Palladium-Catalyzed Tandem Reactions To Form 1-Vinyl-1*H*-isochromene Derivatives[1]

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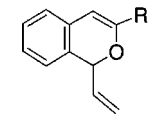
The palladium-catalyzed reaction of pinacolone with *tert*-butyldimethyl(3-(2-bromophenyl)allyloxy)-silane results in direct formation of 1-vinyl-3-*tert*-butyl-1*H*-isochromene. This is the result of a ketone arylation followed by an intramolecular cyclization of the enolate with the allylic system. The use of a lithium diamide base appears to be essential for success. The *tert*-butyldimethylsilyl protecting group is also an essential choice as it furnishes the appropriate reactivity to promote allylic substitution after the aryl coupling process. The use of more effective leaving groups, such as acetate, results in reaction of the allylic group, and no aryl coupling is observed. Through the appropriate selection of phosphine ligand and solvent, either the cyclized isochromene product or the noncyclized intermediate may be formed selectively. A short combinatorial study of the scope and limitations of the reaction, involving 24 ketones, is described.

During the course of a project directed at the synthesis of structural analogues of the anti-cancer molecule bryostatin,[2] we required a method for the synthesis of 1-vinyl-1*H*-isochromenes **1**. Toward this end, the reaction of a suitable ketone **2** with a (*o*-bromophenyl)allylic ether **3** to give **4**, followed by a palladium-catalyzed cyclization appeared to be an attractive approach. For the first step, we were confident that a palladium-catalyzed ketone arylation reaction would be effective.[3] However, since such reactions are typically carried out at elevated temperatures (ca. 80 °C), we anticipated that the protecting group R would be required to *not* activate the reagent toward allylic substitution since this would give an undesired product. Allylic acetates, for example, are known to react with ketones under palladium-catalyzed reactions at room temperature.[4]



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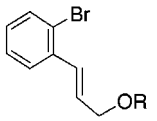
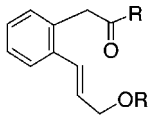


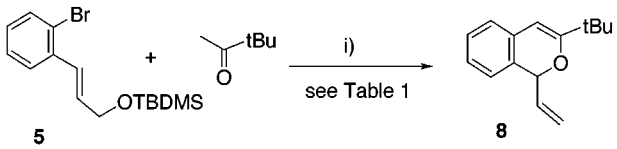
3 (R=protecting group)



4 (R=protecting group)

For our initial experiments, we chose to investigate the coupling of the *tert*-butyldimethylsilyl-protected allylic alcohol substrate **5** with pinacolone. Our intention at this point was to replace the silyl group with an acetate following the arylation and complete the cyclization in a second step.

Scheme 1. Intramolecular Cyclization Reaction To Form 1-Vinyl-1*H*-isochromenes[a]



5 **8**

[a] Reagents and conditions: (i) ligand, base, toluene/THF or dioxane, [$Pd_2(dba)_3$], 85 °C.

Starting material **5** was prepared from readily available 2-bromobenzaldehyde in three steps in 90% overall yield.[5] Initial attempts to couple **5** to pinacolone following the procedure of Hartwig et al.[3] (NaO-*t*-Bu, Pd/DPPF, toluene, 100 °C) led mainly to the debrominated cinnamyl ether **6**, and no coupling product was observed. Investi-

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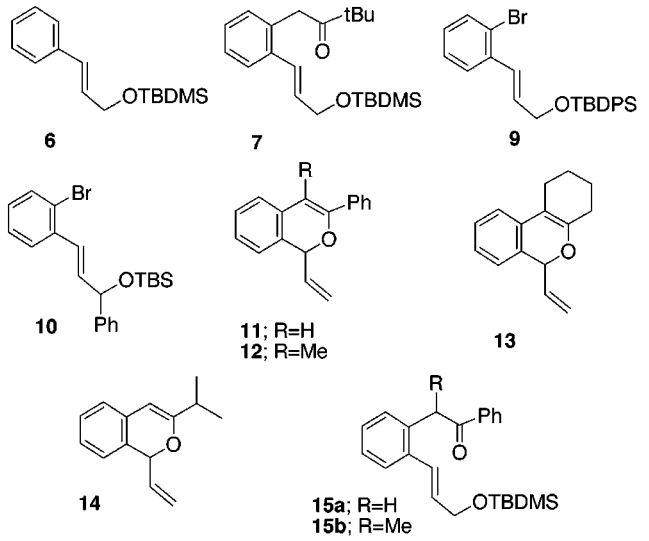
Table 1. Palladium-Catalyzed Coupling Reactions of Ketones with [3-(2-Bromophenyl)allyloxysilanes]

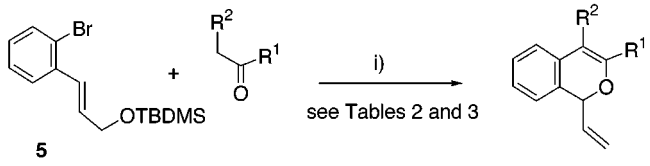
entry	aryl bromide	ketone	solvent	ligand	product	yield (%)	side products	yield (%)
1	5	pinacolone	toluene/THF	DPPF	**8**	67		
2	5	pinacolone	dioxane/THF	DPPF	**8**	71		
3	5	pinacolone	toluene	DPPF		0		
4	9	pinacolone	toluene/THF	DPPF	**8**	54		
5	10	pinacolone	toluene/THF	DPPF		0		
6	5	pinacolone	dioxane	ESPHOS	**8**	15	**7/6**	21/6
7	5	pinacolone	toluene/THF	(*o*-Tol)$_3$P	**8**	61		
8	5	pinacolone	toluene/THF	(*t*-Bu)$_3$P	**8**	27	**7/6**	30/6
9	5	acetophenone	toluene/THF	DPPF	**11**	28		
10	5	propiophenone	toluene/THF	DPPF	**12**	36	**15b**	6
11	5	cyclohexanone	toluene/THF	DPPF	**13**	13	**6**	10
12	5	3-methyl-2-butanone	toluene/THF	DPPF	**14**	34		

gation of several bases such as NaO-*t*-Bu, Na_2CO_3, Cs_2CO_3, and LHMDS gave none of the expected ketone product **7**; however, in the case of LHMDS a new nonpolar product was formed. This turned out to be the 1*H*-isochromene **8**, one of the desired heterocycles. Optimization of this tandem arylation/allylic substitution reaction led to yields of up to 70%. As far as we are aware, this represents the first observation of such a cyclization reaction, which is notable for the involvement of a silyloxy leaving group in the allylic substrate. In contrast, intramolecular reactions of β-keto ester enolates have been reported to form five-membered rings in palladium-catalyzed intramolecular cyclizations.[6] During this work, it appeared that not only must a lithium base be used (NaHMDS and KHMDS failed to give the same product), but a coordinating solvent must also be present (Table 1, entries 1 and 2 vs 3). Trost has reported a similar requirement for a lithium base in an allylic alkylation reaction.[4d] A series of phosphine ligands and ketones were also investigated, and we found that a substantial amount of the intermediate **7** could be isolated when either tri-*tert*-butylphosphine or the bis(diazaphospholidine) ligand SEMI-ESPHOS[7] was used (Table 1, entries 6 and 8). This intermediate, **7**, was then exposed to the reaction conditions in the absence of palladium and ligands. No cyclization occurred after several hours, indicating that the cyclization step was also palladium catalyzed. Tri(*o*-tolyl)phosphine also proved to be a good ligand for 1*H*-isochromene formation (Table 1, entry 7).



Changing the protecting group on the bromide from the TBS to the TBDPS ether did not effect the tandem reaction (Table 1, entry 4). Substitution at the allylic ether carbon with a phenyl group led to an unreactive substrate (Table 1, entry 5). In view of these promising results, a short study was then carried out using a series of alternative ketones; acetophenone (entry 9), propiophenone (entry 10), cyclohexanone (entry 11), and 3-methylbutan-2-one (entry 12). In each case, a cyclic product was formed, although the nonoptimized yields were low to moderate in most cases, suggesting that the reaction could be a versatile one.

Scheme 2. Combinatorial Study of Palladium-Catalyzed Cyclization Reactions[a]



[a] Reagents and conditions: (i) ligand, LHMDS, solvent, [$Pd_2(dba)_3$], 85 °C.

With these results in hand, we decided to carry out a wider study to optimize the reaction and to determine its scope and limitations. This was done through a parallel synthesis approach in collaboration with GlaxoSmithKline (Scheme 2). Four runs of 24 reactions each were planned. The first two runs were designed to find the ideal conditions with pinacolone and acetophenone as test ketones. Four solvents were used (DME, dioxane, DMSO, and DMF) and six ligands (dppf, tri-*tert*-butylphosphine, tricyclohexylphosphine, BINAP, SEMI-ESPHOS,[7] and the biarylphosphine **16**). Our intention was to find idealized conditions for the formation of both the cyclic product **8** or **11** and the intermediate **7** or **15a**. The third and fourth runs were designed to find out more about the substrate scope; 24 different ketones were employed under the optimized conditions for the formation of *both* the intermediate and the cyclic product.

The reactions were assessed by LC of the crude reaction mixtures in the optimization work. In the case of reactions in DME and dioxane, three ratios were determined from the crude reaction mixtures. The first ration was that between the remaining starting material and the products (including debromination, coupling, and cyclization products) to gain insight into the conversion and general reactivity. The second ratio was that between the debromination product and the coupling/cyclization products to assess the cleanliness of the reaction. The third ratio was that between the coupling and the cyclization product to provide a measure of selectivity.

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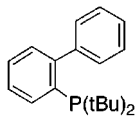
Table 2. Optimization of Palladium-Catalyzed Coupling Reactions of 5 with Acetophenone and Pinacolone[a]

entry	ketone	ligand	substrate solvent	SM/products	**6**/products	intermediate/product
1	acetophenone in dioxane (A)	DPPF (E)	dioxane (K)	50:50	traces of **6**	<1:>99
2		P(*t*-Bu)$_3$ (F)		2:98	10:90	95:5
3		PCy$_3$ (G)		50:50	10:90	67:33
4		BINAP (H)		60:40	25:75	40:60
5		ESPHOS (I)		75:25	43:57	<1:>99
6		**16** (J)		<1:>99	20:80	80:20
7	pinacolone in dioxane (B)	DPPF (E)		<1:>99	<1:>99	<1:>99
8		P(*t*-Bu)$_3$ (F)		<1:>99	<1:>99	67:33
9		PCy$_3$ (G)		<1:>99	8:92	40:60
10		BINAP (H)		15:85	<1:>99	20:80
11		ESPHOS (I)		8:92	30:70	10:90
12		**16** (J)		<1:>99	traces of **6**	10:90
13	acetophenone in DME (C)	DPPF (E)	DME (L)			
14		P(*t*-Bu)$_3$ (F)		<1:>99	15:85	80:20
15		PCy$_3$ (G)		25:75	15:85	70:30
16		BINAP (H)		<1:>99		
17		ESPHOS (I)		85:15	60:40	
18		**16** (J)		<1:>99	33:67	<1:>99
19	pinacolone in DME (D)	DPPF (E)		<1:>99	<1:>99	<1:>99
20		P(*t*-Bu)$_3$ (F)		1:99	2:98	50:50
21		PCy$_3$ (G)		<1:>99	traces of **6**	20:80
22		BINAP (H)		<1:>99	<1:>99	<1:>99
23		ESPHOS (I)		<1:>99	traces of **6**	50:50
24		**16** (J)		<1:>99	<1:>99	<1:>99

[a] Key: (A) 1 mL of a solution of 3 mmol (0.361 g) of acetophenone in 6 mL of dioxane was used; (B) 1 mL of a solution of 3 mmol (0.301 g) of pinacolone in 6 mL of dioxane was used; (C) 1 mL of a solution of 3 mmol (0.361 g) of acetophenone in 6 mL of DME was used; (D) 1 mL of a solution of 3 mmol (0.301 g) of pinacolone in 6 mL of DME was used (1.0−1.5 mL of a 1 M solution of LHMDS in THF was used in each reaction); (E) 0.5 mL of a solution of 0.025 mmol (0.023 g) of $Pd_2(dba)_3$ + 0.05 mmol (0.028 g) of DPPF in 2 mL of THF was used; (F) 0.5 mL of a solution of 0.025 mmol (0.023 g) of $Pd_2(dba)_3$ + 0.1 mmol (0.020 g) of *t*-Bu_3P in 2 mL of THF was used; (G) 0.5 mL of a solution of 0.025 mmol (0.023 g) of $Pd_2(dba)_3$ + 0.1 mmol (0.028 g) of Cy_3P in 2 mL of THF was used. (H) 0.5 mL of a solution of 0.025 mmol (0.023 g) of $Pd_2(dba)_3$ + 0.05 mmol (0.031 g) of BINAP in 2 mL of THF was used; (I) 0.5 mL of a solution of 0.025 mmol (0.023 g) of $Pd_2(dba)_3$ + 0.1 mmol (0.031 g) of S-ESPHOS in 2 mL of THF was used. (J) 0.5 mL of a solution of 0.025 mmol (0.023 g) of $Pd_2(dba)_3$ + 0.1 mmol (0.030 g) of Biaryl-P **16** in 2 mL of THF was used. (K) 1 mL of a solution of 3 mmol (1.142 g) of **5** in 12 mL of dioxane was used; (L) 1 mL of a solution of 3 mmol (1.142 g) of **5** in 12 mL of DME was used.

The results of these reactions are summarized in Table 2 for the reactions involving DME and dioxane as solvent. The reactions in DMSO and DMF gave only complex mixtures of products in low conversions.

As a result of this study, the best conditions for formation of the noncyclized intermediates **7** and **15a** from the pinacolone and acetophenone, respectively, were found to be tri-*tert*-butylphosphine in dioxane (Table 2; entries 2 and 8). The best conditions for formation of the vinyl-1*H*-isochromenes **11** and **8** were found to be, respectively, *o*-biaryldi-*tert*-butylphosphine **16** as ligand in DME (Table 2, entry 18) and DPPF as ligand in DME (Table 2, entry 19). In some cases, these "optimised" conditions were only marginally better than other conditions; for example, BINAP and *o*-biaryl-di-*tert*-butylphosphine **16** were also effective in the synthesis of cyclic



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products from alkyl ketones (entries 21 and 24) and the solvent often had minimal effect (entry 19). Following these studies, a semiquantitative investigation of 24 ketones (Figure 1; 12 aromatic **A1**−**A12** and 12 aliphatic **B1**−**B12**) was undertaken using both sets of conditions to create a library of aryl ketones and vinyl-1*H*-isochromenes (Scheme 2). The results are summarized in Table 3. The reactions were initially carried out on a 0.25 mmol scale and analyzed for evidence of products. In cases where substantial amounts of products were formed, these were isolated and characterized (Figure 2).

In the case of the alkyl ketones, only the simplest gave substantial amounts of cyclized products **17** (Table 3 entries 14, 17, and 18). A larger number of noncyclized intermediates **18** could be isolated (entries 13, 14, 16−18, 21, 22), although these were contaminated by 2,2-biaryl coupling products **19**−**22**. In one example (entry 19), a major side product was a biaryl compound, **23**, arising from a homocouping. These results suggest that the cyclization reactions of alkyl ketones are rather slow compared to the rates of the coupling reactions. In the case of aromatic ketones, a larger proportion of the experiments gave cyclized products **17** (Table 3, entries 1, 8−12) in good conversions. Under the alternative conditions, a still larger proportion of acyclic intermediates **18** could be isolated (Table 3, entries 2, 6−12), essentially free of side products.

In all cases there was no evidence of C-alkylated products (i.e., cyclic ketones), suggesting a strong preference for attack on the allyl cation by the oxygen atom of the enolate. This observation is in agreement with the results of related cyclization reactions in which a choice of O- or C-alkylation was available to the reagents.[6]

These results clearly demonstrate the difference in reactivity that can result from the variation of the ligand and solvent in a simple reaction. This selectivity provides a means for directing reactions toward specific outcomes. To demonstrate the value of such selectivity, we prepared a sample of both the cyclized and uncyclized intermediates from the reaction of **5** with *p*-methoxyacetophenone (Scheme 3). Using the specific conditions for the former process (*o*-biaryl-di-*tert*-butylphosphine as ligand in DME), the isochromene **17d** was formed, while using the specific conditions for the latter (tri-*tert*-butylphosphine in diox-

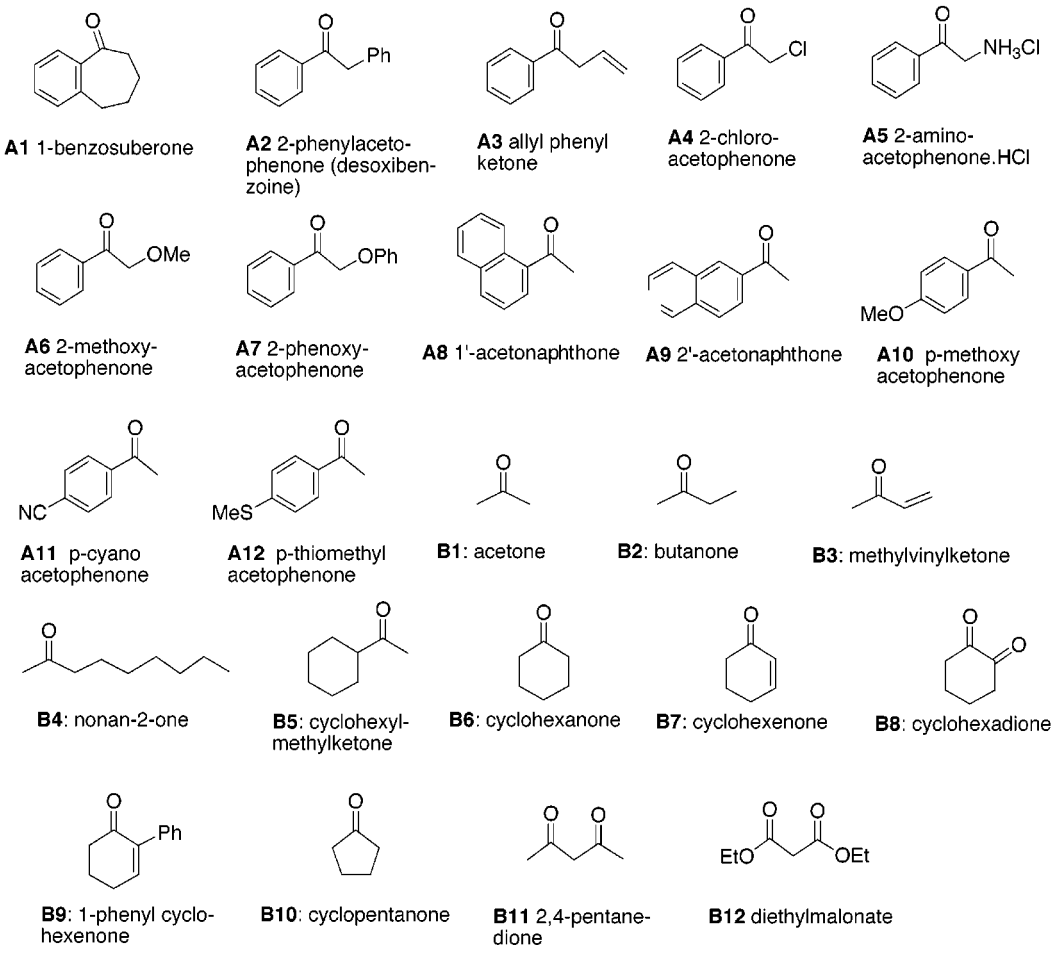
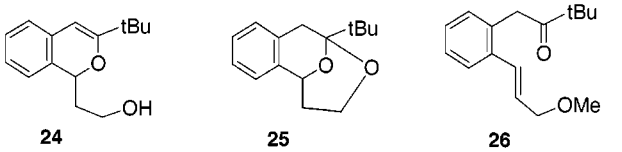


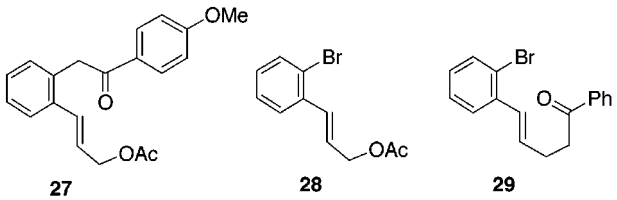
Figure 1. Ketones used in the combinatorial study (A, aromatic; B, aliphatic).

ane),, the acyclic product **18g** was isolated (60% yield after 2.5 h).

Mindful of the synthetic potential of the cyclized products, we have begun to explore the chemistry of these novel materials. In an interesting preliminary experiment, hydroboration of **8** with 9-BBN gave the primary alcohol product **24** in 37% yield together with 28% of the cyclized product **25**, a result of an acid-catalyzed side reaction in the workup. This was confirmed by a second experiment where the acid workup was avoided, which gave only **24** in 72% yield. Presumably, the hydroboration by the hindered reagent is controlled more significantly by steric factors rather than electronic. In another reaction, treatment of **8** with methanolic HCl resulted in ring-opening to give the methoxy allyl ether **26** in low yield (25%).



We recognized the potential for the formation of an enantiomerically enriched product, but were concerned that this would be difficult to achieve at the high reaction temperatures involved. Unfortunately all attempts to achieve the cyclization of ketone **18g** under our conditions failed at room temperature. In contrast, the acetate **27**, made from **18g** via desilylation to the alcohol and acetylation, could be converted to **17d** at room temperature using a combination of SEMI-ESPHOS[7] and palladium (0); however, the yield was low (20%) and the enantiomeric excess remains to be determined.



In a final study, we wished to confirm that the choice of a silyloxyallylic substrate was essential for a successful reaction. This was achieved through the attempted reactions of acetate **28** with both pinacolone and acetophenone under our reaction conditions for cyclization. In the former case, the result was a complex mixture, in the latter case the deacetylated alcohol was the major product, together with a small amount of ketone **29**. The latter result serves to confirm the ability of the silyloxy group to delay the allylc reaction conveniently until after the arylation process has been completed.

Conclusion

In conclusion, we have demonstrated that the use of a combinatorial approach to the optimization of a reaction

Table 3. Palladium-Catalyzed Coupling Reactions of a Series of Ketones (Figure 1) with 5[a]

entry	ketone	procedure A, comments	isolated product(s) (ratio cyclic/acyclic)	procedure B, comments	isolated product(s) (ratio acyclic/cyclic)
1	**A1**	mixture	**17a**, **18a**	mixture, low conversion	
2	**A2**	mixture, low conversion		predominantly acyclic product	**18b**
3	**A3**	mixture, low conversion		mixture, low conversion	
4	**A4**	mixture, low conversion		mixture, low conversion	
5	**A5**	mixture, low conversion		mixture, low conversion	
6	**A6**	mixture, low conversion		mixture	**18c**
7	**A7**	mixture, low conversion		predominantly acyclic product	**18d**
8	**A8**	predominantly cyclic product	**17b** (9:1)	predominantly acyclic product	**18e** (4:1)
9	**A9**	predominantly cyclic product	**17c** (9:1)	predominantly acyclic product	**18f** (13:1)
10	**A10**	predominantly cyclic product	**17d** (9:1)	predominantly acyclic product	**18g** (26:1)
11	**A11**	predominantly cyclic product	**17e** (14:1)	predominantly acyclic product	**18h** (3:1)
12	**A12**	predominantly cyclic product	**17f** (6:1)	predominantly acyclic product	**18i** (9:1)
13	**B1**	mixture, low conversion		mixture	**18j**, **19**
14	**B2**	mixture, low conversion	**17g**	predominantly acyclic product	**18k**, **18l**, **20**
15	**B3**	mixture, low conversion		mixture, low conversion	
16	**B4**	mixture, low conversion		mixture	**18m**, **18n**, **21**
17	**B5**	predominantly cyclic product	**17h** (9:1)	mixture	**18o** (2.2:1), **22**
18	**B6**	mixture	**13**	predominantly acyclic product	**18p**
19	**B7**	mixture, low conversion		mixture	**23**
20	**B8**	mixture, low conversion		mixture, low conversion	
21	**B9**	mixture, low conversion		mixture	**18q**
22	**B10**	mixture, low conversion		mixture	**18r**
23	**B11**	mixture, low conversion		mixture, low conversion	
24	**B12**	mixture, low conversion		mixture, low conversion	

[a] Procedure A: aromatic sustrates; *o*-biaryl-di-*tert*-butylphosphine in DME, aliphatic substrates; DPPF in DME. Procedure B (all substrates): tri-*tert*-butylphosphine in dioxane. See the Experimental Section for full details. Products were characterized to confirm identity; however, isolated yields for these unoptimized reactions were not routinely obtained. "Mixture" indicates the formation of three or more significant (>10%) products by GC analysis. "Low conversion" indicates <10% conversion of substrate, no product being isolated.

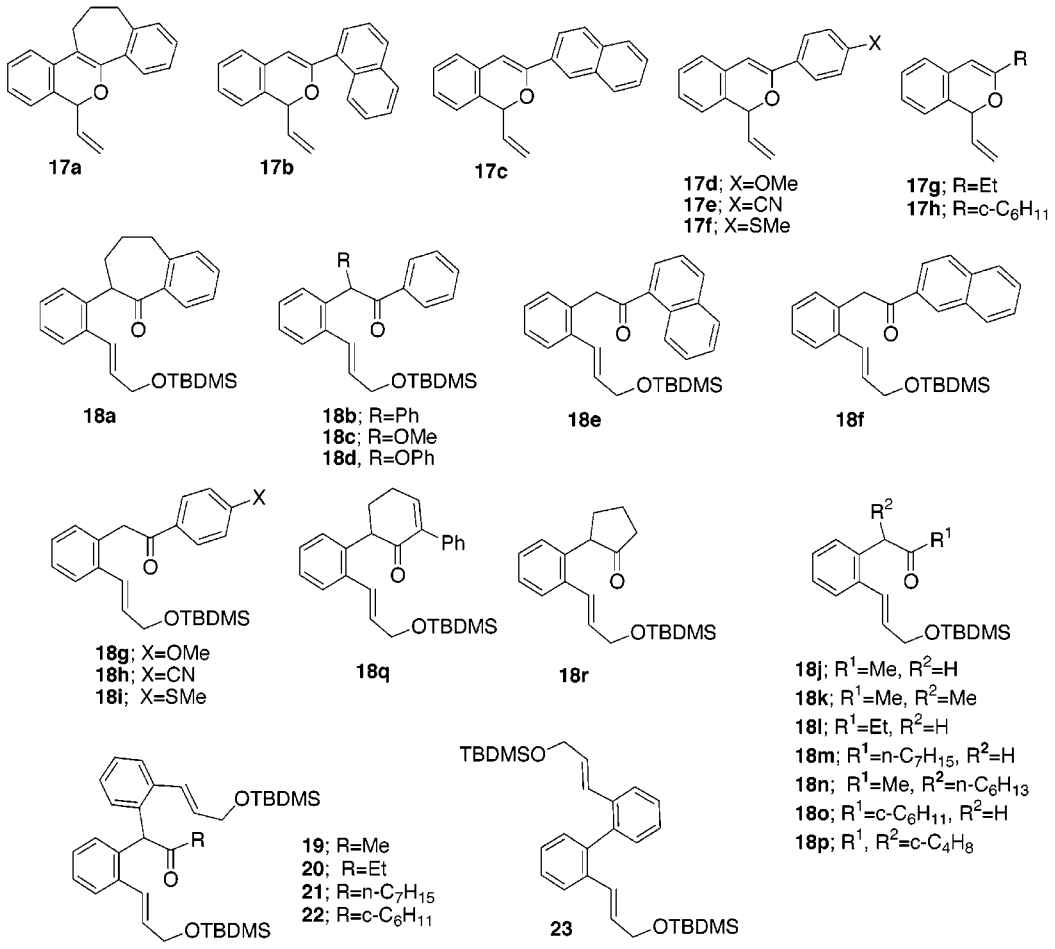
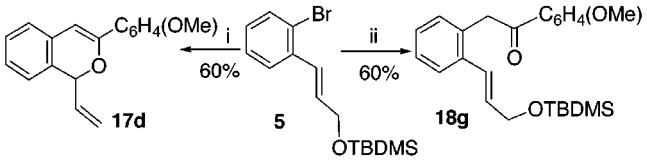


Figure 2. New compounds prepared and characterized in the combinatorial chemistry.

can permit the rapid determination of substrate scope and versatility. In addition, the rapid screening process can assist with the identification of optimum conditions for the specific formation of intermediates in a reaction

Scheme 3. Selective Formation of Cyclic or Acyclic Product[a]



[a] Reagents and conditions: (i) $[Pd_2(dba)_3]$, LiHMDS, DME, (2-$C_6H_5)C_6H_4P(t\text{-}Bu)_2$, (ii) $[Pd_2(dba)]$, LiHMDS, dioxane, $P(t\text{-}Bu)_3$.

sequence. We are continuing to examine the synthetic potential and application of both the cyclized and uncyclized products of the palladium-catalyzed coupling reactions. The results of these studies will be disclosed in due course.

Experimental Section

(*E*:*Z*)-*tert*-Butyldimethyl-[3-(2-bromophenyl)allyloxy]-silane 5. A solution of (*E*:*Z*)-3-(2-bromophenyl)prop-2-en-1-ol (4.5 g, 2.1×10^{-2} mol, 1 equiv) in THF (20 mL) was added to a solution of TBDMSCl (3.3 g, 2.2×10^{-2} mol, 1.05 equiv) in THF (20 mL), followed by a solution of triethylamine (7.6 mL, 5.3×10^{-2} mol, 2.5 equiv) in THF (8 mL) and DMAP (0.13 g, 1.05×10^{-3} mol, 5 mol %) at room temperature. After the mixture was stirred for 3 h, methanol (1 mL) was added, and the resulting mixture was stirred for 1.5 h. The mixture was diluted with DCM (200 mL) and twice extracted with 1 M HCl solution (2×150 mL). The organic layer was dried, and the solvent was evaporated under reduced pressure to yield a mixture of *E*/*Z* isomers (6.5 g, *E*/*Z* = 5:1, 2.9×10^{-2} mol, 95%): IR (NaCl) 2929, 1250, 834, 776 cm^{-1}; ^1H NMR, ($CDCl_3$, 250 MHz) isomer *E* δ 0.13 (6H, s), 0.96 (9H, s), 4.38 (2H, dd, J = 4.6, 1.8 Hz), 6.23 (1H, dt, J = 15.9, 4.9 Hz), 6.97 (1H, d, J = 15.6 Hz), 7.00−7.60 (4H, m). Isomer *Z*: δ 0.13 (6H, s), 0.96 (9H, s), 4.29 (2H, dd, J = 6.4, 1.5 Hz), 5.93 (1H, dt, J = 11.6, 6.4 Hz), 6.58 (1H, d, J = 11.6 Hz), 7.00−7.60 (4H, m); ^{13}C NMR ($CDCl_3$, 60 MHz) δ −4.3, 19.3, 26.8, 64.5, 124.5, 127.9, 128.3, 128.9, 129.4, 133.0, 133.9, 137.9; MS (CI) *m*/*z* 328 $[M]^+$, 326 $[M + H]^+$, 271, 269, 191, 116; HRMS (CI) *m*/*z* 326.070358 (calcd for $C_{15}H_{23}{}^{79}BrOSi$ 326.070155).

General Procedure for Synthesis of Substituted 1-Vinyl-1*H*-isochromenes. To a solution of LHMDS (1 M in THF, 3 equiv) was slowly added a solution of the ketone (2 equiv) at 5 °C. A solution of $Pd_2(dba)_3$ (5% mol) and ligand (10% mol) in solvent was added at room temperature, followed by a solution of (*E*/*Z*)-*tert*-butyldimethyl[3-(2-bromophenyl)allyloxy]-silane **5** (1 equiv). The reaction mixture was heated to 100 °C overnight and quenched with 1 M HCl solution at room temperature. The mixture was twice extracted with DCM, the combined organic layers were dried, and the solvent was evaporated under reduced pressure yielding the crude product. The crude product was purified by flash chromatography or by preparative TLC. In the case of the parallel synthesis work, the reactions were carried out on a 24-position Radleys greenhouse parallel synthesizer coupled to a robotic system for analysis by GC.

***tert*-Butyldimethyl(3-phenylallyoxy)silane 6:** ^1H NMR ($CDCl_3$, 250 MHz) δ 0.11 (6H, s), 0.94 (9H, s), 4.35 (2H, dd, J = 4.9, 1.5 Hz), 6.28 (1H, dt, J = 15.9, 4.9 Hz), 6.59 (1H, d, J = 15.6 Hz), 7.10−7.40 (5H, m).

***tert*-Butyldimethylsilyl-2-(2-oxo-2-*tert*-butylethyl)-cinnamyl ether 7:** IR (NaCl) 2956, 2931, 2858, 1712, 836, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.00 (6H, s), 0.83 (9H, s), 1.14 (9H, s), 3.80 (2H, s), 4.23 (2H, dd, J = 4.7, 1.9 Hz), 6.02 (1H, dt, J = 16.0, 4.7 Hz), 6.54 (1H, d, J = 16.0 Hz), 6.85−7.40 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) −5.4, 18.2, 25.8, 26.4, 40.8, 44.3, 63.8, 126.3, 126.5, 126.9, 127.0, 130.3, 131.4, 132.4, 136.9, 212.3; MS (EI) *m*/*z* 345$[M - H]^+$, 243, 215; HRMS (EI) *m*/*z* 345.212265 (calcd for $C_{21}H_{33}O_2Si$ 345.224984).

1-Vinyl-3-*tert*-butyl-1*H*-isochromene 8: IR (NaCl) 2954, 1638, 1085, 914, 750 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.16 (9H, s), 5.16 (1H, dt, J = 17.1, 1.3 Hz), 5.23 (1H, dt, J = 10.4, 1.3 Hz), 5.46 (1H, d, J = 6.6 Hz), 5.67 (1H, s), 6.15 (1H, ddd, J = 17.1, 10.4, 6.6 Hz), 6.90−7.30 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 35.5, 79.3, 97.7, 118.2, 123.8, 124.9, 126.2, 128.5, 129.4, 132.0, 136.7, 164.2; MS (EI) *m*/*z* 214 $[M]^+$, 187, 129; HRMS (EI) *m*/*z* 214.136173 (calcd for $C_{15}H_{18}O$ 214.135765).

(*E*:*Z*)-*tert*-Butyldiphenyl[3-(2-bromophenyl)allyloxy]-silane 9. A solution of (*E*:*Z*)-3-(2-bromophenyl)prop-2-en-1-ol (1.04 g, 91% in toluene, 4.9×10^{-3}mol, 1 equiv) in DCM (10 mL) was added to a solution of *tert*-butyldiphenylchlorosilane (1.45 mL, 5.46×10^{-3} mol, 1.1 equiv) in DCM (2 mL), followed by a solution of triethylamine (2.0 mL, 1.4×10^{-2} mol, 2.5 equiv) in DCM (2 mL) and DMAP (0.065 g, 5.0×10^{-4} mol, 10 mol %) at room temperature. After the mixture was stirred for 3 h, methanol (0.25 mL) was added and the resulting mixture was stirred for 1.5 h. The mixture was twice extracted with 1 M HCl solution (2×15 mL). The organic layer was dried, and the solvent was evaporated under reduced pressure to yield a mixture of *E*/*Z* isomers (1.98 g, *E*/*Z* = 5:1, 4.4×10^{-3} mol, 90%): IR (NaCl) 2967, 2929, 2834, 2366, 1272, 1109, 716 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) isomer *E* δ 1.11 (9H, s), 4.41 (2H, dd, J = 4.4, 1.9 Hz), 6.22 (1H, dt, J = 15.6, 4.3 Hz), 7.00−7.80 (15H, m); isomer *Z* δ 1.07 (9H, s), 4.34 (2H, dd, J = 6.4, 1.5 Hz), 6.00 (1H, dt, J = 11.5, 6.6 Hz), 7.00−7.80 (15H, m); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 19.7, 27.2, 64.6, 124.1, 127.9, 128.1, 128.5, 128.9, 130.0, 130.1, 132.1, 133.3, 133.9, 136.0, 137.5; MS (CI) *m*/*z* 470 $[M + NH_4]^+$, 468 $[M + NH_4]^+$, 453, 451, 412, 410, 395, 393; HRMS (CI) 468.136962 (calcd for $C_{25}H_{27}{}^{79}BrOSi{\cdot}NH_4$ 468.135829).

(*E*)-*tert*-Butyldimethyl[3-(2-bromophenyl)-1-phenyl-allyloxy]silane 10. A solution of (*E*)-3-(2-bromophenyl)-1-phenylprop-2-en-1-ol (0.30 g, 1.0×10^{-3} mol, 1 equiv) in DCM (1 mL) was added to a solution of *tert*-butyldimethylchlorosilane (0.18 g, 1.14×10^{-3} mol, 1.1 equiv) in DCM (1 mL), followed by a solution of triethylamine (0.4 mL, 2.8×10^{-3} mol, 2.8 equiv) in DCM (1 mL) and DMAP (0.02 g, 1.6×10^{-4} mol, 15 mol %) at room temperature. After being stirred for 2 days the solvent was evaporated under reduced pressure to give an oily residue. The product was isolated by flash column chromatography (20 mL silica gel, eluent ether/petroleum ether 1:19) to give the product (yield = 0.14 g, 3.3×10^{-4} mol, 33%): IR (NaCl) 2973, 2946, 2865, 1492, 1263, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.03 (3H, s), 0.11 (3H, s), 0.94 (9H, s), 5.37 (1H, d, J = 5.7 Hz), 6.17 (1H, dd, J = 15.6, 6.0 Hz), 7.03 (1H, d, J = 15.5 Hz), 6.80−7.60 (9H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.4, −4.1, 26.3, 75.7, 120.5, 124.2, 126.5, 127.6, 127.9, 128.7, 129.0, 129.8, 133.2, 136.4, 137.3; MS (EI) *m*/*z* 404 $[M]^+$, 402 $[M]^+$, 347, 345, 273, 271, 192; HRMS (CI) *m*/*z* 402.101418 (calcd for $C_{21}H_{27}{}^{79}BrOSi$ 402.101455).

1-Vinyl-3-phenyl-1*H*-isochromene 11: IR (NaCl) 2926, 1255, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.29 (1H, dt, J = 18.0, 1.2 Hz), 5.30 (1H, dt, J = 10.0, 1.2 Hz), 5.71 (1H, d, J = 6.1 Hz), 6.19 (1H, ddd, J = 17.0, 10.0, 6.1 Hz), 6.43 (1H, s), 7.40−7.45 (7H, m), 7.74−7.78 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.4, 101.0, 118.3, 124.3, 124.9, 125.4, 125.4, 126.9, 128.6, 128.7, 128.7, 129.2, 130.0, 131.5, 134.8, 136.1, 163.8; MS (CI) *m*/*z* 235 $[M + H]^+$, 105; HRMS (EI) *m*/*z* 234.104176 (calcd for $C_{17}H_{14}O$ 234.104465).

***tert*-Butyldimethylsilyl-2-(2-oxo-2-phenylethyl)-cinnamyl ether 15a:** IR (NaCl) 2955, 2930, 2856, 1687, 1266, 837, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.02 (6H, s), 0.84 (9H, s), 4.30 (2H, dd, J = 4.5, 1.9 Hz), 4.38 (2H, s), 6.17 (1H, dt, J = 15.5, 4.5 Hz), 6.71 (1H, d, J = 15.6 Hz), 7.10−8.10 (9H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.9, 26.2, 43.6, 64.1, 126.8, 126.9, 127.8, 128.7, 128.8, 129.0, 130.8,131.0, 132.3, 133.6, 164.0; MS (EI) *m*/*z* 385 $[M + NH_3D]^+$, 368 $[M + D]^+$, 310, 251, 236; HRMS (CI) *m*/*z* 384.1967 (calcd for $C_{23}H_{30}O_2Si{\cdot}NH_4$ 384.2017).

1-Vinyl-3-phenyl-4-methyl-1*H*-isochromene 12: IR (NaCl) 2925, 1489, 1244, 1016, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (3H, s), 5.25 (1H, dt, J = 17.0, 1.2 Hz), 5.30 (1H, dt, J = 10.0, 1.2 Hz), 5.51 (1H, d, J = 6.6 Hz), 6.23 (1H, ddd, J = 17.0, 10.0, 6.8 Hz), 7.00−7.50 (9H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 79.1, 119.1, 122.1, 124.6, 126.9, 128.3, 128.3, 128.5, 128.8, 130.1, 130.1, 131.0, 133.9, 135.8, 136.4,

164.2; MS (EI) *m/z* 249 $[M + H]^+$, 248 $[M]^+$, 221, 191, 143; HRMS (EI) *m/z* 248.119930 (calcd for $C_{18}H_{16}O$ 248.120115).

***tert*-Butyldimethylsilyl-2-(2-oxo-2-phenyl-1-methyl-ethyl)cinnamyl ether 15b:** IR (NaCl) 2933, 1686, 1258, 837, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.00 (6H, s), 0.82 (9H, s), 1.34 (3H, d, $J = 6.7$ Hz), 3.73 (1H, q, $J = 6.7$ Hz), 4.30 (2H, dd, $J = 4.6$, 1.9 Hz), 6.13 (1H, dt, $J = 15.0$, 4.6 Hz), 6.85−7.35 (8H, m), 7.65−7.73 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4, 18.2, 25.7, 43.9, 63.5, 125.7, 126.8, 127.1, 127.8, 128.2, 128.2, 128.5, 128.5, 132.4, 132.6, 135.0, 136.0, 138.8, 200.4; MS (CI) *m/z* 380 $[M]^+$, 323, 231, 149, 129, 105; HRMS (EI) *m/z* 380.216667 (calcd for $C_{24}H_{32}O_2Si$ 380.217159).

1-Vinyl-3,4-bicyclohexanyl-1*H*-isochromene 13: IR (NaCl) 2954, 1638, 1085, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64 (4H, m), 2.10 (2H, m), 2.25 (2H, m), 5.16 (1H, dt, $J =$ 17.1, 1.3 Hz), 5.20 (1H, dt, $J = 10.4$, 1.3 Hz), 5.31 (1H, d, $J =$ 6.8 Hz), 6.01 (1H, ddd, $J = 17.1$, 10.4, 6.6 Hz), 6.80−7.30 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 35.5, 79.3, 97.7, 118.2, 123.8, 124.9, 126.2, 128.5, 129.4, 132.0, 136.7, 164.2; MS (CI) *m/z* 213 $[M + H]^+$, 134, 117; HRMS (EI) *m/z* 212.120811 (calcd for $C_{15}H_{16}O$ 212.120115).

1-Vinyl-3-(2-propyl)-1*H*-isochromene 14: IR (NaCl) 2974, 804, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (6H, dd, $J =$ 6.8, 1.8 Hz), 2.41 (1H, sep, $J = 7.0$ Hz), 5.16−5.30 (2H, m), 5.50 (1H, d, $J = 6.4$ Hz), 5.61 (1H, s), 6.14 (1H, ddd, $J = 17.1$, 10.4, 6.4 Hz), 6.90−7.30 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.0, 32.1, 78.6, 97.8, 117.3, 122.8, 124.3, 125.5, 127.9, 128.7, 131.1, 135.5, 161.5; MS (EI) *m/z* 200 $[M]^+$, 167, 149; HRMS (EI) *m/z* 200.120167 (calcd for $C_{14}H_{16}O$ 200.120115).

***tert*-Butyldimethylsilyl-2-(2-oxo-[4′-methoxyphenyl]-ethyl)cinnamyl Ether 18g. Scale-up from the Parallel Synthesis.** A solution of 4-methoxyacetophenone **A10** (0.92 g, 6.13×10^{-3} mol, 2 equiv) in dioxane (5 mL) was added to a solution of LHMDS (12.5 mL, 1 M in THF, 1.25×10^{-2} mol, 4 equiv) at 0 °C. A solution of tris(dibenzylideneacetone)-dipalladium (0.070 g, 7.6×10^{-5} mol, 5% mol) and tri-*tert*-butylphosphine (0.062 g, 3.1×10^{-4} mol, 10% mol) in dioxane (5 mL) was added at room temperature followed by **5** (1.00 g, 3.05×10^{-3} mol, 1 equiv) in dioxane (5 mL). The mixture was then heated to 90 °C. After 3 h, the reaction mixture was allowed to cool to room temperature and was partitioned between 1 M HCl solution (100 mL) and DCM (200 mL). The organic layer was dried, and the solvent was evaporated under reduced pressure to give an oil. The product was isolated by flash column chromatography (150 mL silica gel, eluent ethyl acetate/petroleum ether 1:49) to give the product as a yellow oil (yield = 0.41 g, 93% in ethyl acetate, 1.84×10^{-3} mol, 60%): IR (NaCl) 3008, 2932, 2857, 1682, 1601, 1512, 1259, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ isomer *E* 0.05 (6H, s), 0.86 (9H, s), 3.88 (3H, s), 4.20−4.40 (4H, m), 6.17 (1H, dt, $J =$ 15.6, 4.7 Hz), 6.73 (1H, dt, $J = 15.6$, 1.7 Hz), 7.10−8.10 (8H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.9, 18.7, 22.1, 26.3, 43.4, 64.1, 126.9, 126.9, 127.7, 127.8, 128.9, 129.7, 130.9, 132.2, 132.8, 134.6, 137.3, 144.3, 197.4; MS (EI) *m/z* 396 $[M]^+$, 380, 265; HRMS (EI) *m/z* 396.212006 (calcd for $C_{24}H_{32}O_3Si$ 396.212074).

2-(3-*tert*-Butyl-1*H*-isochromen-1-yl)ethanol 24. A solution of 9-BBN (1.0 mL, 0.5 M in THF, 5.0×10^{-4} mol, 2 equiv) was added to a solution of **8** (0.05 g, 2.3×10^{-4} mol, 1 equiv) in THF (1 mL) at room temperature. After the mixture was stirred for 2 h, methanol (0.5 mL) and H_2O_2 (30%, 0.25 mL) were added. After 1.5 h the solvent was evaporated under reduced pressure. The residue was partitioned between DCM and 1 M HCl. The organic layer was dried, and the solvent was removed under reduced pressure. The product was isolated by flash column chromatography (20 mL silica gel, eluent ether/petroleum ether 1:99) to give the product (yield = 0.020 g, 8.6×10^{-5} mol, 37%) and **25** as side product (0.015 g, 6.5×10^{-5} mol, 28%). Avoiding the acidic workup gave **24** in 72% yield. **2-(3-*tert*-Butyl-1*H*-isochromen-1-yl)ethanol 24**: IR (NaCl) 3322, 2964, 1642, 1085, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (9H, s), 2.00−2.40 (2H, m), 3.70−4.00 (2H, m), 5.25 (1H, dd, $J = 8.6$, 4.6 Hz) 5.69 (1H, s), 6.90−7.20 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 35.1, 36.0, 60.0, 75.9, 97.8, 123.7, 123.8, 126.3, 128.3, 131.8, 131.8, 164.1; MS (EI) *m/z* 232 $[M]^+$, 187, 129; HRMS (CI) *m/z* 232.146076 (calcd for $C_{15}H_{20}O2$ 232.146330). **25**: IR (NaCl) 2957, 1132, 1099, 944, 766, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (9H, s), 1.20−1.40 (1H, m), 2.44 (1H, tt, $J = 12.0$, 5.2 Hz), 2.80 (1H, d, $J = 1.8$ Hz), 3.35 (1H, d, $J = 1.8$ Hz), 3.65−3.90 (2H, m), 5.07 (1H, d, $J = 4.6$ Hz), 6.95−7.25 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 31.2, 39.0, 57.2, 70.4, 99.8, 124.4, 125.4, 126.6, 127.4, 135.1, 136.7; MS (EI) *m/z* 232 $[M]^+$, 187, 130; HRMS (CI) 232.146725 (calcd for $C_{15}H_{20}O_2$ 232.146330).

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Supporting Information Available: Detailed experimental procedures, data from the parallel synthesis, and full characterization of all new compounds not featured in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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