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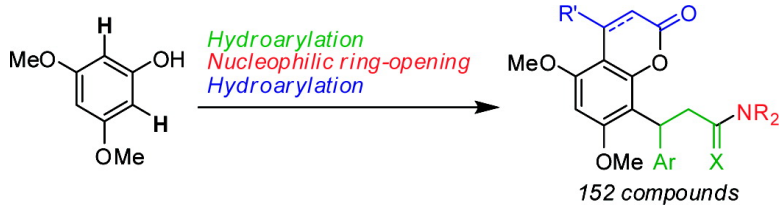

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Article

Chemical Libraries via Sequential C−H Functionalization of Phenols

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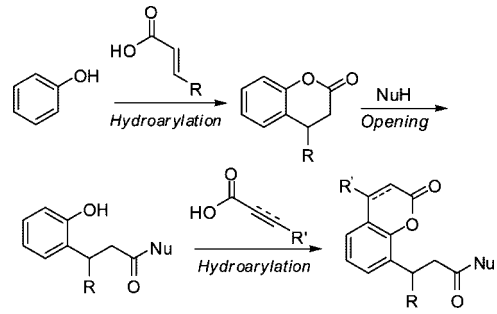
Phenols provide a useful template for diversification via sequential hydroarylation reactions. Specifically, a protocol has been developed that begins with the hydroarylation of cinnamic acids by 3,5-dimethoxyphenol to produce dihydrocoumarins. This activated ester undergoes facile ring-opening with amines to form a C−N bond and regenerate a phenol. The resulting phenol can be further functionalized via a second hydroarylation reaction. Thus, in 3–4 steps, a phenol is coupled with a cinnamic acid, an amine, and a cinnamic or propiolic acid.

Introduction

Iterative coupling of a moderately diverse subset of small molecules (i.e., amino acids, saccharides) allows Nature to produce larger molecules (peptides, polysaccharides) that exhibit an incredible array of structure and function. The efficiency of these processes is due in part to the use of a single reaction type to produce diverse structures.[1] With this in mind, we are interested in developing sequences for the production of drug-like small molecules that are based on sequential hydroarylation of olefins and alkynes with phenols.[2–4] Hydroarylation allows C−C bonds to be formed with high atom economy from simple phenol substrates; the atom economy, coupled with the base-solubility of the reactants, makes hydroarylation ideal for parallel synthesis.[5] Hydroarylation of unsaturated acids and esters with phenols not only produces C−C bonds but also produces activated esters that readily react with nucleophiles.[6] Importantly, the nucleophilic ring opening of the lactone regenerates a phenol that can potentially undergo a second hydroarylation, thus allowing the production of a diverse set of coumarin analogs (Scheme 1). Given the wide variety of biological activities supported by the coumarin scaffold,[7] new methods for the parallel synthesis of unknown classes of coumarins for biological screening are desirable.[8]

To begin, it was necessary to validate the hydroarylation−nucleophilic opening−hydroarylation synthetic protocol. To do so, a variety of dihydrocoumarins were prepared using our TFA-mediated hydroarylation.[5a] 3,5-Dimethoxyphenol was chosen as the initial phenol template because each ortho-position is activated by three electron-donating groups, which was expected to facilitate a variety of electrophilic substitutions.[9] The initial hydroarylation of cinnamic acids with 3,5-dimethoxyphenol can be readily adapted to parallel synthesis by employing an acid-scavenger to remove any unreacted

Scheme 1



phenol and cinnamic acid starting materials (Scheme 2). The polystyrene-supported MP-carbonate was very effective, providing the dihydrocoumarins in high yield and >95% purity. The acid-mediated synthesis of dihydrocoumarins was also scaled up to produce ~10 g quantities of dihydrocoumarins, as was necessary for library synthesis.[10] The ring-opening of the dihydrocoumarins with piperidine readily occurred, as expected on the basis of literature precedent.[6] Any remaining piperidine was scavenged using the polystyrene-supported isocyanate (MP-NCO). This sequence afforded the phenolic propanamide **5** in 88% overall yield and >95% purity (Scheme 2).

Attempted hydroarylation of cinnamic acids with the resulting phenolic propanamide **5** under our standard TFA-mediated hydroarylation conditions proved to be problematic.[5a] Apparently, under the acidic conditions, cyclization back to the dihydrocoumarins (**3**) was much faster than hydroarylation. While higher temperatures did afford significantly more of the hydroarylation product, the yields were not high and the product was formed as a ~1:1 mixture of diastereomers (Scheme 3). The palladium-catalyzed hydroarylation of alkynes was somewhat more effective and provided the product coumarin in moderate yield;[2] reversion back to dihydrocoumarin accounted for the mass balance.

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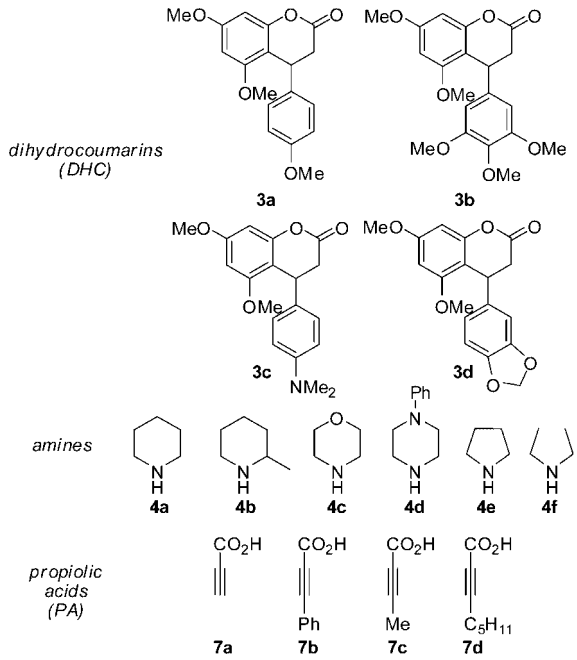
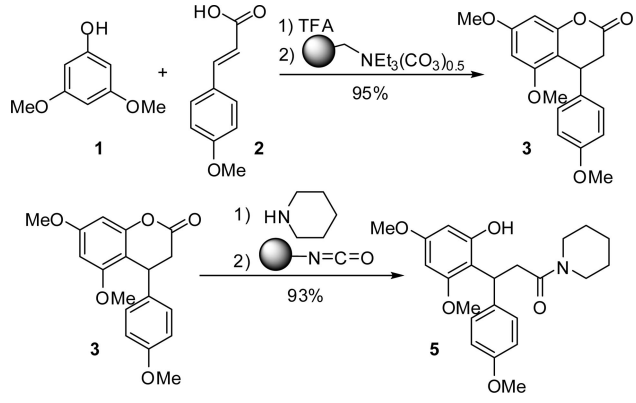
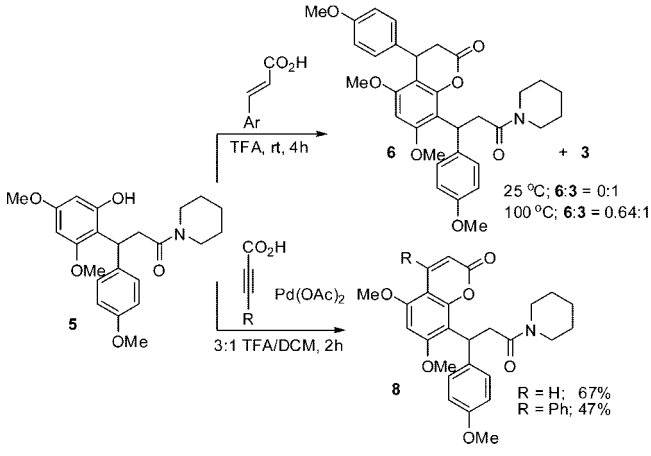


Figure 1. Sublibraries utilized.

Scheme 2

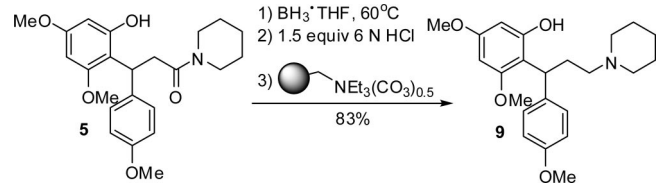


Scheme 3



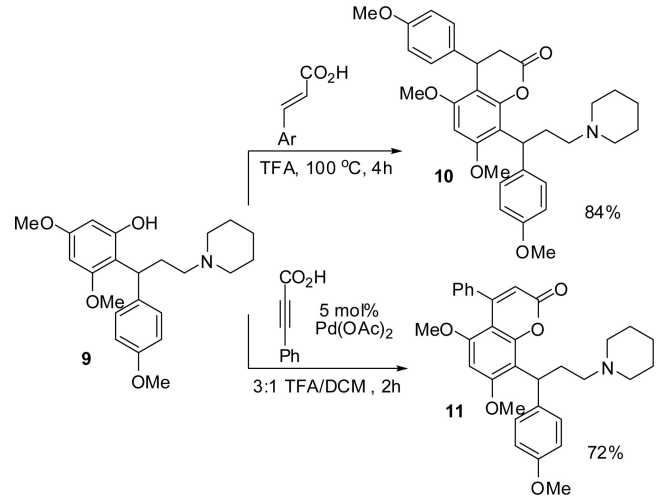
To avoid the problematic reversion of compound **5** to dihydrocoumarin **3**, we investigated a route wherein the amide is reduced to the amine prior to hydroarylation. It is reported that such amides can be reduced with borane and the amines purified by a capture−release protocol using a polymer-supported sulfonic acid.[6b] Such a strategy was used for the synthesis of libraries of compounds similar to **9** that are analogs of the antimuscaric agent Detrol LA.[11] Attempts to mimic this protocol with our specific substrates led to very low yields of recovered amine (<30%). Thus, we have developed a modified procedure that avoids the capture−release protocol and focuses on scavenging excess reagents. Ultimately, reduction of the amide was accomplished by treatment with $BH_3 \cdot THF$, followed by HCl to cleave the borane−amine complex then MP-carbonate (MP = macroporous poly(styrene-*co*-divinylbenzene)) to scavenge the acids and neutralize the product (Scheme 4). This process produced compound **9** in good yield and >95% purity, as determined by ^1H NMR spectroscopy.

Scheme 4



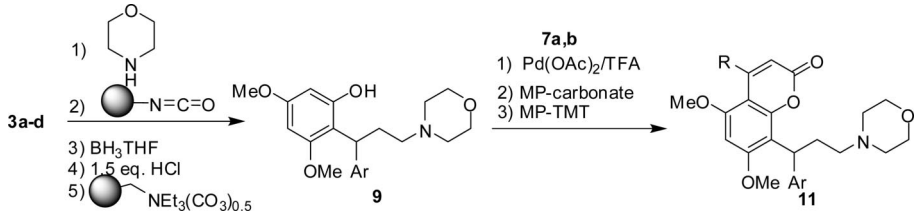
As expected, the yields of hydroarylation are much higher with the amine reactant (**9**), which cannot revert to the dihydrocoumarin in a manner similar to substrate **5**. The TFA-catalyzed hydroarylation of a cinnamic acid provided the product dihydrocoumarin in 84% yield as a ~1:1 mixture of diastereomers after acid scavenging with MP-carbonate (Scheme 5).[12] In addition, Fujiwara hydroarylation of phenylpropiolic acid formed the expected racemic coumarin **11** in 72% yield after scavenging the acids with MP-carbonate and removal of the palladium with MP-TMT.[13]

Scheme 5



Having validated the methodology, we tested our ability to perform the procedure in parallel by preparing an 8-member demonstration library (Scheme 6). Thus, four dihydrocoumarins (**3a–d**) were allowed to react with morpholine at 60 °C in THF in a Bohdan Miniblock XT. The ring-opening was directly followed by reduction of the amide and hydroarylation of either propiolic acid or phenyl propiolic acid. The resulting compounds were generally quite pure (HPLC purities or crude material ranged from 62−95%) but were ultimately purified by mass-directed fractionation to

Scheme 6



Scheme 7

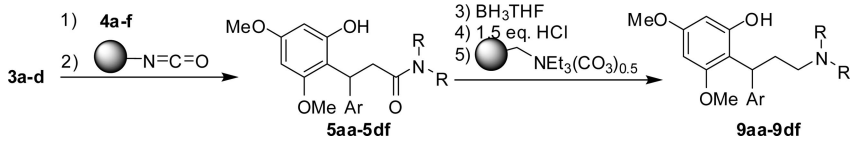


Table 1. Yields and Purities of Coumarins **11**

DHC	amine	PA	product	yield[a]	purity[b]
3a	**4c**	**7a**	**11aca**	57	98
3a	**4c**	**7b**	**11acb**	65	>99
3b	**4c**	**7a**	**11bca**	50	99
3b	**4c**	**7b**	**11bcb**	53	99
3c	**4c**	**7a**	**11cca**	36	96
3c	**4c**	**7b**	**11ccb**	32	>99
3d	**4c**	**7a**	**11dca**	46	99
3d	**4c**	**7b**	**11dcb**	55	93

[a] Isolated after mass-directed fractionation (MDF). [b] Determined by HPLC.

Table 2. Yields and Purities of Ring-Opened Products

		5		**9**	
DHC	amine	yield[a]	purity[b]	yield[a]	purity[b]
3a	**4a**	40	>99	69	>99
3a	**4b**	41	>99	62	>99
3a	**4c**	44	>99	71	>99
3a	**4d**	47	>99	80	>99
3a	**4e**	68	>99	69	>99
3a	**4f**	50	>99	61	94
3b	**4a**	45	>99	56	>99
3b	**4b**	47	>99	62	99
3b	**4c**	50	98	55	>99
3b	**4d**	50	>99	41	>99
3b	**4e**	51	>99	67	98
3b	**4f**	56	>99	69	95
3c	**4a**	39	99	67	>99
3c	**4b**	17	>99	55	>99
3c	**4c**	41	99	57	>99
3c	**4d**	45	96	69	>99
3c	**4e**	37	>99	76	97
3c	**4f**	31	>99	60	92
3d	**4a**	38	99	53	>99
3d	**4b**	35	>99	41	>99
3d	**4c**	50	>99	50	>99
3d	**4d**	55	>99	52	98
3d	**4e**	62	>99	57	>99
3d	**4f**	50	>99	44	94

[a] Isolated after mass-directed fractionation (MDF). [b] Determined by HPLC.

provide coumarins **11** in 32–65% overall yield and 93–99% purity (Table 1).

Given the success of the demonstration library, we chose to pursue a somewhat larger library of coumarins that are derived from both phenolic propanamides (**5**) and phenolic propylamines (**9**). We began by producing a 24-member library of phenolic propanamides (**5**) by hydroarylation of cinnamic acids with 3,5-dimethoxyphenol to provide dihydrocoumarins **3**. The resulting dihydrocoumarins underwent nucleophilic ring opening with secondary amines **4a**−**f** (Scheme 7). A portion of this library was subjected to mass-directed fractionation, which provided the phenolic propanamides (**5**) in 31–68% yield and 96–99% purity. These yields are much lower than those observed for single benchtop reactions, which typically provide yields that are >90%. The low yields reflect our choice to obtain high purities at the expense of yield.[14]

The remaining crude samples of **5** were split into two pools, one of which was subjected to reduction by borane using the protocol described above. Once again, a small portion of this phenolic propylamine library was purified by mass directed fractionation, resulting in the isolation of compounds **9** in 41–80% overall yield (23–50 mg quantities) and 92–99% purity (Table 2).

Next, the remaining pool of crude material **5** was subjected to conditions for Fujiwara hydroarylation with propiolic acids **7a**−**b**. Analysis and purification (MDF) of the resulting library shows that 46 of the 48 reactions provided product (**8**) in 4–63% overall yield (Scheme 8, Table 3). Moreover, 34 of the library members were isolated in high 92–99% purity. Once again, the somewhat low yields are likely the result of competing formation of dihydrocoumarins from **5** (vida supra). Nonetheless, the method was quite capable of producing the products in substantial (9–42 mg) quantities for biological screening. Analysis of the yield/purity data reveals that dimethylaniline containing dihydrocoumarin **3c** was a poor substrate in this reaction, particularly, when coupled with 2-methypiperidine (**4b**) and morpholine (**4c**); each of these reactions failed to give over 10% yield of hydroarylation products.

In parallel with the reactions of **5**, the phenolic propylamines **9** were treated with propiolic acids **7a**−**d** (Scheme 8). The overall yields for formation of **11** (5–100%, average yield = 31%, Figure 2) were substantially lower than those observed in our demonstration library (average yield = 49%). Once again, we partially attribute this to our emphasis on high compound purity during purification by MDF. However, it is clear from the data that the reactions with propiolic and phenypropiolic acids (left half of Figure 2), which were used in the demonstration library, provided significantly higher yields than reactions involving hydroarylation of alkyl-substituted propiolic acids (right half of Figure 2). Nonetheless, 75 of the 96 library members were obtained in >90% purity and substantial quantity (4–92 mg).[15]

Table 3. Yields and Purities of 3-Coumaryl Propanamides (**8**)[c]

product	yield (%)[a]	purity (%)[b]	product	yield (%)[a]	purity (%)[b]	product	yield (%)[b]	purity (%)[b]	product	yield (%)[a]	purity (%)[b]
8aaa	22	97	**8caa**	5	5	**8aab**	14	96	**8cab**	4	44
8aba	37	99	**8cba**	5	14	**8abb**	16	95	**8cbb**	6	48
8aca	39	96	**8cca**	15	>99	**8acb**	28	92	**8ccb**	20	>99
8ada	30	99	**8cda**	21	83	**8adb**	16	97	**8cdb**	17	97
8aea	51	96	**8cea**	30	>99	**8aeb**	63	95	**8ceb**	47	87
8afa	44	>99	**8cfa**	27	99	**8afb**	44	84	**8cfb**	28	99
8baa	8	46	**8daa**	11	85	**8bab**	4	35	**8dab**	0	-
8bba	18	80	**8dba**	10	94	**8bbb**	7	74	**8dbb**	0	-
8bca	19	95	**8dca**	29	99	**8bcb**	35	98	**8dcb**	21	99
8bda	21	99	**8dda**	22	99	**8bdb**	5	98	**8ddb**	11	97
8bea	28	93	**8dea**	34	99	**8beb**	35	97	**8deb**	36	99
8bfa	27	97	**8dfa**	26	>99	**8bfb**	37	98	**8dfb**	33	95

[a] Isolated after mass-directed fractionation (MDF). [b] Determined by HPLC. [c] Product **8cba** is derived from **3c** + **4b** + **7a**.

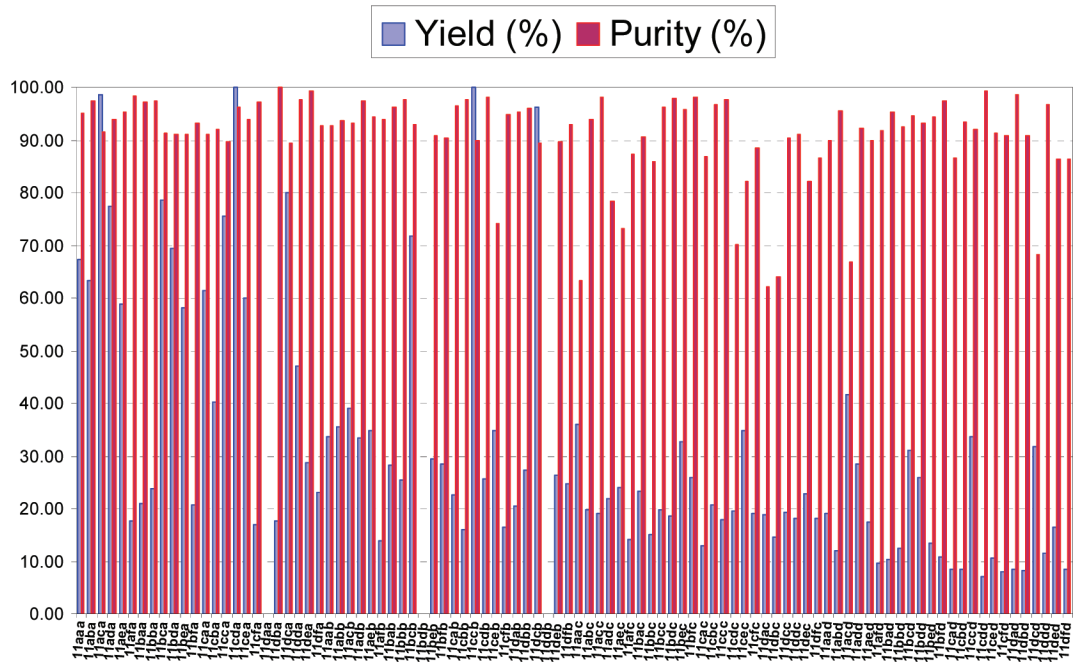
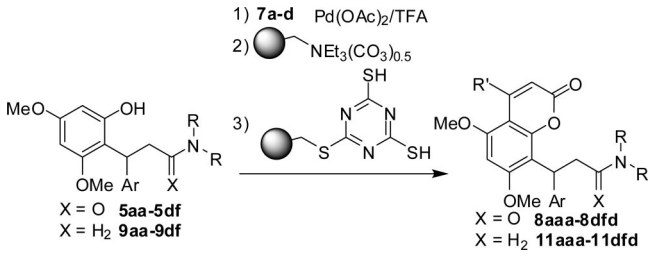


Figure 2. Yields and purities of 8-(3-aminopropyl)coumarins (**11**). See Supporting Information for exact data.

Scheme 8



In conclusion, we have demonstrated that phenols are useful templates for diversification via a hydroarylation, ring-opening, hydroarylation reaction sequence. Two coumarin libraries (48 and 96 members) were prepared using this strategy. In addition, two 24-member libraries of intermediate phenols were produced in the process. Of the possible 192 compounds, 157 were obtained in >90% purity. The biological activity of these compounds is currently being evaluated.

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Supporting Information Available. Experimental details and ^{1}H and ^{13}C NMR spectra of library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Phenols other than 3,5-dimethoxyphenol did not routinely provide high yields in the second hydroarylation. See Supporting Information for details.

(10) NaOH and NaHCO3 washes were used for the large scale purifications.

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(14) The hypothesis that purification is responsible for the low yield is supported by the fact that products **9** are obtained in higher yield than products **5** even though **9** is formed from **5**.

(15) Three compounds were lost because of a collection trigger failure during mass directed fractionation.

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