## Scheme 1


been reported to undergo anion translocation from the ortho position to the benzyl position. ${ }^{19}$

Considering that polystyrene can be lithiated with $n$ butyllithium, one could consider employing other resins. Of the most common commercially available resin alternatives (Tentagel, ${ }^{20}$ Argopore, and PEGA ${ }^{21}$ ), only PEGA does not contain polystyrene. However, PEGA is constructed of secondary amides and tertiary methylamides, which are not compatible with $n$-butyllithium. Newer PEG-based resins from Meldal's group, e.g., SPOCC, ${ }^{22}$ do not contain amide groups, and they should be stable to $n$-butyllithium. Anyway, our attempts to employ the PEG-containing Tentagel failed to yield significant product. While the rigid structure of macroporous resins, like Argopore, should be better suited to supporting ionic species, ${ }^{23}$ we obtained no product from Argopore- $\mathrm{NH}_{2}$. Polytetrahydrofuran cross-linked polystyrene (pTHF-PS) resins ${ }^{14}$ were initially shown to give higher yields in the DoM chemistry, ${ }^{12}$ but because these (pTHFPS) resins were not commercially available at the time of our experiments, ${ }^{24}$ we chose to employ standard aminomethylated divinylbenzene cross-linked polystyrene ( $1 \%$ cross-linked).

In our synthetic route (Scheme 1), aromatic carboxylic acids or acid chlorides (I) are coupled to aminomethylated polystyrene. The corresponding secondary benzamides (II) are then ortho-lithiated with excess $n$-butyllithium, forming a dark dianion. Addition of ketones or aldehydes to the dianion (III) forms an alcohol (IV). When it is heated in toluene at $90{ }^{\circ} \mathrm{C}$, a cyclative cleavage occurs, yielding the desired phthalide ( $\mathbf{V}$ ) without the need of any cleavage reagents.

The synthetic route has the following key factors: (1) The linker used is the most simple linker possible, which minimizes undesired reactions with butyllithium. (2) The directing metalation group functions as the linker such that no additional functionality is required to direct the lithiation. (3) The cleavage of the product occurs via a cyclative mechanism that can only cleave products that have been ortho-lithiated and trapped with the electrophile, thereby producing products of high purity without the need of additional cleavage reagents. (4) The cleavage is of a "traceless" nature, or more correctly stated, the functionality required to attach the first reactant to the resin is an inherent part of the desired product, though it is somewhat hidden. We are in agreement with Bräse and Dahmen ${ }^{25}$ and Maclean

Table 1. Yields from the Optimization Reactions

| Entry | Base (eq.) | Temp. $\left({ }^{\circ} \mathrm{C}\right)$ | Product | Yield ${ }^{\text {a,b }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | PhLi (7) | -10 |  | 6 |
| 2 | " | 0 | " | 11 |
| 3 | " | 10 | " | 15 |
| 4 | " | 25 | " | 34 |
| 5 | $n-\mathrm{BuLi}(7)$ | 0 | " | 34 |
| 6 | " | -20 |  | 18 |
| 7 | $"$ | 0 | " | 27 |
| 8 | " | 20 | " | 18 |
| 9 | $n-\mathrm{BuLi}$ (2) | 0 |  | 8 |
| 10 | $n-\mathrm{BuLi}$ (4) | " | " | 26 |
| 11 | $n-\mathrm{BuLi}$ (6) | " | " | 30 |
| 12 | $n-\mathrm{BuLi}$ (8) | " | " | 32 |
| 13 | $n-\mathrm{BuLi}$ (10) | " | " | 27 |

${ }^{a}$ Isolated yields. ${ }^{b}$ A total of 10 equiv of the ketone was added 5 min after the lithium base, and the mixture was shaken for 30 min at the lithiation temperature, heated to $25^{\circ} \mathrm{C}$, and shaken for an additional 1 h . After the resin was washed, the phthalide was cleaved from the resin by heating to $90^{\circ} \mathrm{C}$ in toluene for 16 h .
et al. ${ }^{26}$ that the term "traceless linker" should be reserved for systems where a $\mathrm{C}-\mathrm{H}$ bond is formed at the site where the compound was attached to the resin, and we suggest the term "hidden linker" for systems such as ours, in which the functionality used to link the compound to the solid support is incorporated into the compound class being synthesized upon cleavage such that the linker is somewhat hidden, though definitely not traceless. ${ }^{27}$ An interesting difference between the cyclative cleavage shown here and those most commonly seen in solid-phase synthesis is that here the weaker nucleophile, the alcohol, is used to displace the amine. In general, the case is just the opposite; an amine is used to displace an alcohol.

Our initial reactions ${ }^{12}$ were performed using sec-butyllithium/TMEDA, but we found that milder conditions, i.e., $n$-butyllithium, gave higher yields. It turned out that even phenyllithium could be used, though at higher temperatures (Table 1, entries 1-5). Because we have not seen any reports of phenyllithium used in ortho-lithiation, we found this result quite interesting. As expected, LDA was not sufficiently basic to deprotonate the system. The reaction also yielded good results using $n$-butyllithium/TMEDA ${ }^{4}$ when toluene was used as the solvent instead of THF.

Temperature conditions for the DoM of secondary benzamides in solution vary from $-78^{\circ} \mathrm{C}$ to reflux in THF, though Hauser et al..$^{28}$ reported that a temperature of $0{ }^{\circ} \mathrm{C}$ was optimal. We found that $0{ }^{\circ} \mathrm{C}$ was also the optimal temperature for our solid-phase system (Table 1, entries 6-8) and that 6- 8 equiv of $n$-butyllithium were necessary to maximize the yield (Table 1, entries 9-13). While $0^{\circ} \mathrm{C}$ is a reasonable temperature for the DoM of secondary benzamides, in general, lithiations are performed at a much colder temperature, usually at $-78^{\circ} \mathrm{C}$. It is most noteworthy that

Table 2. Aryl Carboxylic Acids and Acid Chlorides Used in the DoM Synthesis (1-18)


1


4


7


$13^{a}$


16


2


5



11


14


17




12

15


${ }^{a}$ No product was obtained when this reagent was employed.
Boehm and Showalter ${ }^{11}$ had also employed a temperature of $0^{\circ} \mathrm{C}$ for the DoM of their MOM-protected phenol. Perhaps temperatures of around $0^{\circ} \mathrm{C}$ are required to perform solidphase DoM of arene systems because of the kinetic effects of the resin. We did not observe any increase in yield by increasing the lithiation time from 2 to 30 min , so we chose to use a short lithiation time of 5 min , expecting this would minimize any unwanted reactions between the $n$-butyllithium and the polystyrene. The excess butyllithium (7 equiv) was not washed out from the resin before the addition of the electrophiles, so as to avoid quenching the anions. The excess butyllithium (7 equiv) was countered with the use of excess electrophile (10 equiv) to avoid any further lithiation of the system.

An assortment of aryl carboxylic acids and acid chlorides (Table 2) were coupled to the aminomethylated polystyrene. The corresponding benzamides or pyridinylamides were then tested in the phthalide synthesis. While the reaction worked well with para-substituted benzamides and o-chlorobenzamide (12), benzamides with meta-substitutions did not react well. The sterically hindered benzamide $\mathbf{8}$ did not yield any phthalide. However, the failure of benzamides $\mathbf{3}$ and $\mathbf{1 8}$ was less expected because they are not especially hindered. Most interesting was the failure of $\mathbf{1 0}$ because 3-methoxy benzamides have been shown to lithiate at the 2-position in

## Scheme $\mathbf{2}^{a}$


${ }^{a} \mathbf{A}$ : 4,4'-dichlorobenzophenone (Table 3). ${ }^{b} \mathbf{R}$ : 4-anisaldehyde, (Table 3).
solution ${ }^{29}$ and have been used to synthesize phthalides. ${ }^{30}$ The fine line between steric hindrance and cooperative lithiation can be seen by comparing the products obtained from benzamides 9 and $\mathbf{1 7}$ (Scheme 2). Benzamide 9 is sterically less hindered than $\mathbf{1 0}$ at the 2-position, and the oxygens in the benzo $[1,3]$ dioxole system direct the lithiation to the 2 and 5 positions, though the cooperative effects of the benzamide should lead to a mostly 2 -lithiated species. The product A9 confirms lithiation at the 2-position, though the lower yields obtained would indicate that there is still some steric hindrance or possibly some lithiation at the 5-position. While $\mathbf{1 0}$ is most certainly lithiated at the 2-position (confirmed by the presence of the colored dianion), the added hindrance of the freely rotating methoxy group presumably prevents the lithiated species from reacting with the benzophenone. Because the 3-methyl group of benzamide $\mathbf{1 7}$ is not an ortho-directing group, both C-2 and C-6 lithiation can be envisaged. The isolated product (R17) was formed from the 6-lithiated benzamide, indicating that the 2-lithiated benzamide was too sterically hindered to react with the anisaldehyde ( $\mathbf{R}$ ). In a similar reaction with 3-methyl- $N$ phenylbenzamide ${ }^{31}$ in solution, the C-6 lithiation product was isolated in $75 \%$ yield but no mention of the C-2 lithiation product is made; so whether the 3-methyl group leads to pure C-6 lithiation is not clear. The failure of the 3,5dimethylbenzamide (18) to yield product indicates that there is too much steric hindrance for the addition to occur between the amide and the methyl group.

The lack of reactivity of these meta-substituted benzamides are especially interesting because similar benzamides have been used in the synthesis of phthalides in solution. ${ }^{32}$ Whether these effects are purely due to slower solid-phase kinetics or to steric hindrance from the polystyrene backbone is not clear, though the benzylamide linkage does place the reaction center very close to the polystyrene backbone. The

Table 3. Electrophiles Used in the DoM Synthesis (A- Y)

${ }^{a}$ Mixture of cis and trans isomers. ${ }^{b}$ No product was obtained when these electrophiles were employed.
use of spacers, like poly(ethylene glycol) (PEG), have been shown to decrease the steric hindrance caused by the polystyrene backbone, ${ }^{33}$ so performing the DoM synthesis on a resin with an aliphatic spacer ${ }^{34}$ may yield better results with these meta-substituted benzamides.

An assortment of electrophiles (benzophenones, benzaldehydes, acetophenones, and an epoxide) were tested in the phthalide synthesis (Table 3), and most of the electrophiles reacted successfully in the reaction. Decafluorobenzophenone (F) did not yield any product probably because of electronic effects, and 3,3'-dinitrobenzophenone $(\mathbf{H})$ also failed to yield significant product in the synthesis. However, alkyllithiums are not commonly used together with aromatic nitro compounds because they have been shown to undergo nucleophilic substitution ortho and para to the nitro group. ${ }^{35}$ The presence of chlorines ortho to the nitro groups apparently counters the effect of the nitro groups, and we found that 3,3'-dinitro-4,4'-dichlorobenzophenone (I) yielded the desired phthalides in high purity, though in relatively lower yields. An attempt to use tetrahydroxybenzophenone (J) as its tetralithium salt failed to yield any product, and the tetra-TBDMS-protected version of ( $\mathbf{J}$ ) also failed to react most likely because of steric hindrance. The reaction with the fused system ( $\mathbf{L}$ ) also failed in the reaction despite the success of similar reactions in solution, ${ }^{36}$ and the epoxide (M) did not yield the desired isocoumarin. ${ }^{30}$ While anisaldehyde (R) produce a reasonable yield (23\%), the tertiary aminobenzaldehydes ( $\mathbf{P}$ and $\mathbf{Q}$ ) reacted poorly, providing on average $12 \%$
yield (Table 5). Interestingly, several acetophenones were successful in yielding the desired phthalides, indicating that the addition reaction is faster than the enolization. While there are examples of similar reactions in which the electrophiles contained R-protons, ${ }^{37}$ one would generally transmetalate ${ }^{38}$ the lithiated species to avoid enolate formation. Some enolate formation may indeed occur, yielding the starting benzamide, though this does not lead to any byproducts in the cleaved product due to the phthalidespecific cyclative cleavage. While the addition to acetone $(\mathbf{Y})$ was possible, no product was obtained from reactions with other simple aliphatic ketones or aldehydes (propionaldehyde, hexanal, cyclohexanone, 2,6-dimethyl-heptan-4-one, 4-methyl-pentan-2-one, and nonan-5-one).

Because we had previously shown that heterocyclic aldehydes could be employed in the synthesis, ${ }^{12}$ we wanted to see if heterocyclic acids and acid chlorides could be employed; therefore, nicotinic acid (13) and isonicotinoyl chloride hydrochloride (14) were tested in the synthesis. The nicotinic acid (13) did not yield any product. However, isonicotinoyl chloride hydrochloride (14) worked quite well, with an average yield of $31 \%$ (Table 4).

Thirteen phthalides were synthesized while examining the scope of this method, and their structures are shown in Table 4. A library of phthalides was synthesized by crossing seven aryl carboxylic acids or acid chlorides with 12 electrophiles (Table 5). The crude products were analyzed by ${ }^{1} \mathrm{H}$ NMR, and many of the compounds were also characterized by liquid

Table 4. Structures and Yields of Phthalides Synthesized To Examine the Scope of the DoM Reaction


Table 5. Isolated Yields of Phthalide Library Synthesized from Aryl Carboxylic Acids and Acid Chlorides 1-9 and Electrophiles A- Q

|  | benzamide resin |  |  |  |  |  |  |  |
| :---: | :---: | ---: | ---: | ---: | ---: | ---: | ---: | :--- |
| electrophile | $\mathbf{1}$ | $\mathbf{2}$ | $\mathbf{4}$ | $\mathbf{5}$ | $\mathbf{6}$ | $\mathbf{7}$ | $\mathbf{9}$ | average $^{a}(\%)$ |
| $\mathbf{A}$ | 21 | 55 | 69 | 59 | 48 | 52 | 17 | 46 |
| $\mathbf{B}$ | 24 | $30^{b}$ | 59 | 19 | $43^{b}$ | $41^{b}$ | $7^{b}$ | 32 |
| $\mathbf{C}$ | 49 | 50 | 63 | 49 | 48 | 41 | $11^{b}$ | 44 |
| $\mathbf{D}$ | 23 | 53 | 68 | 43 | 35 | 46 | $6^{b}$ | 39 |
| $\mathbf{E}$ | 32 | 48 | 70 | 56 | 47 | 50 | 10 | 45 |
| $\mathbf{G}$ | 14 | 49 | 62 | 0 | 42 | 41 | 52 | 37 |
| $\mathbf{I}$ | 13 | 15 | 19 | 30 | 12 | 14 | 29 | 19 |
| $\mathbf{K}$ | 28 | 51 | 65 | 38 | 52 | 50 | 4 | 41 |
| $\mathbf{N}$ | 52 | 76 | $2^{b}$ | 50 | 48 | 48 | 7 | 40 |
| $\mathbf{O}$ | 61 | 60 | 70 | 51 | 48 | 47 | 5 | 49 |
| $\mathbf{P}$ | $\mathbf{N A}^{c}$ | 8 | 16 | 20 | 0 | 10 | 16 | 12 |
| $\mathbf{Q}$ | 19 | 10 | 16 | 17 | 4 | 6 | 14 | 12 |
| average $(\%)$ | 31 | 42 | 48 | 36 | 36 | 37 | 15 | 35 |

[^0]chromatography- mass spectrometry (LCMS) and ${ }^{13} \mathrm{C}$ NMR. The average purity was $93 \%$ as determined by LCMS- ELS (energy loss spectroscopy) analysis of 44 library members.

## Scheme 3



While the overall average yield of $35 \%$ is quite modest, higher yields have been shown to be attainable on polytetrahydrofuran cross-linked polystyrene resins. ${ }^{12}$ Furthermore, the yields for DoM reactions performed in solution are generally quite modest, 40-70\%, ${ }^{3}$ and while more extensive metalation has been reported to occur using small amounts of THF in $n$-hexane, ${ }^{39}$ these conditions are not compatible with polystyrene-based resins because these resins do not swell in $n$-hexane.

Since the techniques of lithium- halogen exchange ${ }^{8}$ and iodine- magnesium exchange ${ }^{40}$ have been demonstrated on solid-phase and are useful in the synthesis of phthalides, these methods were also investigated (Scheme 3) using 2-iodobenzoic acid (16). The lithium- iodine exchange reaction worked as well as the DoM reaction, producing $4 \%, 30 \%$, and $35 \%$ yield when 2,5 , and 7 equiv of $n$-butyllithium were employed, respectively. Considering that these results resemble those of the DoM synthesis, it is possible that the reaction may in fact be occurring via an in situ DoM reaction. If the $\mathrm{Li}-\mathrm{I}$ exchange is faster than the deprotonation of the secondary benzamide, an intramolecular proton transfer may occur, protonating the ortho-position, and this ortho-position would subsequently be lithiated via DoM with the next equivalent $n$-butyllithium. The intramolecular proton transfer could be circumvented by either using tertiary benzamides amides or by first removing the amide proton with a different base (e.g., LDA or NaH ) prior to the lithium- halogen exchange. These methods were, however, not investigated because the usefulness of the lithium- iodine exchange reaction for the synthesis of phthalides is quite limited, given our success with the DoM reaction. In contrast, the magne-sium- iodine exchange reaction would allow the use of functionalities that cannot tolerate the basicity and nucleophilicity of $n$-butyllithium and is therefore an interesting supplement to the DoM synthesis. Our magnesium- iodine exchange reaction produced only $12 \%$ yield, but considering that the reaction was not optimized, we are optimistic about the use of this technique for the synthesis of more diverse phthalides.

Attempts to perform the phthalide synthesis using other linkers were also made but were not very fruitful. The reaction using a MBHA linker failed to yield appreciable product. Some success was achieved using a DHP linker ${ }^{41}$ with a 2-aminoethanol spacer (Scheme 4). While the cyclic cleavage via heating in dioxane only produced around $3 \%$ of the desired phthalide (R7), cleavage of the THP linkage with pyridinium $p$-toluenesulfonate (PPTS) produced a 7:1 mixture of VI and VII, equivalent to $6 \%$ of the DoM product. While the failure of MBHA may be explained by steric effects, the low conversion of the DHP linker with the 2-aminoethanol spacer cannot because it appears to be less hindered than both the MBHA linkage and the benzylamine

## Scheme $4^{a}$


${ }^{a}$ Reagents: (a) PPTS \& $\mathrm{HO}\left(\mathrm{CH}_{2}\right)_{2} \mathrm{NH}-\mathrm{Fmoc}$; (b) $20 \%$ piperidine/DMF; (c) 4-isopropylbenzoic acid and 1,3-diisopropyl carbodiimide; (d) $n$ - BuLi ; (e) 4-anisaldehyde; (f) PPTS.
linkage. This leads us to suspect that the oxygens of the THP moiety may interfere with the DoM of the benzamide. Regardless of the cause, the failure of these linkers substantiate our original assumption, namely, that linkers of low complexity are desirable for solid-phase DoM because they minimize unwanted interactions.

## Conclusion

Conditions for the solid-phase DoM of benzamides have been described, and when combined with a cyclative cleavage, phthalides of high purity can be synthesized. Compared to what is commonly performed in solution, higher temperatures and milder bases were found to be advantageous. The phthalide synthesis was demonstrated to perform well with a variety of benzophenones, acetophenones, and aryl aldehydes. Resin-bound benzamides possessing meta substitutions were observed to be much less reactive than those reported in solution reactions. The method was further investigated by the parallel synthesis of 100 well-defined phthalides. Solid-phase methods for the synthesis of phthalides via lithium- iodine exchange and magnesium- iodine exchange were also shown to be feasible.

## Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Butyllithium in hexanes was purchased from Aldrich, and their concentrations were determined using N -pivaloyl- $o$-toluidine. ${ }^{42}$ Tetrahydrofuran was distilled from sodium/benzophenone under $\mathrm{N}_{2} .{ }^{1} \mathrm{H}$ NMR and protondecoupled ${ }^{13} \mathrm{C}$ NMR spectra were recorded on a Varian 400 MHz instrument in $\mathrm{CDCl}_{3}$ unless otherwise noted. Proton and carbon chemical shifts are reported in ppm using residual $\mathrm{CHCl}_{3}$ as an internal standard at 7.26 and 77.0 ppm , respectively. Unless otherwise stated, reactions were performed under $\mathrm{N}_{2}$ in oven-dried glass test tubes fitted with a septum, and the reactions were mixed using an orbital shaker. Resins were washed or filtered off using syringes equipped with polypropylene frits. Note that Teflon reactors with Teflon frits were tested but gave reduced yields.

General Method for Coupling Aryl Carboxylic Acids to AM-PS Resin. A 100 mL round-bottom flask equipped with a magnetic stirrer was charged with $2.0 \mathrm{~g}(1.13 \mathrm{mmol} /$ $\mathrm{g}, 2.26 \mathrm{mmol}$ ) of aminomethylated polystyrene ( $1 \% \mathrm{DVB}$ )
resin (AM-PS) and dichloromethane ( 30 mL ). After 5 min , the aryl acid ( 11.3 mmol ) was added, followed by $1,3-$ diisopropylcarbodiimide ( 11.3 mmol ). After 2 h at room temperature with gentle stirring, the resin was washed with DCM, DMF, MeOH, and $n$-hexane ( 40 mL of each solvent) and dried in vacuo. If the resin tested positive in a Kaiser amine test, ${ }^{43}$ the coupling was repeated until a negative test was obtained.

General Method for Coupling Aryl Acid Chlorides to AM-PS Resin. A 100 mL round-bottom flask equipped with a magnetic stirrer was charged with $2.0 \mathrm{~g}(1.13 \mathrm{mmol} / \mathrm{g}, 2.26$ $\mathrm{mmol})$ of AM-PS resin and dichloromethane ( 30 mL ). After 5 min , triethylamine ( 11.3 mmol ) was added followed by the aryl acid chloride ( 11.3 mmol ). After 2 h at room temperature with gentle stirring, the resin was washed, dried, and tested for free amines as described above.

General Method for the Parallel Synthesis of Phthalides via DoM. Benzamide resin ( 0.10 mmol ) was placed in a dry test tube and swelled in dry THF ( 2 mL ). The reaction mixture was cooled to $0^{\circ} \mathrm{C}$ while shaking at 600 rpm , and n-butyllithium ( $0.7 \mathrm{mmol}, 1.6 \mathrm{M}$ in hexanes) was added. After 5 min the ketone ( 1.0 mmol ) was added (in 1 mL of THF if soluble; otherwise, it is added as a solid together with 1 mL of THF) and the reaction mixture was shaken for an additional 30 min at $0^{\circ} \mathrm{C}$. The mixture was then heated to $25^{\circ} \mathrm{C}$, and after 1 h , methanol ( $200 \mu \mathrm{~L}$ ) was added. The resin was washed with THF, DCM, DMF, MeOH, and $n$-hexane ( 10 mL of each solvent). The resin was heated to $90^{\circ} \mathrm{C}$ in toluene, shaken at 200 rpm for 16 h , and filtered, and the filtrate was concentrated on a vacuum centrifuge to yield the phthalide. The phthalides were analyzed by ${ }^{1} \mathrm{H}$ NMR and were generally found to be greater than $90 \%$ pure. Residual toluene detected via ${ }^{1} \mathrm{H}$ NMR was subtracted from the yields and was found to be avoidable by performing the cleavage in dioxane at $85^{\circ}$ for 16 h . Data for the phthalides are listed below.

Preparation of Phthalide A16 via Lithium- Halogen Exchange. The same procedure as above was followed using 2-iodobenzamide resin 16 ( $0.10 \mathrm{mmol}, 0.90 \mathrm{mmol} / \mathrm{g}$ ) and 4,4'-dichlorobenzophenone (A). Removal of the solvent yielded 12.6 mg ( $35 \%$ yield) of the phthalide $\mathbf{A 1 6}$.

Preparation of Phthalide A16 via Magnesium- Iodine Exchange. 2-Iodobenzamide resin 16 ( $0.10 \mathrm{mmol}, 0.90$ $\mathrm{mmol} / \mathrm{g}$ ) was swollen in THF ( 2 mL ) and cooled to - 30 ${ }^{\circ} \mathrm{C}$. Isopropylmagnesium chloride ( $0.7 \mathrm{mmol}, 2 \mathrm{M}$ in THF) was added while shaking the reaction mixture at 600 rpm . After the reaction mixture was shaken at $-30^{\circ} \mathrm{C}$ for 30 min , $4,4^{\prime}$-dichlorobenzophenone (A) ( 1.0 mmol in 1 mL THF) was added. The mixture was shaken at $-30^{\circ} \mathrm{C}$ for 30 min , heated to $25{ }^{\circ} \mathrm{C}$, and shaken an additional hour. After methanol $(200 \mu \mathrm{~L})$ was added, the resin was washed and cleaved as described in the DoM synthesis. Removal of the solvent yielded 4.2 mg ( $12 \%$ yield) of the phthalide A16.
Extension and Benzamidation of the DHP Linker. A 100 mL round-bottom flask was charged with DHP-resin $2.0 \mathrm{~g}(0.98 \mathrm{mmol} / \mathrm{g}, 1.96 \mathrm{mmol})$ and dichloroethane $(30 \mathrm{~mL})$. After $5 \mathrm{~min}, \mathrm{~N}$-Fmoc-ethanolamine $(1.67 \mathrm{~g}, 5.88 \mathrm{mmol})$ and pyridinium $p$-toluenesulfonate (PPTS) $(0.49 \mathrm{~g}, 1.96 \mathrm{mmol})$ were added. After refluxing for 48 h the resin was filtered
off, washed with DCM $(4 \times 20 \mathrm{~mL})$, DMF, MeOH , and $n$-hexane ( 25 mL of each of the last three solvents), and dried in vacuo at $50^{\circ} \mathrm{C}$. The resin was then gently stirred in $20 \%$ piperidine/DMF for 4 h , filtered off, and washed. The benzamide was formed using 7, and the procedure above for arylcarboxylic acids was employed two times to obtain a negative Kaiser test.

Cleavage of the DHP Linkage. The resin above ( 0.1 mmol, $0.82 \mathrm{mmol} / \mathrm{g}$ ) was placed in a test tube, and 1:1 DCE/ tert-butyl alcohol ( 2 mL ) and PPTS ( $75 \mathrm{mg}, 0.3 \mathrm{mmol}$ ) were added. The mixture was shaken at 200 rpm at $60^{\circ} \mathrm{C}$ for 16 h. The resin was filtered off and washed with ethyl acetate $(20 \mathrm{~mL})$. The filtrate was washed with $\mathrm{NaOH}(2 \times 20 \mathrm{~mL})$ and $\mathrm{HCl}(2 \times 20 \mathrm{~mL})$ and dried over $\mathrm{MgSO}_{4}$. The solvent was removed in vacuo, and the residue was dried in vacuo at $50{ }^{\circ} \mathrm{C}$ to yield $8.4 \mathrm{mg}(41 \%)$ of VI. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.24(\mathrm{~d}$, $J$ ) $6.8,6 \mathrm{H}), 2.93(\mathrm{sept}, J) 6.8,1 \mathrm{H}), 3.15(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 3.61 (br s, 2 H ), $3.81(\mathrm{t}, J$ ) 4.8, 2 H ), $7.26(\mathrm{~d}, J) 8.4,2$ $\mathrm{H}), 7.72(\mathrm{~d}, J)$ 8.0, 2 H ). ${ }^{13} \mathrm{C}$ NMR: $\delta 23.8,34.1,43.0$, 62.4, 126.6, 127.1, 131.2, 152.9, 168.6. LCMS: m/z 208 $\left(\mathrm{MH}^{+}\right)$.

Spectral Data for Phthalides Compounds. Product identification by the benzamide (1-14) and the ketone (A$\mathbf{Y}$ ) was employed. Phthalides not listed here can be found in the Supporting Information.

N1. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.36(\mathrm{~s}, 9 \mathrm{H}), 6.94(\mathrm{~d}, J) 9.2,2 \mathrm{H}\right)$, $7.02(\mathrm{~d}, J) 8.8,2 \mathrm{H}), 7.11-7.15(\mathrm{~m}, 1 \mathrm{H}), 7.23-7.28(\mathrm{~m}$, $2 \mathrm{H}), 7.32-7.38(\mathrm{~m}, 7 \mathrm{H}), 7.53(\mathrm{dd}, J) \quad 0.8,1.2,1 \mathrm{H}), 7.61$ (dd, $J$ ) $1.6,8.0,1 \mathrm{H}$ ), $7.86(\mathrm{dd}, J) \quad 0.8,8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 31.3,35.7,91.3,118.0,119.4,120.5,123.0,123.7$, $125.4,126.8,127.0,128.3,128.4,128.9,129.7,135.4,141.1$, 152.1, 156.3, 157.6, 158.5, 169.5. LCMS: $m / z 435\left(\mathrm{MH}^{+}\right)$.

O1. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.37(\mathrm{~s}, 9 \mathrm{H}), 5.06(\mathrm{~s}, 2 \mathrm{H}), 6.92(\mathrm{~d}, J)$ $8.4,2 \mathrm{H}), 7.22(\mathrm{~d}, J) \quad 9.2,2 \mathrm{H}), 7.33-7.41(\mathrm{~m}, 10 \mathrm{H})$, 7.52- $7.53(\mathrm{~m}, 1 \mathrm{H}), 7.60(\mathrm{dd}, J) \quad 0.8,8.4,1 \mathrm{H}), 7.85(\mathrm{dd}$, J) $0.8,8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 31.3,35.7,70.1,91.5,114.5$, $123.0,125.3,126.8,126.9,127.3,127.9,128.2,128.3,128.5$, 128.7, 133.4, 136.6, 141.3, 152.3, 158.4, 158.7, 169.6. LCMS: m/z $449\left(\mathrm{MH}^{+}\right)$.

S1. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.35$ (s, 9 H ), 3.16- 3.19 (m, 4 H ), 3.86 (s, 4 H), 6.87 (br s, 2 H), 7.19 (d, J ) 8.8, 2 H), 7.35- 7.38 (m, 5 H$), 7.50(\mathrm{~s}, 1 \mathrm{H}), 7.58(\mathrm{dd}, J) \quad 1.6,8.0,1 \mathrm{H}), 7.84(\mathrm{~d}$, $J$ ) 8.0, 1 H$).{ }^{13} \mathrm{C}$ NMR: $\delta 31.4,35.7,48.9,66.7,91.6$, $114.9,120.4,120.5,123.0,125.3,126.8,128.1,128.3,128.4$, 141.3, 152.3, 158.3, 169.7. LCMS: m/z $428\left(\mathrm{MH}^{+}\right)$.

T1. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.35$ ( $\mathrm{s}, 9 \mathrm{H}$ ), 2.01 ( $\mathrm{s}, 3 \mathrm{H}$ ), 3.79 ( $\mathrm{s}, 3$ H), 6.87 (d, J ) 9.2, 2 H ), 7.33 (d, J ) 8.8, 2 H ), 7.377.37 (m, 1 H ), 7.56 (dd, $J$ ) 1.6, 8.0, 1 H ), 7.81 (dd, J ) $0.8,8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 27.4,31.4,35.7,55.3,87.5$, $113.9,118.3,118.4,122.6,125.2,126.6,126.7,132.8,154.5$, 158.6, 159.3, 169.8. LCMS: m/z 311 ( $\mathrm{MH}^{+}$).

U1. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.35$ (s, 9 H ), 2.02 (s, 3 H ), 2.33 ( $\mathrm{s}, 3$ H), 7.16 (d, J ) 8.0, 2 H ), 7.32 (d, J ) 8.4, 2 H ), 7.39 (dd, J ) $0.8,1.6,1 \mathrm{H}), 7.55(\mathrm{dd}, J) \quad 1.6,8.0,1 \mathrm{H}), 7.81(\mathrm{dd}, J$ ) $0.8,8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 21.1,21.1,27.4,27.4,31.3$, $31.3,35.7,87.5,118.3,118.3,122.5,125.0,125.2,126.7$, 129.2, 137.9, 138.0, 154.5, 158.5, 169.8. LCMS: m/z 295 $\left(\mathrm{MH}^{+}\right)$.

Y1. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.38$ ( $\mathrm{s}, 9 \mathrm{H}$ ), 1.66 ( $\mathrm{s}, 6 \mathrm{H}$ ), 7.34 ( $\mathrm{s}, 1$ H), $7.54(\mathrm{dd}, J) \quad 1.6,8.4,1 \mathrm{H}), 7.78(\mathrm{~d}, J) \quad 8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 27.5,31.4,35.7,85.3,116.8,116.9,122.6,125.2$, 126.6, 155.2, 158.4, 169.7. LCMS: m/z $219\left(\mathrm{MH}^{+}\right)$.

N2. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.36(\mathrm{~d}, J) 6.0,6 \mathrm{H}\right), 4.64$ (sept, $J$ ) $6.0,1 \mathrm{H}), 6.93-6.95(\mathrm{~m}, 3 \mathrm{H}), 7.00-7.03(\mathrm{~m}, 3 \mathrm{H}), 7.12(\mathrm{t}$, J ) 7.2, 1 H ), 7.26- $7.29(\mathrm{~m}, 2 \mathrm{H}), 7.32-7.40(\mathrm{~m}, 7 \mathrm{H})$, $7.83(\mathrm{~d}, J) 8.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 21.9,70.8,90.5,110.2$, $116.9,117.3,118.0,119.3,123.7,126.8,127.5,128.3,128.4$, $128.9,129.7,135.3,141.0,154.5,156.3,157.6,162.9,169.2$. LCMS: $m / z 437\left(\mathrm{MH}^{+}\right)$.

O2. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.37$ (dd, $J$ ) 1.2, $6.0,6 \mathrm{H}$ ), 4.63 (sept, J ) $6.0,1 \mathrm{H}), 5.06(\mathrm{~s}, 2 \mathrm{H}), 6.91-6.94(\mathrm{~m}, 3 \mathrm{H}), 7.00(\mathrm{dd}$, J) $2.0,8.8,1 \mathrm{H}), 7.24(\mathrm{~d}, J) 9.2,2 \mathrm{H}), 7.32-7.41(\mathrm{~m}, 10$ H), $7.82(\mathrm{~d}, J) \quad 8.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 21.9,70.1,70.8$, 90.7, 110.2, 114.6, 116.9, 117.4, 126.8, 127.3, 127.4, 127.9, 128.2, 128.3, 128.5, 128.7, 133.2, 136.6, 141.2, 154.7, 158.7, 162.8, 169.3. LCMS: $m / z 451\left(\mathrm{MH}^{+}\right)$.

D4. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.15(\mathrm{t}, J) 6.8,6 \mathrm{H}\right), 3.34(\mathrm{q}, J) 6.8$, $4 \mathrm{H}), 6.60(\mathrm{~d}, J) 9.2,2 \mathrm{H}), 7.13(\mathrm{~d}, J) \quad 8.8,2 \mathrm{H}), 7.32-$ 7.37 (m, 3 H ), $7.43(\mathrm{~d}, J) 6.8,1 \mathrm{H}), 7.44-7.48(\mathrm{~m}, 4 \mathrm{H})$, 7.60-7.62 (m, 2 H ), 7.72- 7.72 (m, 1 H ), 7.75 (dd, J) 1.6, 8.0, 1 H ), 7.98 (d, $J$ ) 8.0, 1 H ). ${ }^{13} \mathrm{C}$ NMR: $\delta 12.6,44.3$, 92.3, 110.9, 122.5, 124.5, 126.0, 126.5, 126.8, 127.5, 128.0, 128.3, 128.4, 128.8, 128.9, 139.7, 141.5, 147.1, 147.7, 153.4, 169.7. LCMS: $m / z 434\left(\mathrm{MH}^{+}\right)$.

E4. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 6.97(\mathrm{~d}, J) \quad 8.8,4 \mathrm{H}\right), 7.03(\mathrm{~d}, J) \quad 8.4$, $4 \mathrm{H}), 7.13(\mathrm{t}, J) \quad 7.6,2 \mathrm{H}), 7.33-7.37(\mathrm{~m}, 8 \mathrm{H}), 7.44-7.52$ (m, 3 H ), 7.60-7.63 (m, 2 H$)$, 7.71- 7.71 (m, 1 H$), 7.79$ (dd, $J$ ) 1.2, 8.0, 1 H ), $8.01(\mathrm{~d}, J) \quad 7.6,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 91.2,118.1,119.4,122.4,123.8,124.3,126.3,127.5,128.7$, 129.0, 129.7, 135.2, 139.4, 147.5, 152.8, 156.2, 157.7, 169.3. LCMS: $m / z 547\left(\mathrm{MH}^{+}\right)$.

K4. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 3.80(\mathrm{~s}, 6 \mathrm{H}), 6.87(\mathrm{~d}, J) 8.8,4 \mathrm{H}\right)$, $7.30(\mathrm{~d}, J) \quad 8.8,4 \mathrm{H}), 7.41-7.48(\mathrm{~m}, 3 \mathrm{H}), 7.59-7.61(\mathrm{~m}$, $2 \mathrm{H}), 7.67$ (dd, $J$ ) $0.4,1.6,1 \mathrm{H}$ ), 7.75 (dd, $J$ ) 1.6, 8.0, 1 H), 7.98 (dd, $J$ ) $0.4,8.0,1 \mathrm{H}$ ). ${ }^{13} \mathrm{C}$ NMR: $\delta 55.3,91.6$, 113.7, 122.3, 124.3, 126.1, 127.5, 128.4, 128.5, 128.5, 129.0, 133.0, 139.6, 147.3, 153.3, 159.5, 169.5. LCMS: m/z 423 $\left(\mathrm{MH}^{+}\right)$.

O4. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 5.07(\mathrm{~s}, 2 \mathrm{H}), 6.95(\mathrm{~d}, J) 9.2,2 \mathrm{H}\right)$, 7.29 (d, J ) 8.8, 2 H), 7.35- 7.51 (m, 13 H), 7.61 (dd, J) $1.2,8.0,2 \mathrm{H}), 7.71-7.72(\mathrm{~m}, 1 \mathrm{H}), 7.77(\mathrm{dd}, J) 1.2,8.0$, $1 \mathrm{H}), 8.00(\mathrm{dd}, J) \quad 0.8,8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 70.1,91.5$, 114.6, 122.4, 124.3, 126.2, 126.9, 127.3, 127.5, 127.9, 128.3, $128.4,128.5,128.5,128.6,128.7,129.0,133.0,136.5,139.5$, 141.0, 147.3, 152.9, 158.8, 169.4. LCMS: m/z $469\left(\mathrm{MH}^{+}\right)$.

O5. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 5.07(\mathrm{~s}, 2 \mathrm{H}), 6.95(\mathrm{~d}, J) 9.2,2 \mathrm{H}\right)$, 7.19 (d, J ) 8.8, 2 H ), 7.33-7.43 (m, 10 H ), 7.80 (d, J) $0.8,1 \mathrm{H}$ ), 7.83 (dd, $J$ ) $0.8,8.0,1 \mathrm{H}$ ), 8.06 (dd, $J$ ) 0.8 , $8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 70.1,91.9,114.9,121.1(\mathrm{q}, J)$ 3.9), 126.6, 126.6, 126.7, 126.7, 127.3, 128.0, 128.5, 128.6, 128.7, 132.1, 135.7 (q, $J$ ) 32), 136.4, 140.1, 152.6, 159.1, 168.1. LCMS: m/z $461\left(\mathrm{MH}^{+}\right)$.

A6. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.18(\mathrm{t}, J) 7.2,6 \mathrm{H}\right), 3.41(\mathrm{q}, J) 7.2$, $4 \mathrm{H}), 6.45(\mathrm{~d}, J) \quad 2.4,1 \mathrm{H}), 6.75(\mathrm{dd}, J$ ) $2.0,9.2,1 \mathrm{H})$, 7.28-7.30 (m, 8 H$), 7.70(\mathrm{~d}, J) \quad 9.6,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta$ $12.4,45.1,89.2,103.9,111.1,112.8,127.4,128.5,134.4$, 139.8, 152.12, 154.1, 169.4. LCMS: $m / z 426\left(\mathrm{MH}^{+}\right)$.

E6. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.16(\mathrm{t}, J) 7.2,6 \mathrm{H}\right), 3.42(\mathrm{q}, J) 7.2$, $4 \mathrm{H}), 6.53(\mathrm{~d}, J) \quad 2.0,1 \mathrm{H}), 6.75(\mathrm{dd}, J) 2.4,8.8,1 \mathrm{H})$, 6.95 (d, J ) 8.8, 4 H), 7.01 (d, J ) 7.6, 4 H), 7.11 (t, J ) 8.8, 2 H ), 7.32- $7.36(\mathrm{~m}, 8 \mathrm{H}), 7.71(\mathrm{~d}, J) 8.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 12.4,45.1,90.0,104.3,112.6,118.0,119.2,123.6$, 127.2, 128.7, 129.7, 136.2, 151.9, 154.9, 156.5, 157.3, 169.8. LCMS: m/z $542\left(\mathrm{MH}^{+}\right)$.

G6. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.21(\mathrm{t}, J) 7.6,6 \mathrm{H}\right), 3.44(\mathrm{q}, J) 7.2$, $4 \mathrm{H}), 6.46(\mathrm{~d}, J) 2.0,1 \mathrm{H}), 6.84(\mathrm{dd}, J) 2.4,8.8,1 \mathrm{H})$, 7.77 (d, J ) 8.8, 1 H ), 7.82 (s, 4 H ), 7.92 ( $\mathrm{s}, 2 \mathrm{H}$ ). ${ }^{13} \mathrm{C}$ NMR: $\delta 12.1,45.4,87.3,103.1,110.2,113.8,118.7,121.4$, 123.0, 124.1, 125.2, 127.0, 128.1, 128.2, 128.9, 132.3 (q, $J$ ) 3.5), 143.1, 151.9, 152.6, 165.2, 168.0. LCMS: $m / z 630$ $\left(\mathrm{MH}^{+}\right)$.

K6. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.18(\mathrm{t}, J) 7.2,6 \mathrm{H}\right), 3.40(\mathrm{q}, J) 7.2$, $4 \mathrm{H}), 3.79(\mathrm{~s}, 6 \mathrm{H}), 6.50(\mathrm{~d}, J) 2.0,1 \mathrm{H}), 6.73(\mathrm{dd}, J) 2.4$, $8.8,1 \mathrm{H}), 6.84(\mathrm{~d}, J) 8.8,4 \mathrm{H}), 7.28(\mathrm{~d}, J$ ) $8.8,4 \mathrm{H}$ ), 7.69 (d, $J$ ) 8.8,1 H). ${ }^{13} \mathrm{C}$ NMR: $\delta 12.4,45.1,55.3,104.3$, 112.5, 113.5, 127.1, 128.5, 133.9, 151.8, 155.4, 159.3, 170.1. LCMS: m/z $418\left(\mathrm{MH}^{+}\right)$.

N6. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.18(\mathrm{t}, J) 7.2,6 \mathrm{H}\right), 3.41(\mathrm{q}, J) 7.2$, $4 \mathrm{H}), 6.55(\mathrm{~d}, J$ ) $2.4,1 \mathrm{H}), 6.74$ (dd, J ) $2.0,8.8,1 \mathrm{H}$ ), 7.94 (d, J ) 8.4, 2 H), 7.01 (d, J ) 7.6, 2 H), 7.11 (t, J ) 7.6, 1 H ), 7.30- 7.35 (m, 7 H ), 7.40- 7.42 (m, 2 H ), 7.71 (d, $J$ ) 8.8, 1 H ). ${ }^{13} \mathrm{C}$ NMR: $\delta 12.4,45.1,90.2,104.4,112.6$, 118.0, 119.2, 123.5, 126.9, 127.2, 128.1, 128.2, 129.0, 129.7, 136.1, 141.7, 151.9, 154.8, 156.5, 157.3, 169.9. LCMS: $m / z$ $450\left(\mathrm{MH}^{+}\right)$.

O6. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.18(\mathrm{t}, J) 7.2,6 \mathrm{H}\right), 3.41(\mathrm{q}, J) 7.2$, $4 \mathrm{H}), 5.05(\mathrm{~s}, 2 \mathrm{H}), 6.54(\mathrm{~d}, J) \quad 2.0,1 \mathrm{H}), 6.74(\mathrm{dd}, J) 2.4$, $8.8,1 \mathrm{H}), 6.92(\mathrm{~d}, J) \quad 8.4,2 \mathrm{H}), 7.26-7.42(\mathrm{~m}, 12 \mathrm{H}), 7.70$ (d, $J$ ) 8.8, 1 H ). ${ }^{13} \mathrm{C}$ NMR: $\delta 12.4,45.1,70.0,90.3,104.5$, 112.6, 114.4, 126.9, 127.1, 127.3, 127.9, 128.0, 128.1, 128.5, $128.8,133.9,136.7,141.9,151.8,155.0,158.6,170.0$. LCMS: $m / z 464\left(\mathrm{MH}^{+}\right)$.

A7. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.32(\mathrm{~d}, J) 6.8,6 \mathrm{H}\right), 3.07$ (sept, $J$ ) $6.8,1 \mathrm{H}), 7.27(\mathrm{~d}, J) 8.8,4 \mathrm{H}), 7.33(\mathrm{~d}, J) 9.2,5 \mathrm{H})$, 7.48 (dd, $J$ ) 1.2, 7.6, 1 H ), 7.88 (d, $J$ ) 8.0, 1 H ). ${ }^{13} \mathrm{C}$ NMR: $\delta 23.9,34.8,90.2,121.6,123.2,126.1,128.3,128.4$, 128.7, 134.7, 139.2, 151.5, 156.6, 169.0. LCMS: m/z 397 $\left(\mathrm{MH}^{+}\right)$.

D7. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.15(\mathrm{t}, J) 7.2,6 \mathrm{H}$ ), $1.29(\mathrm{dd}, J) 1.2$, $7.2,6 \mathrm{H}), 3.02$ (sept, $J$ ) $6.8,1 \mathrm{H}$ ), $3.33(\mathrm{q}, J) 6.8,4 \mathrm{H}$ ), 6.58 (d, J ) 8.8, 2 H ), 7.07 (d, J ) 9.2, 2 H ), 7.30- 7.33 (m, 3 H ), $7.39(\mathrm{~d}, J) 8.0,1 \mathrm{H}$ ), 7.43 (dd, $J$ ) 1.2, 7.6, 2 H), $7.82(\mathrm{~d}, J) \quad 7.6,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 12.6,23.9,34.8$, $44.3,80.7,92.1,110.9,121.9$. 123.6, 125.6, 126.8, 127.5, $127.9,128.2,128.8,141.7,147.6,153.1,155.8,169.9$. LCMS: $m / z 400\left(\mathrm{MH}^{+}\right)$.

E7. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.30(\mathrm{~d}, J) 7.2,6 \mathrm{H}$ ), 3.04 (sept, $J$ ) $6.8,1 \mathrm{H}), 6.95(\mathrm{~d}, J$ ) 8.4, 4 H$), 7.02$ (d, J ) 7.6, 4 H ), $7.12(\mathrm{t}, J) 5.6,2 \mathrm{H}), 7.26-7.36(\mathrm{~m}, 9 \mathrm{H}), 7.43(\mathrm{~d}, J) 8.0$, $1 \mathrm{H}), 7.86(\mathrm{~d}, J) \quad 8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 23.9,34.8,91.0$, 118.0, 119.4, 121.7, 123.7, 125.9, 127.9, 128.6, 129.7, 135.4, 152.5, 156.2, 156.3, 157.6, 169.4. LCMS: $m / z 513\left(\mathrm{MH}^{+}\right)$.

G7. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.31$ (d, $J$ ) 6.8, 6 H ), 3.11 (sept, $J$ ) $6.8,1 \mathrm{H}), 7.36(\mathrm{t}, J) \quad 0.8,1 \mathrm{H}), 7.58(\mathrm{dd}, J) \quad 1.6,8.0,1$ H), 7.77 (s, 4 H), 7.94 (s, 2 H ), 7.96 (d, J ) 8.0, 1H). ${ }^{13} \mathrm{C}$ NMR: $\delta 23.8,34.9,88.3,121.1,121.3,122.8,123.4(\mathrm{t}, J)$
3.8), 124.0, 126.9, 126.9, 127.1, 129.6, 132.6 (q, J) 33.8), 142.4, 149.2, 158.0, 167.6. LCMS: $m / z 601\left(\mathrm{MH}^{+}\right)$.

K7. ${ }^{1} \mathrm{H}$ NMR: $\delta 1.29(\mathrm{~d}, J) 6.8,6 \mathrm{H}$ ), 3.03 (sept, $J$ ) $6.8,1 \mathrm{H}$ ), 3.79 (s, 6 H ), $6.84(\mathrm{~d}, J$ ) 9.2, 4 H ), 7.24 (d, J ) 8.8, 4 H ), $7.32(\mathrm{t}, J) 0.8,1 \mathrm{H}), 7.40(\mathrm{dd}, J) 1.2,8.0,1$ H), 7.83 (d, $J$ ) $8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 23.9,34.8,55.3$, 91.4, 113.6, 121.7, 125.7, 127.7, 128.4, 133.3, 153.0, 156.0, 159.4, 169.7. LCMS: m/z $389\left(\mathrm{MH}^{+}\right)$.

O7. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 1.29(\mathrm{~d}, J) 6.8,6 \mathrm{H}\right), 3.04$ (sept, $J$ ) $6.8,1 \mathrm{H}), 5.06(\mathrm{~s}, 2 \mathrm{H}), 6.93(\mathrm{~d}, J) \quad 8.8,2 \mathrm{H}), 7.22(\mathrm{~d}, J)$ $8.8,2 \mathrm{H}), 7.32-7.43(\mathrm{~m}, 12 \mathrm{H}), 7.85(\mathrm{~d}, J) 8.0,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta$ 23.9, 34.8, 70.1, 91.4, 114.6, 121.8, 123.4, 125.8, $126.8,127.3,127.8,128.0,128.2,128.3,128.5,128.7,133.3$, 136.6, 141.2, 152.6, 156.1, 158.7, 169.6. LCMS: m/z 435 $\left(\mathrm{MH}^{+}\right)$.

A14. ${ }^{1} \mathrm{H}$ NMR: $\left.\delta 7.25(\mathrm{~d}, J) \quad 8.8,4 \mathrm{H}\right), 7.35(\mathrm{~d}, J) 8.8$, 4 H), 7.86 (dd, $J$ ) $1.2,5.2,1 \mathrm{H}), 8.92$ (d, $4.8,1 \mathrm{H}), 9.00$ (s, 1 H ). ${ }^{13} \mathrm{C}$ NMR: $\delta 90.7,119.3,119.4,128.1,129.1,133.2$, 135.4, 137.7, 145.1, 145.9, 150.1, 167.1. LCMS: m/z 356 $\left(\mathrm{MH}^{+}\right)$.

G14. ${ }^{1} \mathrm{H}$ NMR: $\delta 7.78(\mathrm{~s}, 4 \mathrm{H}), 7.95$ (dd, $J$ ) 1.2, 5.2, 1 H), 7.98 (s, 2 H ), $9.06(\mathrm{~d}, J) 5.2,1 \mathrm{H}), 9.12(\mathrm{~s}, 1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR: $\delta 88.8,119.9,119.9,121.1,123.8,124.0,126.5$, 132.7, 133.1 (q, $J$ ) 34.4), 141.2, 142.6, 145.7, 151.8, 165.9. LCMS: $m / z 560\left(\mathrm{MH}^{+}\right)$.

O14. ${ }^{1} \mathrm{H}$ NMR: $\delta 5.05$ ( $\mathrm{s}, 2 \mathrm{H}$ ), 6.94 (d, J ) 8.8, 2 H ), 7.21 (d, J ) 8.8, 2 H), 7.36- 7.40 (m, 10 H$), 7.83$ (dd, J ) $1.2,4.8,1 \mathrm{H}), 8.88(\mathrm{~d}, J) 4.8,1 \mathrm{H}), 9.01(\mathrm{~d}, J) 0.8,1 \mathrm{H})$. ${ }^{13}$ C NMR: $\delta 70.1,91.9,114.9,119.0,119.0,126.6,127.3$, $128.0,128.5,128.7,128.8,131.8,133.2,136.4,139.9,146.1$, 146.3, 149.8, 159.1, 167.8. LCMS: m/z $394\left(\mathrm{MH}^{+}\right)$.

Supporting Information Available. Tabular data ( ${ }^{1} \mathrm{H}$ NMR, ${ }^{13}$ C NMR and LCMS, ELS) for approximately 60 phthalides, and ${ }^{1} \mathrm{H}$ NMR spectra for 26 randomly selected phthalides included as testimony to the general purities of the crude products obtained from the reaction. This material is available free of charge via the Internet at http:// pubs.acs.org.

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[^0]:    ${ }^{a}$ Purities generally greater than $90 \%\left({ }^{1} \mathrm{H}\right.$ NMR). ${ }^{b}$ The presence of significant amounts of impurities prevented ${ }^{1} \mathrm{H}$ NMR assignments from being made. $M+H$ signals detected via LCMS analysis. ${ }^{c}$ Reaction not performed.

