accessed through the allylboration of imines.[8] Several natural products containing a γ-butyrolactam ring are also known (Figure 1),[9] and these compounds also exhibit interesting biological properties in their own right.[10] Therefore, it was decided to include α-*exo*-methylene-γ-butyrolactams as part of this diverse library. Various routes to further functionalize these γ-lactones and lactams were investigated, and these results led to the formation of α-*exo*-alkylidene and α-alkylated γ-lactones as well as α-*exo*-alkylidene and α-alkylated γ-lactams. These differing scaffolds are grouped into smaller sublibraries and are described below, along with detailed reaction optimization and sublibrary preparation that occurred for the various reaction types.

2. Scaffold Optimization and Library Synthesis

2.1. α-*exo*-Methylene-γ-Lactones. On the basis of previous work in our group[6] revolving around the allylboration reaction of aldehydes using 2-alkoxycarbonyl allylboronates,

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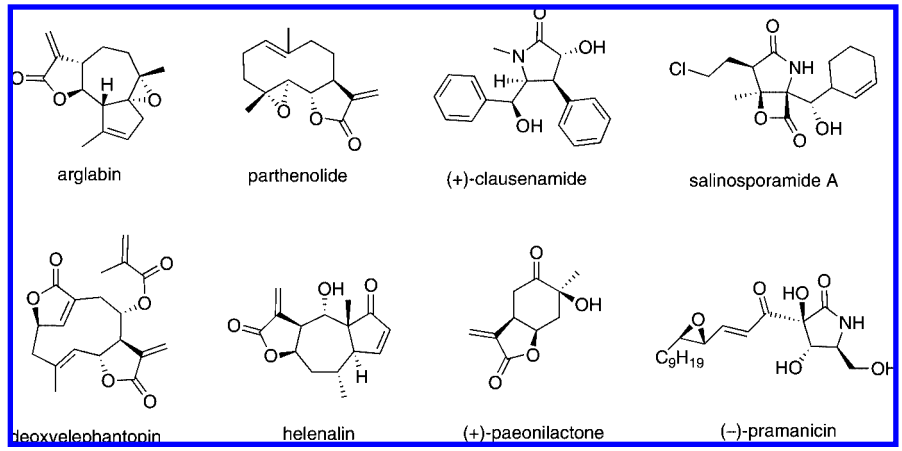


Figure 1. Selected natural products containing an α-*exo*-methylene-γ-lactone or γ-lactam ring.

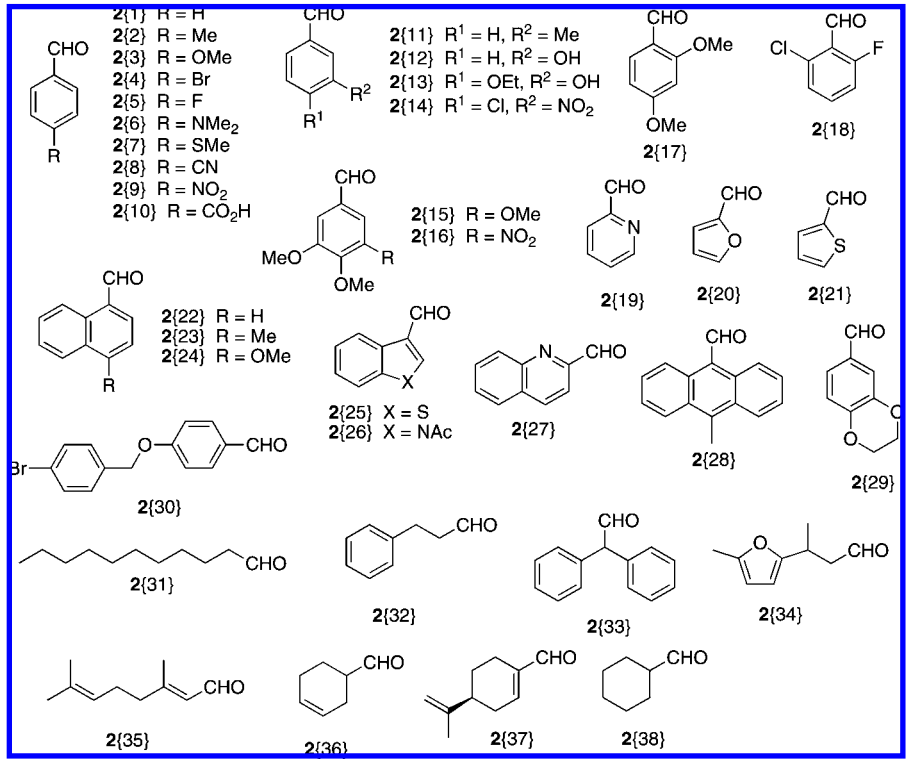
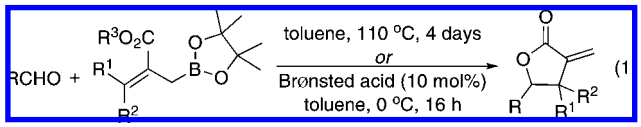


Figure 2. Aldehyde diversity reagents **2**{*1*−*38*}.

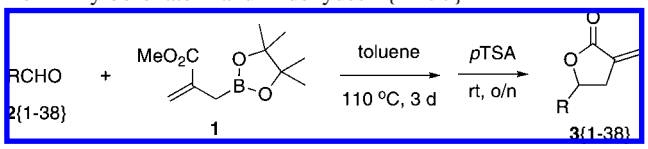
we have shown that α-*exo*-methylene-γ-butyrolactones could be easily accessed using either thermal or Brønsted acid-catalyzed conditions (eq 1).



This previous work and our general expertise in allylboration reactions meant that no optimization was required for this sublibrary. The thermal allylboration reaction requires significantly longer reaction times and substantially elevated temperatures as compared to the Brønsted acid-catalyzed allylboration conditions.[6] However, because of the technological challenge of carrying out a large number of reactions at 0 °C, it was chosen to prepare the α-*exo*-methylene-γ-lactone scaffold using thermal allylboration conditions. Toward this end, allylboronate **1** was reacted with a wide variety of aldehydes **2**{*1*−*38*} (Figure 2) to provide the desired lactone products **3**{*1*−*38*} (Table 1).

One will note the generality of aldehydes that can be utilized in the allylboration reaction. A variety of substituted aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes are all suitable substrates for this reaction. All reactions were carried out simultaneously in solution phase using a parallel synthesizer, quenched with aqueous $NaHCO_3$, and extracted with ethyl acetate. Crude reaction mixtures were purified by preparatory HPLC. To focus on product purity rather that recovered yields, a very conservative fraction collection threshold was employed for this sublibrary, as well as all other sublibraries reported in this article. While conventional purification using flash chromatography provided reaction products with typically >50% recovered yields on a larger scale, careful purification using preparatory

Table 1. Synthesis of α-*exo*-Methylene-γ-lactones **3**{*1*−*38*} from Allylboronate **1** and Aldehydes **2**{*1*−*38*}



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	**3**{*1*}	73	20	**3**{*20*}	37
2	**3**{*2*}	46	21	**3**{*21*}	6
3	**3**{*3*}	9	22	**3**{*22*}	36
4	**3**{*4*}	59	23	**3**{*23*}	27
5	**3**{*5*}	1	24	**3**{*24*}	6
6	**3**{*6*}	1	25	**3**{*25*}	5
7	**3**{*7*}	22	26	**3**{*26*}	4
8	**3**{*8*}	19	27	**3**{*27*}	6
9	**3**{*9*}	49	28	**3**{*28*}	9
10	**3**{*10*}	3	29	**3**{*29*}	28
11	**3**{*11*}	60	30	**3**{*30*}	7
12	**3**{*12*}	45	31	**3**{*31*}	14
13	**3**{*13*}	19	32	**3**{*32*}	23
14	**3**{*14*}	49	33	**3**{*33*}	21
15	**3**{*15*}	14	34	**3**{*34*}	4
16	**3**{*16*}	10	35	**3**{*35*}	6
17	**3**{*17*}	1	36	**3**{*36*}	20
18	**3**{*18*}	18	37	**3**{*37*}	3
19	**3**{*19*}	0.4	38	**3**{*38*}	18

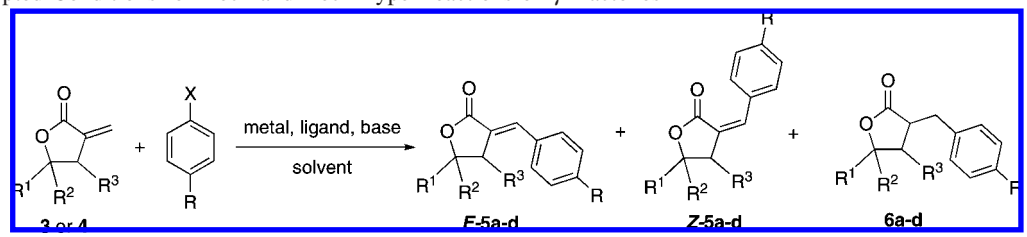
[a] Isolated yield after preparatory HPLC. See purity table in Supporting Information.

HPLC afforded the library members with lower reported yields but in >90% purity for 80% of the library members according to a random analysis. This careful purification protocol explains the lower yields compared to the individual examples involving flash-chromatographic purification on normal silica gel. For example, **3**{*3*} and **3**{*5*} were isolated in yields of 32% and 70%, respectively, when purified by flash chromatography as compared to only 9% and 1%, respectively, when purified by HPLC. For this analysis of purity, two or three members of each sublibrary were chosen at random and analyzed by HPLC-ESMS and NMR spectroscopy to further confirm their identity and purity. As shown in the Supporting Information, 20 randomly selected compounds from the complete library (∼10% of the library) were analyzed and characterized.

2.2. α-*exo*-Alkylidene-γ-lactones. We next turned our attention to the modification of these simple γ-lactones **3** because many of the bioactive natural products containing this ring moiety are also further functionalized. When looking at the structure of the α-*exo*-methylene-γ-lactones, it was obvious to us that the most suitable modification would be to further modify the *exo*-methylene group. Moreover, substrates containing a less electrophilic α-*exo*-methylene-γ-lactone moiety might help to mitigate the promiscuous reactivity of these compounds in biological systems and allow for more selective targeting. Alkenes can be commonly modified through many different types of reactions. Heck coupling reactions, conjugate additions, cross-metathesis, Morita−Baylis−Hillman reactions, cycloadditions, and various other oxidation or reduction reactions are just a few of the possibilities that are available to functionalize this methylene group.[11] Initially, we hoped to be able to modify γ-lactones **3** via ruthenium-mediated cross-metathesis. There had been a few previous reports by Howell and co-workers,[12] as well as by Cossy and co-workers,[13] on the use of cross-metathesis to functionalize similar types of α-*exo*-methylene-β-lactones. Initial trials were conducted to investigate the feasibility of utilizing cross-metathesis in our library synthesis, however, the cross-metathesis proved to be rather finicky in its ability to functionalize these α-*exo*-methylene-γ-lactones. Some reactions would proceed smoothly and go to about 70% completion, while others would stop at about the 20% completion point.[14] All attempts to bring about further conversion in these reactions failed, including adding more catalyst and also utilizing various additives. Various additives are known to help increase the percent conversion in difficult cross metathesis reactions, including 2,6-dichlorobenzoquinone[12] and B-chlorocatecholborane.[13] Because our desire was to build a library using standard conditions that would apply to all reactions carried out, it was deemed that cross-metathesis was unsuitable for broad modifications to our substrates. This was a rather unfortunate setback because cross-metathesis would have made use of the vast number of commercially available terminal alkenes and allowed for a sizable sublibrary to be generated. We decided to attempt other transformations that would provide similar types of modified products. The next reaction of choice was the Heck reaction. Indeed, there is a vast amount of literature available that makes use of Heck or Heck-type reactions to couple alkenes to aryl or alkyl halides or pseudohalides.[15] The coupling of α,β-unsaturated enoates (present in our substrate lactone **3**) to aryl halides, however, is much less investigated. Moreover, alkenes that are gem-disubstituted are somewhat problematic in Heck reactions because of steric hindrance and competing β-hydrogen eliminations.[15c] With these limiting factors in mind, a search of the literature did provide some insight into utilizing the α-*exo*-methylene-γ-lactones as coupling partners in Heck or Heck-type reactions.[16] We began by screening a wide variety of standard conditions and protocols that are typically used for Heck reactions (Table 2). The structures of the lactone substrates used in these initial experiments are shown in Figure 3. Lactones **4**{*1*−*4*} have been previously reported in the literature.[6c]

Since phosphines are sometimes problematic during product purification, we initially tried a few sets of Heck reactions that avoid the use of phosphine-containing ligands (entries 1−4, Table 2). These efforts proved futile, and all of these reactions resulted in minimal to none of the desired products being obtained. We then switched to the Jeffery conditions[17] in hopes of bringing about further conversion. This procedure proved to be successful because the desired coupling product was obtained as the major product in a moderate yield (entry 5). However, the presence of two side products *Z*-**5c** and **6c** caused significant problems with the purification, and the desired product could not be isolated in pure form. These two cross-coupling byproducts coeluted with the desired product *E*-**5c**, both during flash chromatography and also during preparatory scale HPLC. This purification issue would be a serious problem should these conditions be utilized during library synthesis. Heck reaction conditions without the phase transfer catalyst were then attempted using the same lactone substrate **4**{*2*} (entry 6). Longer reaction times were required, and the reaction never

Table 2. Attempted Conditions for Heck and Heck-Type Reactions on γ-Lactones



entry	substrate[a]	coupling partner (R, X)	catalyst/ligand/additive[b]	base[b]	solvent	temp/time	yield (%)[c]	ratio of products (*E*-**5**/*Z*-**5**/**6**)[d]
1	**4**{*1*}	R = NO_2, X= I	$Pd(OAc)_2$/none/none	KOAc	DMF	80 °C/24 h	0	N/A
2	**4**{*1*}	R = H, X = I	$Pd(OAc)_2$/DABCO/none	K_2CO_3	DMF	120 °C/48 h	0	N/A
3	**3**{*38*}	R = Me, X = $B(OH)_2$	$Pd(OAc)_2$/none/$Cu(OAc)_2$	LiOAc	DMF	100 °C [e]/4 h	16 [f]	(*E*-**5a**/*Z*-**5a**/**6a**) 5.6:7.2:1[g]
4	**4**{*2*}	R = Me, X = $B(OH)_2$	$Pd(OAc)_2$/none/$Cu(OAc)_2$	LiOAc	DMF	100 °C [e]/4 h	7	(*E*-**5b**/*Z*-**5b**/**6b**) 1:0:0
5	**4**{*2*}	R = H, X = I	$Pd(OAc)_2$/PPh_3/Bu_4NBr	K_2CO_3	MeCN	90 °C/24 h	64	(*E*-**5c**/*Z*-**5c**/**6c**) 22:1:3[g]
6	**4**{*2*}	R = H, X = I	$Pd(OAc)_2$/PPh_3/none	Cs_2CO_3	MeCN	90 °C/48 h	23	(*E*-**5c**/*Z*-**5c**/**6c**) 1:0:0
7	**3**{*1*}	R = Ph, X = I	$Pd(OAc)_2$/PPh_3/none	Cs_2CO_3	MeCN	90 °C/6 h	53	(*E*-**5d**/*Z*-**5d**/**6d**) 1:0:0
8	**4**{*2*}	R = Ph, X = Br	$Pd(OAc)_2$/PPh_3/none	Cs_2CO_3	MeCN	90 °C/12 h	0	N/A
9	**3**{*1*}	R = Ph, X = Br	$Pd(OAc)_2$/PPh_3/none	Cs_2CO_3	MeCN	90 °C/48 h	0	N/A

[a] Refer to the Supporting Information for the synthesis of the lactones used as substrates. [b] Refer to the Supporting Information for stoichiometry of all reagents and catalyst. [c] Yields are reported after flash chromatography, unless otherwise specified. [d] Ratio of products was determined based on the yield of each component. [e] Reaction done under microwave conditions. [f] Yield is after preparatory HPLC purification. [g] Ratio determined by integration of crude ^{1}H NMR spectra.

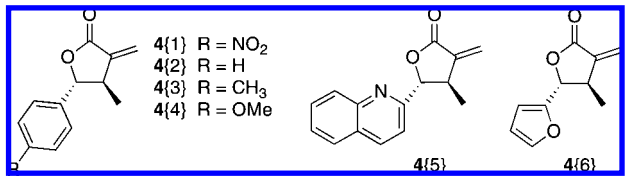


Figure 3. α-Methylene-β-methyl-γ-lactone substrates **4**{*1*−*6*}.

reached completion even after refluxing for 48 h. However, neither of the previously observed byproducts was detected under these reaction conditions. Because this could be a scenario where steric hindrance between the methyl group in the β-position and the palladium catalyst was playing a role in reduced reactivity of the γ-lactone substrate, a similar but less sterically demanding lactone substrate was used as the alkene coupling partner. Thus, with lactone **3**{*1*} lacking the methyl group in the β-position, the desired product *E*-**5d** was obtained as the sole product with a decent yield (entry 7). Aryl bromides were also attempted as substrates for this reaction (entries 8 and 9), because they would be useful in library preparation because of the large number of commercially available ones as compared to aryl iodides. However, even with longer reaction times, none of the desired coupling products were obtained when aryl bromides were used as substrates.

With conditions in hand that would provide the desired α-alkylidene γ-lactone products and would also be amenable to library synthesis, we then set about choosing substrates for the synthesis of this sublibrary with the α-alkylidene scaffold. Toward this end, four different α-*exo*-methylene-γ-lactones that contained differing functionality in the γ-position and contained only hydrogens in the β-position were chosen because of the problems discussed above. They were coupled with aryl iodides **7**{*1*−*5*} shown in Figure 4.

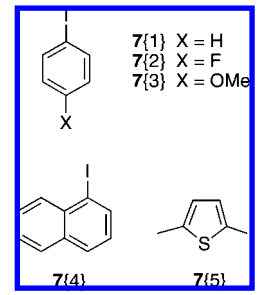
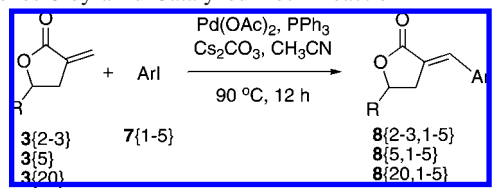


Figure 4. Aryl iodides **7**{*1*−*5*} used as coupling partners.

Aryl iodides **7**{*1*−*5*} were chosen to be used as a diverse set of coupling partners in the Heck reactions on the basis of commercial availability, price, and possible biological relevance. The Heck reactions were carried out according to Table 3 to provide the desired cross-coupling products in the form of α-alkylidene-γ-lactones **8**. All 20 reactions were carried out simultaneously using a parallel synthesizer, and the resulting α-alkylidene-γ-lactones **8** were purified by preparatory HPLC. It should be noted that some of the isolated products did contain trace amounts (~5% by ^{1}H NMR) of the undesired coupling byproduct with opposite (*Z*) alkene geometry.

2.3. α-Alkylated-γ-Lactones. Our attention next turned to another sublibrary scaffold by modifying α-*exo*-methylene-γ-lactones **3** in such a way as to obtain the saturated form of the lactone, that is, α-alkylated γ-lactones. One could simply hydrogenate the *exo*-methylene group to obtain α-methyl-γ-lactones, and there is precedent in achieving this transformation in a stereoselective fashion.[6b] However, it would be ideal if one could go directly from an α-*exo*-methylene-γ-lactones **3** to an α-alkylated γ-lactone, and in doing so, introduce additional chemical functionality. Some of the methods mentioned in the previous section would be applicable here, such as conjugate additions or oxidations.

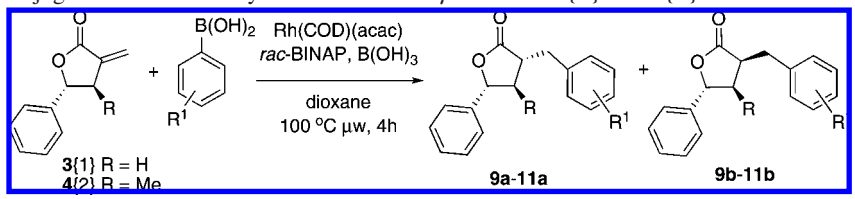
Table 3. Synthesis of α-Alkylidene-γ-lactones **8** by a Pd-Catalyzed Heck Reaction



entry	substrate	coupling partner	compound	R, Ar	yield (%)[a]
1	**3**{*2*}	**7**{*1*}	**8**{*2,1*}	R = 4-MeC$_6$H$_4$, Ar = C$_6$H$_5$	13
2	**3**{*2*}	**7**{*2*}	**8**{*2,2*}	R = 4-MeC$_6$H$_4$, Ar = 4-FC$_6$H$_4$	21
3	**3**{*2*}	**7**{*3*}	**8**{*2,3*}	R = 4-MeC$_6$H$_4$, Ar = 4-MeOC$_6$H$_4$	19
4	**3**{*2*}	**7**{*4*}	**8**{*2,4*}	R = 4-MeC$_6$H$_4$, Ar = 1-naphthyl	12
5	**3**{*2*}	**7**{*5*}	**8**{*2,5*}	R = 4-MeC$_6$H$_4$, Ar = 5-methyl-2-thiophenyl	8
6	**3**{*3*}	**7**{*1*}	**8**{*3,1*}	R = 4-MeOC$_6$H$_4$, Ar = C$_6$H$_5$	7
7	**3**{*3*}	**7**{*2*}	**8**{*3,2*}	R = 4-MeOC$_6$H$_4$, Ar = 4-FC$_6$H$_4$	6
8	**3**{*3*}	**7**{*3*}	**8**{*3,3*}	R = 4-MeOC$_6$H$_4$, Ar = 4-MeOC$_6$H$_4$	16
9	**3**{*3*}	**7**{*4*}	**8**{*3,4*}	R = 4-MeOC$_6$H$_4$, Ar = 1-naphthyl	18
10	**3**{*3*}	**7**{*5*}	**8**{*3,5*}	R = 4-MeOC$_6$H$_4$, Ar = 5-methyl-2-thiophenyl	2
11	**3**{*5*}	**7**{*1*}	**8**{*5,1*}	R = 4-FC$_6$H$_4$, Ar = C$_6$H$_5$	12
12	**3**{*5*}	**7**{*2*}	**8**{*5,2*}	R = 4-FC$_6$H$_4$, Ar = 4-FC$_6$H$_4$	7
13	**3**{*5*}	**7**{*3*}	**8**{*5,3*}	R = 4-FC$_6$H$_4$, Ar = 4-MeOC$_6$H$_4$	17
14	**3**{*5*}	**7**{*4*}	**8**{*5,4*}	R = 4-FC$_6$H$_4$, Ar = 1-naphthyl	5
15	**3**{*5*}	**7**{*5*}	**8**{*5,5*}	R = 4-FC$_6$H$_4$, Ar = 5-methyl-2-thiophenyl	2
16	**3**{*20*}	**7**{*1*}	**8**{*20,1*}	R = 2-furanyl, Ar = C$_6$H$_5$	17
17	**3**{*20*}	**7**{*2*}	**8**{*20,2*}	R = 2-furanyl, Ar = 4-FC$_6$H$_4$	13
18	**3**{*20*}	**7**{*3*}	**8**{*20,3*}	R = 2-furanyl, Ar = 4-MeOC$_6$H$_4$	31
19	**3**{*20*}	**7**{*4*}	**8**{*20,4*}	R = 2-furanyl, Ar = 1-naphthyl	11
20	**3**{*20*}	**7**{*5*}	**8**{*20,5*}	R = 2-furanyl, Ar = 5-methyl-2-thiophenyl	3

[a] Isolated yields after preparatory HPLC. See purity table in Supporting Information.

Table 4. Rh-Catalyzed Conjugate Addition of Arylboronic Acids to γ-Lactones **3**{*1*} and **4**{*2*}



entry	substrate	R	R^1	yield[a] (%)	product	product ratio[b,c] (**a**:**b**)
1	**3**{*1*}	H	4-Me	66	**9**	1.2:1
2	**4**{*2*}	Me	4-Me	74	**10**	1:10
3	**3**{*1*}	H	2-Me	86	**11**	2.8:1

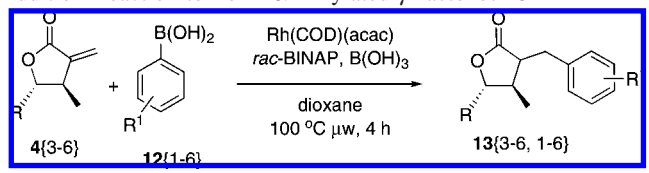
[a] Isolated yield after flash chromatography. [b] Product ratio was determined by comparison of peak height in the ^{1}H NMR spectra. [c] Relative stereochemistry of products was determined by TROESY experiments (see Supporting Information).

Instead, we were more interested in metal-catalyzed reductive alkylations for carrying out this transformation from α-*exo*-methylene-γ-lactones **3** to α-alkylated γ-lactones. There are many reports in the literature where aryl halides or aryl boronic acids are added to α,β-unsaturated ketones and esters through the use of palladium or rhodium catalysts,[18] but most of these examples involve unsubstituted or 1,2-disubstituted α,β-unsaturated ketones and esters and not the *gem*-disubstituted α,β-unsaturated substrates related to γ-lactones **3**. On the other hand, a promising report was recently disclosed where hindered *gem*-disubstituted α,β-unsaturated esters were utilized in rhodium-catalyzed conjugate addition reactions to form the saturated products.[19] The reaction published by Frost and co-workers uses rhodium to catalyze the 1,4-addition of arylboronic acids to α-benzyl acrylates under microwave heating, and the rhodium enolates that are subsequently formed are then protonated by the boric acid present in the reaction mixture to provide α,α′-dibenzyl esters. With this report in hand, we immediately set out to test these conditions on α-*exo*-methylene-γ-lactones **4**{*2*} and **3**{*1*} (Table 4).

We were satisfied to see that α-*exo*-methylene-γ-lactones **3** and **4** are suitable substrates for this rhodium-catalyzed conjugate addition/protonation reaction. γ-Lactone **4**{*2*} containing a methyl group in the β-position gave a better selectivity in terms of the cis/trans ratio of the α-alkylated lactones, which seems intuitive based on the fact that protonation by B(OH)$_3$ would occur from the least hindered face. Even though this observation is based on only one example and may not be generally applicable, we chose α-methylene-γ-lactones containing a methyl in the β-position as substrates in the synthesis of the sublibrary based on the α-alkylated-γ-lactone scaffold (Table 5).

The four α-*exo*-methylene-γ-lactones **4**{*3*−*6*} (Figure 3) were subjected to rhodium-catalyzed conjugate 1,4-addition/protonation reaction conditions with boronic acids **12**{*1*−*6*} (Figure 5) under microwave heating to provide the desired α-alkylated-γ-lactones (Table 5).

Table 5. Rh-Catalyzed Conjugate Addition Reaction to Form α-Alkylated-γ-lactones **13**



entry	substrate	coupling partner	compound	R, R^1	yield (%)[a]
1	**4**{*3*}	**12**{*1*}	**13**{*3,1*}	R = 4-MeC_6H_5, R^1 = H	92
2	**4**{*3*}	**12**{*2*}	**13**{*3,2*}	R = 4-MeC_6H_5, R^1 = 4-OCH_3	64
3	**4**{*3*}	**12**{*3*}	**13**{*3,3*}	R = 4-MeC_6H_5, R^1 = 2-CH_3	86
4	**4**{*3*}	**12**{*4*}	**13**{*3,4*}	R = 4-MeC_6H_5, R^1 = 4-Br	88
5	**4**{*3*}	**12**{*5*}	**13**{*3,5*}	R = 4-MeC_6H_5, R^1 = 4-OC_6H_5	58
6	**4**{*3*}	**12**{*6*}	**13**{*3,6*}	R = 4-MeC_6H_5, R^1 = 3,5-$(CF_3)_2$	25
7	**4**{*4*}	**12**{*1*}	**13**{*4,1*}	R = 4-$MeOC_6H_5$, R^1 = H	84
8	**4**{*4*}	**12**{*2*}	**13**{*4,2*}	R = 4-$MeOC_6H_5$, R^1 = 4-OCH_3	76
9	**4**{*4*}	**12**{*3*}	**13**{*4,3*}	R = 4-$MeOC_6H_5$, R^1 = 2-CH_3	82
10	**4**{*4*}	**12**{*4*}	**13**{*4,4*}	R = 4-$MeOC_6H_5$, R^1 = 4-Br	41
11	**4**{*4*}	**12**{*5*}	**13**{*4,5*}	R = 4-$MeOC_6H_5$, R^1 = 4-OC_6H_5	15
12	**4**{*4*}	**12**{*6*}	**13**{*4,6*}	R = 4-$MeOC_6H_5$, R^1 = 3,5-$(CF_3)_2$	63
13	**4**{*5*}	**12**{*1*}	**13**{*5,1*}	R = 2-quinolinyl, R^1 = H	78
14	**4**{*5*}	**12**{*2*}	**13**{*5,2*}	R = 2-quinolinyl, R^1 = 4-OCH_3	50
15	**4**{*5*}	**12**{*3*}	**13**{*5,3*}	R = 2-quinolinyl, R^1 = 2-CH_3	62
16	**4**{*5*}	**12**{*4*}	**13**{*5,4*}	R = 2-quinolinyl, R^1 = 4-Br	51
17	**4**{*5*}	**12**{*5*}	**13**{*5,5*}	R = 2-quinolinyl, R^1 = 4-OC_6H_5	53
18	**4**{*5*}	**12**{*6*}	**13**{*5,6*}	R = 2-quinolinyl, R^1 = 3,5-$(CF_3)_2$	61
19	**4**{*6*}	**12**{*1*}	**13**{*6,1*}	R = 2-furanyl, R^1 = H	75
20	**4**{*6*}	**12**{*2*}	**13**{*6,2*}	R = 2-furanyl, R^1 = 4-OCH_3	83
21	**4**{*6*}	**12**{*3*}	**13**{*6,3*}	R = 2-furanyl, R^1 = 2-CH_3	82
22	**4**{*6*}	**12**{*4*}	**13**{*6,4*}	R = 2-furanyl, R^1 = 4-Br	76
23	**4**{*6*}	**12**{*5*}	**13**{*6,5*}	R = 2-furanyl, R^1 = 4-OC_6H_5	51
24	**4**{*6*}	**12**{*6*}	**13**{*6,6*}	R = 2-furanyl, R^1 = 3,5-$(CF_3)_2$	9

[a] Isolated yield after preparatory HPLC. See purity table in Supporting Information.

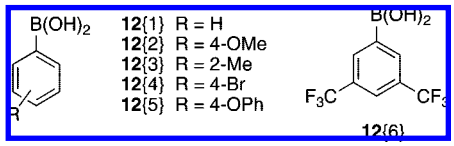


Figure 5. Boronic acids **12**{*1*−*6*} for Rh-catalyzed conjugate addition reaction.

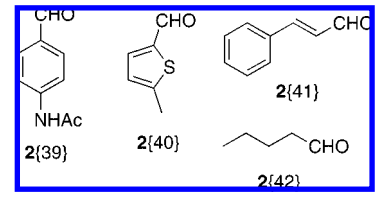
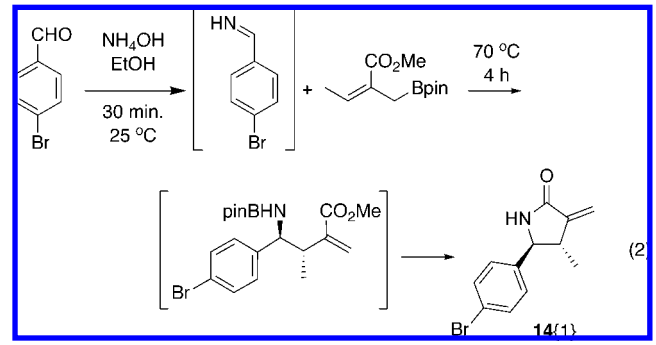


Figure 6. Additional aldehyde substrates **2**{*39*−*42*} for sublibrary of β-unsubstituted α-methylene-γ-lactams **15**.

The reactions were run sequentially in the microwave reactor, and after all 24 reaction combinations were completed, they were filtered through a small pad of celite with ethyl acetate, concentrated, and purified via preparatory HPLC to provide the desired α-alkylated-γ-lactones **13**{*3*−*6,1*−*6*}. These compounds were obtained as mixtures of 3,4-cis and 3,4-trans isomers (usually >10:1 ratio), and further separation was not attempted.

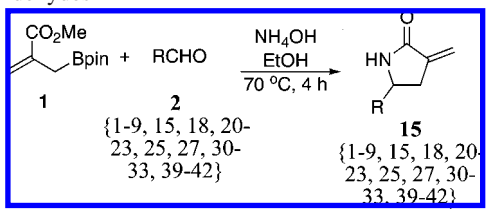
2.4. α-*exo*-Methylene-γ-Lactams. As discussed earlier, there is an abundance of literature containing interesting α-*exo*-methylene-γ-lactones, both in the form of natural products and as parts of synthetic analogues. One closely related type of compound to the γ-lactones is the α-*exo*-methylene-γ-lactam scaffold. Even though there are significantly fewer reports compared to the γ-lactones, there are still a considerable number of natural products that contain a γ-lactam as part of their structures (Figure 1). The synthesis of γ-lactams has been the focus of several reports in the literature;[20] however, several known routes are tedious in accessing this core structure. Our group recently optimized an expeditious route to accessing these α-methylene-γ-lactam core structures.[21] With this new protocol, imines are formed in situ from ammonia and aldehydes and then are allylated using a 2-alkoxy-carbonyl allylboronate. Because of the ester functionality present in the reagent, the homoallylic amine intermediate formed from the allylation reaction then undergoes in situ lactamization to afford substituted β-methyl α-methylene-γ-lactams, such as **14**{*1*}, in a single step (eq 2).[21]



Utilizing this key transformation, we synthesized a small sublibrary of α-*exo*-methylene-γ-lactams using aldehydes **2**{*1*−*9,15,18,20*−*23,25,27,30*−*33*} (Figure 2) and **2**{*39*−*42*} (Figure 6), together with allylboronate **1** (Table 6).

The α-*exo*-methylene-γ-lactams (**15**) were synthesized by this route using a parallel synthesizer and subsequently

Table 6. Formation of α-*exo*-Methylene-γ-lactams **15** Utilizing **1** and Aldehydes **2**



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	**15**{*1*}	53	14	**15**{*22*}	11
2	**15**{*2*}	61	15	**15**{*23*}	5
3	**15**{*3*}	14	16	**15**{*25*}	45
4	**15**{*4*}	36	17	**15**{*27*}	30
5	**15**{*5*}	37	18	**15**{*30*}	2
6	**15**{*6*}	3	19	**15**{*31*}	35
7	**15**{*7*}	9	20	**15**{*32*}	13
8	**15**{*8*}	12	21	**15**{*33*}	12
9	**15**{*9*}	76	22	**15**{*39*}	4
10	**15**{*15*}	18	23	**15**{*40*}	39
11	**15**{*18*}	10	24	**15**{*41*}	48
12	**15**{*20*}	38	25	**15**{*42*}	45
13	**15**{*21*}	34			

[a] Isolated yield after preparatory HPLC. See purity table in Supporting Information.

worked up using the standard extraction protocol[21] and purified by preparatory HPLC. Typical yields for this reaction are in the range of 45−90%,[21] so it is uncertain at this point why significantly lower yields were observed in a few cases. Neither electronic nor steric factors seem to be responsible. Larger scale reactions were performed with a subset of aldehydes **2,** using typical bench-scale techniques to obtain α-*exo*-methylene-γ-lactams **15** in sufficient quantities so as to carry out further investigations on the functionalization of this α-*exo*-methylene-γ-lactam scaffold. These studies are described below.

2.5. *N*-Arylated α-*exo*-Methylene-γ-Lactams. As with the γ-lactones, we aimed to determine the extent to which the α-*exo*-methylene-γ-lactam scaffold (such as the one present in **14**{*1*}) could be functionalized. With the nitrogen in the γ-lactam ring, these γ-lactams have one additional degree of diversity that can be exploited as compared to the γ-lactones. Several types of reactions could be envisioned to functionalize this nitrogen atom, including alkylation, acylation, and arylation reactions. Our initial interests lied in modulating the γ-lactams via the use of metal catalyzed N-arylation reactions. Over the past few years, Buchwald and co-workers have reported significant new methodologies in the area of copper-catalyzed amidation reactions using aryl halides.[22] In particular, one report[22d] makes use of secondary amides, and more specifically, a γ-lactam as the coupling partner with aryl iodides and aryl bromides. With the reaction conditions from this report in hand, we set out to investigate whether this coupling chemistry could be applied successfully to α-*exo*-methylene-γ-lactams. To this end, we chose a few representative α-*exo*-methylene-γ-lactams **14**{*2*−*3*}[21] and **15**{*9*} (Figure 7) and attempted to couple them with various aryl iodides and bromides (Table 7). From our sampling of the N-arylation reaction conditions, it was apparent that both aryl iodides and aryl bromides are suitable coupling partners with the α-*exo*-methylene-γ-lactams, but since aryl iodides provided the desired products with significantly better yields, they were chosen as components for this sublibrary.

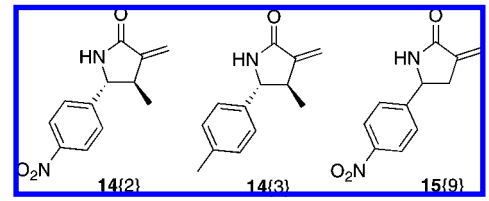
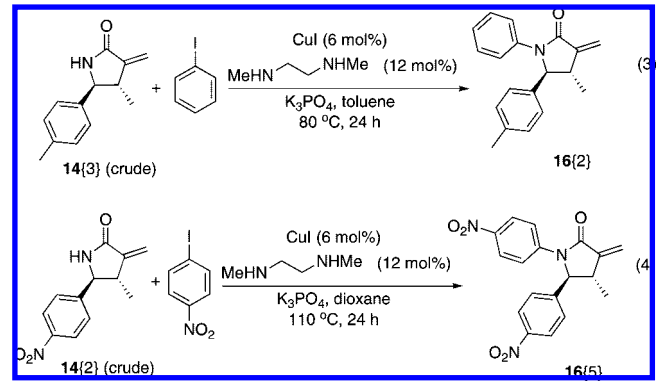


Figure 7. Selected α-*exo*-methylene-γ-lactams **14**{*2*−*3*} and **15**{*9*} for N-functionalization.

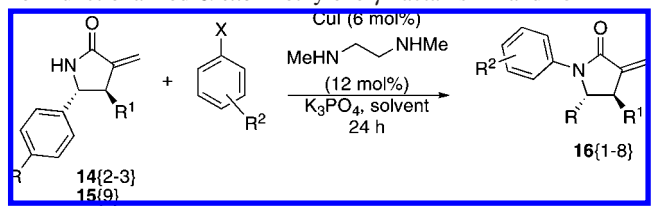
Extensive purification of library intermediates is generally avoided, if at all possible. Extra purification steps in the preparation of a library causes longer sequences and leads to large amounts of solvent waste. With this in mind, we investigated the possibility of utilizing the α-*exo*-methylene-γ-lactams **14** in crude form following the allylation/cyclization reaction for subsequent functionalization reactions. We attempted this strategy with the copper-catalyzed N-arylation of a few selected α-*exo*-methylene-γ-lactams (equations 3 and 4).



Thus, after acidic extraction and solvent removal, the crude γ-lactams **14**{*2*−*3*} were immediately subjected to the N-arylation reaction conditions. We were pleased to find that the N-arylation reactions could proceed smoothly when using crude γ-lactams **14**{*2*−*3*} as substrates. With this chemistry performing well, various γ-lactams **15** (Figure 8) and aryl iodides **7** (Figures 4 and 8) were selected for the preparation of a sublibrary of N-arylated α-*exo*-methylene-γ-lactams **17** (Table 8). All N-arylation reactions for this sublibrary were done using crude samples of α-*exo*-methylene-γ-lactams **15** employing a parallel synthesizer and were subsequently filtered through a short plug of celite and concentrated. The crude mixtures were purified by preparatory HPLC to provide the desired sublibrary members, N-arylated α-*exo*-methylene-γ-lactams **17**.

2.6. N-Arylated α-*exo*-Alkylidene-γ-Lactams. Just as with the α-*exo*-methylene-γ-lactones discussed earlier, we next turned our attention to functionalizing the *exo*-methylene unit of γ-lactams **16** and **17**. The Heck reaction had proved efficient with the γ-lactones (see section 2.2), so we decided to apply the same approach. One test reaction was performed using γ-lactam **16**{*3*}, where it was successfully function-

Table 7. Cu-Catalyzed N-Arylation of Functionalized α-*exo*-Methylene-γ-lactams **14** and **15**



entry	substrate	R^2, X	solvent, temperature	product	yield (%)[a]
1	**14**{*2*}	R^2 = H, X = I	toluene, 80 °C	**16**{*1*}	44
2	**14**{*3*}	R^2 = H, X = I	toluene, 80 °C	**16**{*2*}	80
3	**14**{*3*}	R^2 = 4-NO_2, X= I	toluene, 80 °C	**16**{*3*}	74
4	**15**{*9*}	R^2 = 4-NO_2, X= I	toluene, 80 °C	**16**{*4*}	59
5	**14**{*2*}	R^2 = 4-NO_2, X= I	dioxane, 110 °C	**16**{*5*}	31[b]
6	**14**{*2*}	R^2 = 4-Ph, X = I	dioxane, 110 °C	**16**{*6*}	29[b]
7	**14**{*2*}	R^2 = 4-OMe, X = Br	dioxane, 110 °C	**16**{*7*}	17[b]
8	**14**{*2*}	R^2 = 4-F, X = Br	dioxane, 110 °C	**16**{*8*}	24[b]

[a] Yields reported are isolated yields after flash chromatography, unless otherwise specified. [b] Product was purified by preparatory HPLC. See purity table in Supporting Information.

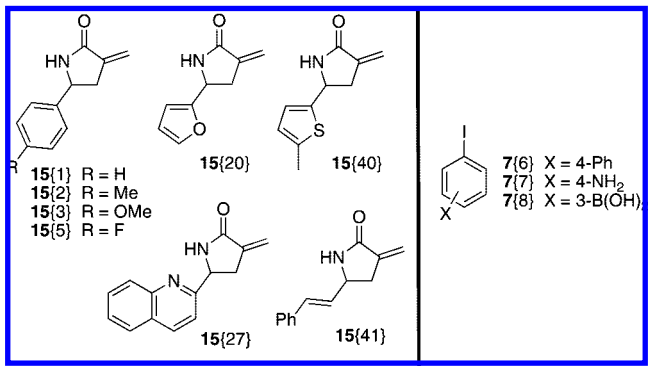
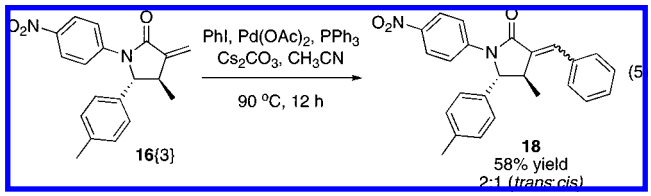


Figure 8. Diversity reagents **15** and **7**{*6*−*8*} to produce N-arylated α-*exo*-methylene-γ-lactams **17**.

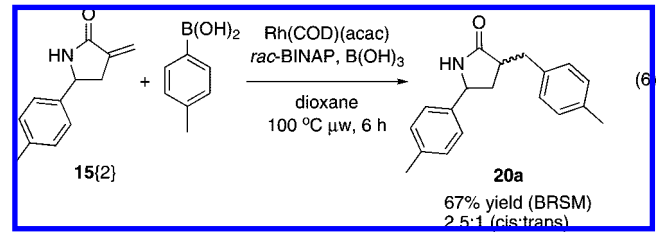
alized using iodobenzene as the coupling partner to form fully substituted lactam **18** (eq 5).



Using the same reaction conditions, the *N*-phenyl α-*exo*-methylene-γ-lactams **17** (Figure 9) were cross-coupled under palladium catalysis with aryl iodides **7**{*1*−*4*} (Figure 4) and **7**{*9*−*10*} (Figure 9) to form the desired *N*-phenyl α-*exo*-alkylidene γ-lactams **19** (Table 9).

These reactions were not quite as efficient as was observed with the corresponding γ-lactones, and in a few cases, the desired product was not obtained. As well, some of the reactions produced a mixture of the desired product and a related byproduct where the double bond had isomerized to yield an internal alkene instead of the desired *exo*-alkene. Nonetheless, the desired products **19** were obtained in modest to good yields under these reaction conditions. The crude reaction mixtures were filtered through a short plug of celite, concentrated, and purified by preparatory HPLC to provide the product as a mixture containing the desired product and minor amounts of the byproduct with the internal double bond.

2.7. α-Alkylated-γ-Lactams. Just as shown above with the corresponding lactones **4** (see section 2.3), here, we applied the conditions for the rhodium-catalyzed conjugate addition reaction with α-*exo*-methylene-γ-lactams **15**. Because Miyaura and co-workers had shown that 1,2-disubstituted α,β-unsaturated amides were suitable substrates for Rh-catalyzed 1,4-addition reactions,[23] we were optimistic that the α-methylene-γ-lactams **15** would also prove to be suitable substrates in this reaction. A test reaction was carried out, and we were delighted that it proceeded smoothly to provide the desired α-alkylated γ-lactam **20a** (eq 6).



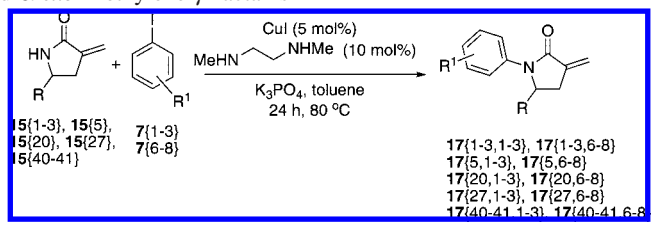
If the reaction was left for a longer period of time, no further conversion was observed, so these reaction conditions were chosen for the synthesis of the sublibrary. The same boronic acids **12**{*1*−*6*} (Figure 5) utilized in making the α-alkylated-γ-lactones were also used for this sublibrary. α-*exo*-Methylene-γ-lactams **15**{*2*−*3*}, **15**{*5*}, and **15**{*20*} (Figure 8) were utilized and, under rhodium catalysis, formed the desired α-alkylated γ-lactams **20**{*2*−*3*,*1*−*6*}, **20**{*5*,*1*−*6*}, and **20**{*20*,*1*−*6*} (Table 10).

The crude reaction mixtures were worked up in an identical fashion to the reactions performed on γ-lactones **4**, and the desired products **20** were isolated through preparatory HPLC. The cis and trans isomers of products **20** were not separated by preparatory HPLC and the diastereomeric ratio (typically >5:1) was determined by ^{1}H NMR (see Supporting Information).

3. Preliminary Screening of a Library Subset

Our HPLC-purified library of substituted γ-lactones and γ-lactams were evaporated and stored as solids or films in small glass vials. A representative subset of 111 members of the compound collection was evaluated in

Table 8. Preparation of N-Arylated α-*exo*-Methylene-γ-lactams **17**

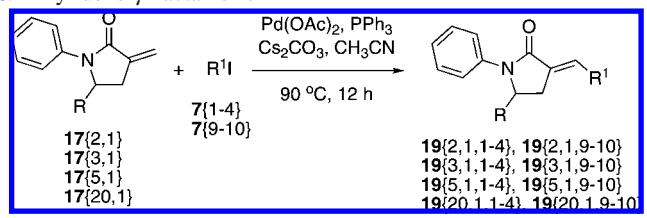


entry	substrate	coupling partner	product	R, R^1	yield (%)[a]
1	**15**{*1*}	**7**{*1*}	**17**{*1,1*}	R = C_6H_5, R^1 = H	2
2	**15**{*1*}	**7**{*2*}	**17**{*1,2*}	R = C_6H_5, R^1 = 4-F	1
3	**15**{*1*}	**7**{*3*}	**17**{*1,3*}	R = C_6H_5, R^1 = 4-OCH_3	45
4	**15**{*1*}	**7**{*6*}	**17**{*1,6*}	R = C_6H_5, R^1 = 4-C_6H_5	11
5	**15**{*1*}	**7**{*7*}	**17**{*1,7*}	R = C_6H_5, R^1 = 4-NH_2	41
6	**15**{*1*}	**7**{*8*}	**17**{*1,8*}	R = C_6H_5, R^1 = 3-$B(OH)_2$	46
7	**15**{*2*}	**7**{*1*}	**17**{*2,1*}	R = 4-MeC_6H_4, R^1 = H	1
8	**15**{*2*}	**7**{*2*}	**17**{*2,2*}	R = 4-MeC_6H_4, R^1 = 4-F	4
9	**15**{*2*}	**7**{*3*}	**17**{*2,3*}	R = 4-MeC_6H_4, R^1 = 4-OCH_3	1
10	**15**{*2*}	**7**{*6*}	**17**{*2,6*}	R = 4-MeC_6H_4, R^1 = 4-C_6H_5	2
11	**15**{*2*}	**7**{*7*}	**17**{*2,7*}	R = 4-MeC_6H_4, R^1 = 4-NH_2	61
12	**15**{*2*}	**7**{*8*}	**17**{*2,8*}	R = 4-MeC_6H_4, R^1 = 3-$B(OH)_2$	42
13	**15**{*3*}	**7**{*1*}	**17**{*3,1*}	R = 4-$MeOC_6H_4$, R^1 = H	6
14	**15**{*3*}	**7**{*2*}	**17**{*3,2*}	R = 4-$MeOC_6H_4$, R^1 = 4-F	70
15	**15**{*3*}	**7**{*3*}	**17**{*3,3*}	R = 4-$MeOC_6H_4$, R^1 = 4-OCH_3	2
16	**15**{*3*}	**7**{*6*}	**17**{*3,6*}	R = 4-$MeOC_6H_4$, R^1 = 4-C_6H_5	5
17	**15**{*3*}	**7**{*7*}	**17**{*3,7*}	R = 4-$MeOC_6H_4$, R^1 = 4-NH_2	68
18	**15**{*3*}	**7**{*8*}	**17**{*3,8*}	R = 4-$MeOC_6H_4$, R^1 = 3-$B(OH)_2$	17
19	**15**{*5*}	**7**{*1*}	**17**{*5,1*}	R = 4-FC_6H_4, R^1 = H	6
20	**15**{*5*}	**7**{*2*}	**17**{*5,2*}	R = 4-FC_6H_4, R^1 = 4-F	38
21	**15**{*5*}	**7**{*3*}	**17**{*5,3*}	R = 4-FC_6H_4, R^1 = 4-OCH_3	50
22	**15**{*5*}	**7**{*6*}	**17**{*5,6*}	R = 4-FC_6H_4, R^1 = 4-C_6H_5	27
23	**15**{*5*}	**7**{*7*}	**17**{*5,7*}	R = 4-FC_6H_4, R^1 = 4-NH_2	27
24	**15**{*5*}	**7**{*8*}	**17**{*5,8*}	R = 4-FC_6H_4, R^1 = 3-$B(OH)_2$	36
25	**15**{*20*}	**7**{*1*}	**17**{*20,1*}	R = 2-furanyl, R^1 = H	31
26	**15**{*20*}	**7**{*2*}	**17**{*20,2*}	R = 2-furanyl, R^1 = 4-F	45
27	**15**{*20*}	**7**{*3*}	**17**{*20,3*}	R = 2-furanyl, R^1 = 4-OCH_3	67
28	**15**{*20*}	**7**{*6*}	**17**{*20,6*}	R = 2-furanyl, R^1 = 4-C_6H_5	4
29	**15**{*20*}	**7**{*7*}	**17**{*20,7*}	R = 2-furanyl, R^1 = 4-NH_2	10
30	**15**{*20*}	**7**{*8*}	**17**{*20,8*}	R = 2-furanyl, R^1 = 3-$B(OH)_2$	29
31	**15**{*27*}	**7**{*1*}	**17**{*27,1*}	R = 2-quinolinyl, R^1 = H	5
32	**15**{*27*}	**7**{*2*}	**17**{*27,2*}	R = C_6H_5, R^1 = 4-F	8
33	**15**{*27*}	**7**{*3*}	**17**{*27,3*}	R = 2-quinolinyl, R^1 = 4-OCH_3	9
34	**15**{*27*}	**7**{*6*}	**17**{*27,6*}	R = 2-quinolinyl, R^1 = 4-C_6H_5	1
35	**15**{*27*}	**7**{*7*}	**17**{*27,7*}	R = 2-quinolinyl, R^1 = 4-NH_2	31
36	**15**{*27*}	**7**{*8*}	**17**{*27,8*}	R = 2-quinolinyl, R^1 = 3-$B(OH)_2$	9
37	**15**{*40*}	**7**{*1*}	**17**{*40,1*}	R = 5-methyl-2-thiophenyl, R^1 = H	2
38	**15**{*40*}	**7**{*2*}	**17**{*40,2*}	R = 5-methyl-2-thiophenyl, R^1 = 4-F	4
39	**15**{*40*}	**7**{*3*}	**17**{*40,3*}	R = 5-methyl-2-thiophenyl, R^1 = 4-OCH_3	1
40	**15**{*40*}	**7**{*6*}	**17**{*40,6*}	R = 5-methyl-2-thiophenyl, R^1 = 4-C_6H_5	1
41	**15**{*40*}	**7**{*7*}	**17**{*40,7*}	R = 5-methyl-2-thiophenyl, R^1 = 4-NH_2	9
42	**15**{*40*}	**7**{*8*}	**17**{*40,8*}	R = 5-methyl-2-thiophenyl, R^1 = 3-$B(OH)_2$	24
43	**15**{*41*}	**7**{*1*}	**17**{*41,1*}	R = β-styryl, R^1 = H	32
44	**15**{*41*}	**7**{*2*}	**17**{*41,2*}	R = β-styryl, R^1 = 4-F	47
45	**15**{*41*}	**7**{*3*}	**17**{*41,3*}	R = β-styryl, R^1 = 4-OCH_3	28
46	**15**{*41*}	**7**{*6*}	**17**{*41,6*}	R = β-styryl, R^1 = 4-C_6H_5	9
47	**15**{*41*}	**7**{*7*}	**17**{*41,7*}	R = β-styryl, R^1 = 4-NH_2	43
48	**15**{*41*}	**7**{*8*}	**17**{*41,8*}	R = β-styryl, R^1 = 3-$B(OH)_2$	2

[a] Isolated yield after preparatory HPLC purification. See purity table in Supporting Information.

high-throughput assays for their ability to inhibit homoserine transacetylase (HTA). Homoserine transacetylase from *Haemophilus influenzae* catalyzes the transfer of an acetyl group from acetyl-CoA to the hydroxyl group of homoserine.[24] This enzyme is the first committed step in the biosynthesis of methionine from aspartic acid.[25,26] HTA is found in fungi, gram positive bacteria, and some gram negative bacteria, however it is absent in higher eukaryotes. This is an important enzyme for organisms in methionine-poor environments such as blood serum. Therefore, inhibition of this enzyme could be deleterious to the organism because methionine is involved in several biochemical processes. The enzyme catalyzes the transfer mechanism via a ping-pong or double displacement mechanism facilitated by a catalytic triad of Ser-His-Asp. The Ser hydroxyl is activated for nucleophilic attack on the carbonyl center of acetyl-CoA by the His residue. This leads to the modification of the enzyme and the release of CoA. The second step of the mechanism involves another nucleophilic attack by the hydroxyl group of homoserine on the labile ester bond formed between the enzyme and the acetyl group. Finally, the acetylated amino

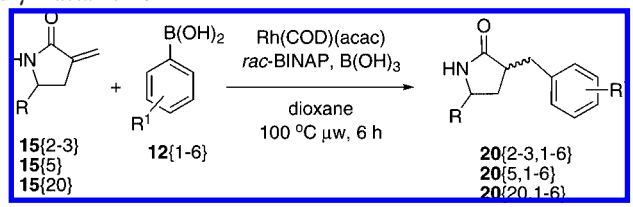
Table 9. Preparation of *N*-Phenyl α-Alkylidene-γ-lactams **19**



entry	substrate	coupling partner	product	R, R^1	yield (%)[a]
1	**17**{*2,1*}	**7**{*1*}	**19**{*2,1,1*}	R = 4-MeC_6H_4, R^1 = C_6H_5	16
2	**17**{*2,1*}	**7**{*2*}	**19**{*2,1,2*}	R = 4-MeC_6H_4, R^1 = 4-FC_6H_4	14
3	**17**{*2,1*}	**7**{*3*}	**19**{*2,1,3*}	R = 4-MeC_6H_4, R^1 = 4-$MeOC_6H_4$	27
4	**17**{*2,1*}	**7**{*4*}	**19**{*2,1,4*}	R = 4-MeC_6H_4, R^1 = 1-naphthyl	10
5	**17**{*2,1*}	**7**{*9*}	**19**{*2,1,9*}	R = 4-MeC_6H_4, R^1 = 4-CN	1
6	**17**{*2,1*}	**7**{*10*}	**19**{*2,1,10*}	R = 4-MeC_6H_4, R^1 = 4-NO_2	0
7	**17**{*3,1*}	**7**{*1*}	**19**{*3,1,1*}	R = 4-$MeOC_6H_4$, R^1 = C_6H_5	20
8	**17**{*3,1*}	**7**{*2*}	**19**{*3,1,2*}	R = 4-$MeOC_6H_4$, R^1 = 4-FC_6H_4	20
9	**17**{*3,1*}	**7**{*3*}	**19**{*3,1,3*}	R = 4-$MeOC_6H_4$, R^1 = 4-$MeOC_6H_4$	21
10	**17**{*3,1*}	**7**{*4*}	**19**{*3,1,4*}	R = 4-$MeOC_6H_4$, R^1 = 1-naphthyl	4
11	**17**{*3,1*}	**7**{*9*}	**19**{*3,1,9*}	R = 4-$MeOC_6H_4$, R^1 = 4-CN	6
12	**17**{*3,1*}	**7**{*10*}	**19**{*3,1,10*}	R = 4-$MeOC_6H_4$, R^1 = 4-NO_2	3
13	**17**{*5,1*}	**7**{*1*}	**19**{*5,1,1*}	R = 4-FC_6H_4, R^1 = C_6H_5	33
14	**17**{*5,1*}	**7**{*2*}	**19**{*5,1,2*}	R = 4-FC_6H_4, R^1 = 4-FC_6H_4	20
15	**17**{*5,1*}	**7**{*3*}	**19**{*5,1,3*}	R = 4-FC_6H_4, R^1 = 4-$MeOC_6H_4$	16
16	**17**{*5,1*}	**7**{*4*}	**19**{*5,1,4*}	R = 4-FC_6H_4, R^1 = 1-naphthyl	16
17	**17**{*5,1*}	**7**{*9*}	**19**{*5,1,9*}	R = 4-FC_6H_4, R^1 = 4-CN	5
18	**17**{*5,1*}	**7**{*10*}	**19**{*5,1,10*}	R = 4-FC_6H_4, R^1 = 4-NO_2	0
19	**17**{*20,1*}	**7**{*1*}	**19**{*20,1,1*}	R = 2-furanyl, R^1 = C_6H_5	6
20	**17**{*20,1*}	**7**{*2*}	**19**{*20,1,2*}	R = 2-furanyl, R^1 = 4-FC_6H_4	25
21	**17**{*20,1*}	**7**{*3*}	**19**{*20,1,3*}	R = 2-furanyl, R^1 = 4-$MeOC_6H_4$	19
22	**17**{*20,1*}	**7**{*4*}	**19**{*20,1,4*}	R = 2-furanyl, R^1 = 1-naphthyl	38
23	**17**{*20,1*}	**7**{*9*}	**19**{*20,1,9*}	R = 2-furanyl, R^1 = 4-CN	1
24	**17**{*20,1*}	**7**{*10*}	**19**{*20,1,10*}	R = 2-furanyl, R^1 = 4-NO_2	5

[a] Isolated yield after preparatory HPLC purification. See purity table in Supporting Information.

Table 10. Formation of α-Alkylated γ-Lactams **20**



entry	substrate	coupling partner	product	R, R^1	yield (%)[a]
1	**15**{*2*}	**12**{*1*}	**20**{*2,1*}	R = 4-MeC_6H_4, R^1 = H	28
2	**15**{*2*}	**12**{*2*}	**20**{*2,2*}	R = 4-MeC_6H_4, R^1 = 4-OCH_3	25
3	**15**{*2*}	**12**{*3*}	**20**{*2,3*}	R = 4-MeC_6H_4, R^1 = 2-CH_3	37
4	**15**{*2*}	**12**{*4*}	**20**{*2,4*}	R = 4-MeC_6H_4, R^1 = 4-Br	32
5	**15**{*2*}	**12**{*5*}	**20**{*2,5*}	R = 4-MeC_6H_4, R^1 = 4-OPh	11
6	**15**{*2*}	**12**{*6*}	**20**{*2,6*}	R = 4-MeC_6H_4, R^1 = 3,5-$(CF_3)_2$	12
7	**15**{*3*}	**12**{*1*}	**20**{*3,1*}	R = 4-$MeOC_6H_4$, R^1 = H	14
8	**15**{*3*}	**12**{*2*}	**20**{*3,2*}	R = 4-$MeOC_6H_4$, R^1 = 4-OCH_3	18
9	**15**{*3*}	**12**{*3*}	**20**{*3,3*}	R = 4-$MeOC_6H_4$, R^1 = 2-CH_3	30
10	**15**{*3*}	**12**{*4*}	**20**{*3,4*}	R = 4-$MeOC_6H_4$, R^1 = 4-Br	26
11	**15**{*3*}	**12**{*5*}	**20**{*3,5*}	R = 4-$MeOC_6H_4$, R^1 = 4-OPh	21
12	**15**{*3*}	**12**{*6*}	**20**{*3,6*}	R = 4-$MeOC_6H_4$, R^1 = 3,5-$(CF_3)_2$	32
13	**15**{*5*}	**12**{*1*}	**20**{*5,1*}	R = 4-FOC_6H_4, R^1 = H	33
14	**15**{*5*}	**12**{*2*}	**20**{*5,2*}	R = 4-FC_6H_4, R^1 = 4-OCH_3	15
15	**15**{*5*}	**12**{*3*}	**20**{*5,3*}	R = 4-FC_6H_4, R^1 = 2-CH_3	26
16	**15**{*5*}	**12**{*4*}	**20**{*5,4*}	R = 4-FC_6H_4, R^1 = 4-Br	26
17	**15**{*5*}	**12**{*5*}	**20**{*5,5*}	R = 4-FC_6H_4, R^1 = 4-OPh	22
18	**15**{*5*}	**12**{*6*}	**20**{*5,6*}	R = 4-FC_6H_4, R^1 = 3,5-$(CF_3)_2$	33
19	**15**{*20*}	**12**{*1*}	**20**{*20,1*}	R = 2-furanyl, R^1 = H	26
20	**15**{*20*}	**12**{*2*}	**20**{*20,2*}	R = 2-furanyl, R^1 = 4-OCH_3	30
21	**15**{*20*}	**12**{*3*}	**20**{*20,3*}	R = 2-furanyl, R^1 = 2-CH_3	16
22	**15**{*20*}	**12**{*4*}	**20**{*20,4*}	R = 2-furanyl, R^1 = 4-Br	15
23	**15**{*20*}	**12**{*5*}	**20**{*20,5*}	R = 2-furanyl, R^1 = 4-OPh	7
24	**15**{*20*}	**12**{*6*}	**20**{*20,6*}	R = 2-furanyl, R^1 = 3,5-$(CF_3)_2$	17

[a] Isolated yield after preparatory HPLC purification. See purity table in Supporting Information.

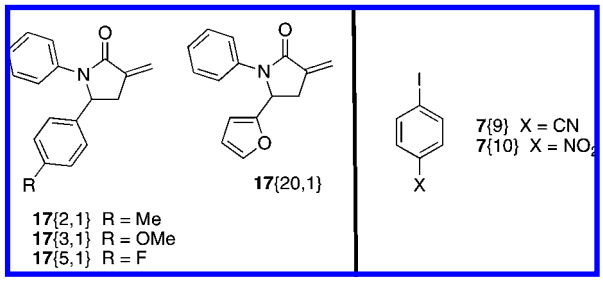


Figure 9. Diversity reagents **17** and **7**{*9*−*10*} for producing *N*-phenyl α-alkylidene-γ-lactams **19**.

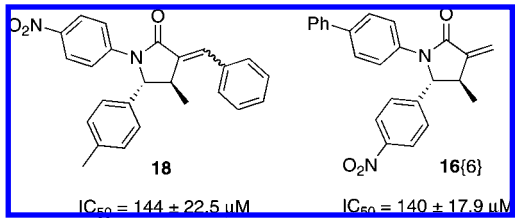


Figure 10. Structures and IC_{50} values for **18** and **16**{*6*}.

acid is released and the enzyme is reconstituted for another round of catalysis.[24,27] On the basis of the role of lactams, lactones, and cephalosporins in the inactivation of enzymes by acylation of the nucleophilic serinyl residue at the active site,[28,29] HTA is a good target for this library of compounds.

To this end, a selection of 111 compounds from the library described above has been screened against HTA at three different incubation times (15, 70, and 200 min) and at 100 μM final concentration. HTA has proven to be insensitive to a panel of β-lactam antibiotics (penicillins and cephalosporins) but was inhibited by several members of the 111 compound library that were tested. From the primary assay, ten compounds (9%) showed inactivation of HTA and were subsequently retested for confirmation. After reassay, five out of ten compounds confirmed their inhibitory activity versus HTA. Four of these five compounds have been resynthesized for further enzymatic characterizations. For two of them, **18** and **16**{*6*} (Figure 10), it was possible to determine IC_{50} values of 144 ± 22.5 and 140 ± 17.9 μM, respectively. The two compounds also showed a time-dependent inhibition, therefore consistent with the predicted mechanism of covalent modification of an enzyme nucleophile. The best inhibitor of HTA reported to date, 6-carbamoyl-3*a*,4,5,9*b*-tetrahydro-3*H*-cyclo-penta[*c*]quinoline-4-carboxylic acid (CTCQC), has an IC_{50} of 4.50 μM with *Cryptococcus neoformans* HTA and it is reversible. CTCQC is a competitive inhibitor for acetyl-CoA and noncompetitive inhibitor of homoserine. CTCQC has no effect on *C. neoformans* growth in minimal medium.[30] Although only two compounds (**18** and **16**{*6*}) showed moderate in vitro inhibition of HTA, these results validate the potential of polysubstituted α-*exo*-alkylidene-γ-lactams as inhibitors of serine nucleophile dependent enzymes.

4. Conclusions

Through a protocol involving a tandem allylboration/cyclization reaction of aldehydes or imines, we have successfully formed a diverse library of α-methylene-γ-lactones and α-methylene-γ-lactams. This reaction sequence uses a wide variety of aldehydes containing a high degree of diversity and allows for the generation of highly substituted γ-lactone and γ-lactam systems in a single step. Furthermore, we have shown that these γ-lactones and γ-lactams can be further modified to increase the degree of substitution and complexity of these small molecules. Through the use of the Heck reaction, the *exo*-methylene could be modified and thus allow for incorporation of various benzylidene groups at the α position. Functionalization of the double bond may allow for selective modulation in the reactivity of these γ-lactones and γ-lactams with biological nucleophiles, thus allowing for more specific interactions and better selectivity as drug candidates. Modification of the γ-lactones and γ-lactams was also carried out through the use of a rhodium-catalyzed conjugate addition reaction of aryl boronic acids to the *exo* methylene, thus providing highly substituted α-alkyl-γ-lactones and α-alkyl-γ-lactams. Again, this type of modification could help in tuning the reactivity of these compounds toward biological targets. Because the α-methylene-γ-lactams contain a nitrogen atom that could be modified, we turned to a copper-catalyzed N-arylation reaction that allowed for the facile arylation of the amide nitrogen atom. This reaction proved to be quite general and various substituted aryl iodides were coupled successfully with the α-methylene-γ-lactams. Preliminary biological screening was carried out with a subset of the compounds synthesized in this library, and a few of the γ-lactams displayed inhibitory activity against homoserine transacetylase from *Haemophilus influenzae*. As only a subset of these compounds were screened against only one family of enzymes, many opportunities remain to be considered for these γ-lactone and γ-lactam libraries as we have engaged into several collaborations for high-throughput screening.

5. Experimental Procedures

5.1. General Procedure for the Synthesis of α-Methylene-γ-lactones 3{*1*−*37*}. Allylboronate **1** (0.16 mmol, 36 mg) and aldehyde **2** (0.18 mmol) were dissolved in 2 mL of toluene in a parallel synthesizer vial under Ar. The reaction mixture was agitated and heated at 110 °C for 3 days. After this point, the reaction was cooled to room temperature and *p*-toluenesulfonic acid (0.48 mmol) was added. The reaction was agitated for 16 h, then quenched with sodium bicarbonate and extracted three times with diethyl ether. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude reaction mixture was purified by preparatory HPLC.

5.1.1. 3-Methylene-5-phenethyl-dihydro-furan-2-one 3-{*32*}: ^{1}H NMR (400 M Hz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 7.23−7.17 (m, 3H), 6.23 (t, 1H, J = 2.8 Hz), 5.63 (t, 1H, J = 2.6 Hz), 4.50 (dddd, 1H, J = 13.0, 13.0, 6.2, 5.0 Hz), 3.04 (dddd, 1H, J = 17.1, 7.8, 2.6, 2.6 Hz), 2.88−2.70 (m, 2H), 2.59 (dddd, 1H, J = 17.2, 6.0, 3.0,3.0 Hz), 2.09−1.99 (dddd, 1H, J = 14.2, 9.4, 7.2, 5.0 Hz).

5.2. General Procedure for the Synthesis of *exo*-Alkylidene-γ-lactones 8. In a parallel synthesizer vial, α-methylene-γ-lactone **3** (0.075 mmol), Cs_2CO_3 (61 mg, 0.19 mmol), palladium (II) acetate (1.1 mg, 0.005 mmol), triph-

enylphosphine (2.6 mg, 0.01 mmol), and aryl iodide **7** (0.083 mmol) were combined. Acetonitrile (2 mL) was added, and the reaction vessel was put under an Ar atmosphere. The reaction was put into the parallel synthesizer and was heated for 6 h at 90 °C with agitation. The crude reaction mixture was then filtered through a short pad of celite and washed with ethyl acetate. The organics were then removed to provide the crude product **8**, which was purified by preparatory HPLC.

5.2.1. *E*-5-(4-Fluoro-phenyl)-3-naphthalen-1-ylmethylene-dihydro-furan-2-one (8{*5*,*4*}): ^{1}H NMR (400 M Hz, $CDCl_3$) δ 8.40 (t, 1H, J = 3.0 Hz), 8.15 (d, 1H, J = 8.3 Hz), 7.91 (d, 1H, J = 7.8 Hz), 7.64−7.47 (m, 4H), 7.38−7.33 (m, 2H), 7.11−7.06 (m, 2H), 5.59 (dd, 1H, J = 7.3, 7.3 Hz), 3.63 (ddd, 1H, J = 17.4, 8.0, 2.7 Hz), 3.13 (ddd, 1H, J = 17.6, 6.6, 3.3 Hz); ^{19}F NMR (376 M Hz, $CDCl_3$) δ −113.5.

5.3. General Procedure for the Synthesis of α-Alkylated γ-Lactones 13. γ-Lactone **4** (0.075 mmol), arylboronic acid (0.30 mmol), Rh(COD)(acac) (1.2 mg, 0.004 mmol), *rac*-BINAP (3.7 mg, 0.006 mmol), boric acid (25 mg, 0.30 mmol), and 1 mL of dioxane were added to a microwave vessel, which was then put under Ar. The vessel was capped and then irradiated for 4 h at 100 °C. The crude reaction mixture was filtered through a short pad of celite, rinsed with ethyl acetate, and concentrated. The crude mixture of **13** was purified by preparatory HPLC to provide the desired compounds.

5.3.1. (3,4-*cis*-3,5-*trans*)-3-(4-Bromo-benzyl)-4-methyl-5-p-tolyl-dihydro-furan-2-one (13{*3*,*4*}): ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.45−7.41 (m, 2H), 7.19−7.14 (m, 2H), 7.14−7.10 (m, 2H), 7.10−7.06 (m, 2H), 4.75 (d, 1H, J = 9.9 Hz), 3.14 (dd, 1H, J = 14.2, 5.4 Hz), 2.99 (dd, 1H, J = 14.2, 6.6 Hz), 2.64 (ddd, 1H, J = 11.7, 6.5, 5.4 Hz), 2.35 (s, 3H), 2.11−2.00 (m, 1H), 0.94 (d, 3H, J = 6.5 Hz). Ratio of isomers is 13.0:1 based on ^{1}H NMR integration.

5.4. General Procedure for the Synthesis of α-Methylene-γ-lactams 15. The corresponding aldehyde **2** (0.21 mmol) was dissolved in 1 mL of EtOH in a parallel synthesizer vessel under Ar. Ammonium hydroxide (30%, 0.4 mL) was added, and the mixture was stirred at room temperature for 30 min. Allylboronate **1** (45 mg, 0.2 mmol) was diluted in 0.5 mL of EtOH and added to the reaction mixture. An additional 0.5 mL EtOH was used as rinse and added to the reaction mixture. The mixture was heated to 70 °C for 4 h. The reaction mixture was then cooled to room temperature, and 1 N HCl was added to quench the reaction and bring the pH of the solution to ∼1. The mixture was extracted four times with diethyl ether, and the organics were combined, dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixtures were purified by preparatory HPLC to give the desired γ-lactam products.

5.4.1. 3-Methylene-5-quinolin-2-yl-pyrrolidin-2-one (15-{*27*}): ^{1}H NMR (500 M Hz, $CDCl_3$) δ 8.20 (d, 1H, J = 9.1 Hz), 8.05 (d, 1H, J = 8.7 Hz), 7.38 (d, 1H, J = 8.7 Hz), 7.74 (ddd, 1H, J = 8.4, 6.8, 1.4 Hz, 7.56 (ddd, 1H, J = 8.1, 7.0, 1.3 Hz), 7.42 (d, 1H, J = 8.5 Hz), 6.75 (br.s, 1H), 6.12 (br.t, 1H, J = 2.9 Hz), 5.45−5.43 (m, 1H), 5.07 (ddd, 1H, J = 8.6, 4.6, 0.9 Hz), 3.48 (ddt, 1H, J = 17.3, 8.8, 2.6 Hz), 2.93 (dddd, 1H, J = 17.4, 5.0, 2.7, 2.7 Hz).

5.5. General Procedure for the Synthesis of N-Arylated α-Methylene-γ-lactams 17. In a Trident synthesizer vessel, CuI (1.0 mg, 0.005 mmol), crude **15** (0.11 mmol), and K_3PO_4 (42 mg, 0.20 mmol) were combined under Ar. Aryl iodide **7** (0.10 mmol) and *N*,*N*′-dimethylethylenediamine (1.1 μL, 0.01 mmol) were added, along with 1 mL of toluene. The reaction mixture was heated to 80 °C overnight with agitation on the parallel synthesizer. The resulting mixture was cooled, filtered through a short plug of celite, washed with ethyl acetate, and concentrated. The crude reaction mixture was purified by preparatory HPLC to give the desired compounds **17**.

5.5.1. 1-(4-Fluoro-phenyl)-5-(4-methoxy-phenyl)-3-methylene-pyrrolidin-2-one (17{*3*,*2*}): ^{1}H NMR (400 M Hz, $CDCl_3$) δ 7.45−7.39 (m, 2H), 7.13−7.08 (m, 2H), 6.98−6.91 (m, 2H), 6.84−6.79 (m, 2H), 6.23−6.21 (m, 1H), 5.48−5.46 (m, 1H), 5.14 (dd, 1H, J = 8.6, 3.7 Hz), 3.76 (s, 3H), 3.36 (ddt, 1H, J = 17.0, 8.6, 2.8 Hz), 2.76−2.68 (m, 1H).

5.6. General Procedure for the Synthesis of *N*-Phenyl α-Alkylidene-γ-lactams 19. In a parallel synthesizer vial, α-methylene-γ-lactam **17** (0.075 mmol), Cs_2CO_3 (61 mg, 0.19 mmol), palladium (II) acetate (1.1 mg, 0.005 mmol), triphenylphosphine (2.6 mg, 0.01 mmol), and aryl iodide **7** (0.083 mmol) were combined. Acetonitrile (2 mL) was added, and the reaction vessel was put under an Ar atmosphere. The reaction was put into the parallel synthesizer and heated for 12 h at 90 °C with agitation. The crude reaction mixture was then filtered through a short pad of celite and washed with ethyl acetate. The organics were then removed to provide the crude product, which was purified by preparatory HPLC.

5.6.1. 3-(4-Methoxy-benzylidene)-1-phenyl-5-p-tolyl-pyrrolidin-2-one (19{*2*,*1*,*3*}): ^{1}H NMR (500 M Hz, $CDCl_3$) δ 7.58−7.52 (m, 3H), 7.45−7.41 (m, 2H), 7.29−7.24 (m, 2H), 7.14−7.04 (m, 5H), 6.93−6.89 (m, 2H), 5.33 (dd, 1H, J = 8.9, 3.5 Hz), 3.83 (s, 3H), 3.65 (ddd, 1H, J = 17.2, 8.6, 2.9 Hz), 2.97 (dt, 1H, J = 17.1, 2.9 Hz), 2.28 (s, 3H). (Ratio of desired product to product with internal alkene was 7:1 based on ^{1}H NMR integration of the methoxy peak.)

5.7. General Procedure for the Synthesis of α-Alkyl-γ-lactams 20. α-Methylene-γ-lactam **15** (0.1 mmol), arylboronic acid **12** (0.40 mmol), Rh(COD)(acac) (1.2 mg, 0.004), *rac*-BINAP (3.7 mg, 0.006 mmol), boric acid (25 mg, 0.40 mmol), and 1 mL of 1,4-dioxane were added to a microwave vessel, which was put under Ar. The vessel was capped and then irradiated for 6 h at 100 °C. The crude reaction mixture was filtered through a short pad of celite, rinsed with ethyl acetate, and concentrated. The crude mixture was purified by preparatory HPLC to provide the desired compounds as a mixture of cis and trans isomers, which were not separated.

5.7.1. 3-(2-Methyl-benzyl)-5-*p*-tolyl-pyrrolidin-2-one(20-{*2*,*3*}): ^{1}H NMR (400 M Hz, $CDCl_3$) δ 7.19−7.09 (m, 8H), 5.86 (br.s, 1H), 4.57 (dd, 1H, J = 9.2, 6.4 Hz), 3.45 (dd, 1H, J = 14.3, 3.9 Hz), 2.86−2.77 (m, 1H), 2.66−2.58 (m, 1H), 2.54−2.46 (m, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 1.65 (ddd, 1H, J = 12.7, 11.0, 9.2 Hz). (Ratio of cis to trans diastereomers was 5.5:1 based on ^{1}H NMR integration of the proton α to the nitrogen.)

5.8. Biochemical Screening for Inhibition of Homoserine Transacetylase. The primary screening was performed in a Molecular Devices SpectraMAX Plus spectrophotometer using a 384-well flat-bottom polystyrene microtiter plates (VWR). The HTA activity was determined by monitoring the production of CoA because of the increase in absorbance at 324 nm upon the titration of 4,4′-dithiodipyridine (DTDP $\varepsilon_{324\ nm} = 19\,800\ M^{-1}\ cm^{-1}$). The reaction volume was 50 μL. Assays were performed in 50 mM HEPES (pH 8.0) containing 0.001% Tween 20, 200 μM *L*-Hse, 2 mM DTDP, and 300 μM acetylCoA. The reaction was started by the addition (5 μL) of enzyme that was preincubated with the compounds. The preincubation mix was in 50 mM HEPES (pH 8.0) containing 8 μg/mL HTA, 100 μM inhibitor and 10% DMSO. Three different preincubation times (15, 70, and 200 min) with HTA were tested. The positive compounds were rescreened in the same way to confirm the inhibitory activity. For IC_{50} determination, a dilution series was performed starting with 500 μM as the highest concentration. The inhibitors were preincubated with HTA for 30 min. From this, IC_{50} values were calculated from linear extrapolation of reaction velocity as a function of the logarithmic of concentration.

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Supporting Information Available. Analytical data (HPLC, MS, ^{1}H NMR), purity table for selected library members, IC_{50} graphs for **18** and **16**{*6*}, and experimental procedures and full compound characterization (NMR, IR, HRMS) for all new compounds and reagents. This material is available free of charge via the Internet at http://pubs.acs.org.

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