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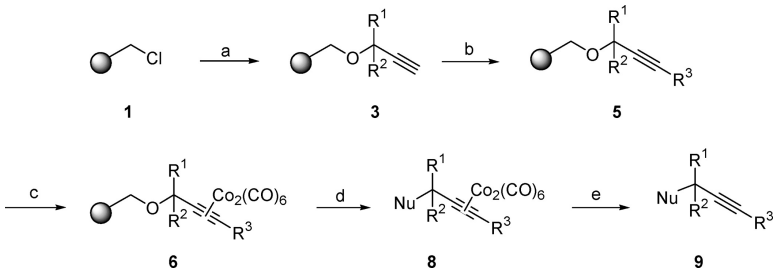

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The Solid-Phase Nicholas Reaction: Scope and Limitations

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Two libraries of α-substituted alkynes has been prepared on solid phase using a sequential Sonogashira/Nicholas reaction approach. The scope of nucleophiles in the Nicholas reaction on solid phase has been investigated, including carbon, oxygen, nitrogen, sulfur, fluoride, and hydride nucleophiles. The conditions for the reaction sequence have been optimized in terms of Lewis acid, catalyst for the Sonogashira step, temperature, reaction time, and decomplexation method, enabling the five-step sequence to be performed in 1 day.

Introduction

Solid-phase synthesis is an important tool for the creation of combinatorial libraries in the drug discovery process. Despite the many new solid-phase reactions that have been reported the past few years,[1] there is, nevertheless, a lack of methods for the coupling of two sp^3-carbon atoms on solid phase. The Nicholas reaction was developed in the 1970s by Kenneth Nicholas[2] and involves the treatment of an alkynol or alkylyl ether with a Lewis acid and the reaction of the cation thus formed with different nucleophiles. The strength of the reaction lies in the fact that it can be used for both the formation of carbon−carbon as well as carbon−heteroatom bonds and also that it involves the coupling of two sp^3-centers, thus complementing the numerous palladium-based methodologies for carbon−carbon cross-coupling.[3]

We have earlier published a short report on the Nicholas reaction on solid phase, involving the reaction of a polymer-bound alkynol with aryl halides via a Sonogashira coupling, followed by treatment with dicobalt octacarbonyl and subsequent reaction with boron trifluoride in conjunction with oxygen or carbon nucleophiles (Scheme 1).[4]

The full scope of nucleophiles in the solid-phase Nicholas reaction was not investigated, however; neither was it determined if the reaction sequence was robust enough for the preparation of combinatorial libraries of substituted alkynes. Other disadvantages of the method were that several of the reaction steps entailed rather long reaction times, often overnight, giving a total reaction time for the whole sequence of up to a week, and chromatographic purification was necessary in many cases to remove excess nucleophile used in the Nicholas reaction. We herein report our full study and optimization of the solid-phase Nicholas reaction, including the use of microwave heating to decrease reaction times, evaluation of different palladium catalysts and Lewis acids, and the use of scavengers to yield pure products without the need for extra purification after cleavage.

Results and Discussion

To test the viability for combinatorial synthesis, we first performed the reaction sequence described in Scheme 1 in a combinatorial format. Polymer-bound alkynol **3** (R^1 = *n*-pentyl, R^2 = H) was prepared batchwise in a fritted vessel and subsequently divided into 20 equivalent portions for further reaction in a Quest 210 synthesizer. The reaction vessels were divided into four series, each containing five vessels, and to each series was added $Pd(PPh_3)_4$, CuI, and the appropriate aryl iodide **4**{*1*−*4*} (Figure 1), followed by degassed piperidine. The polymer **5**{*1*} became bright red, while **5**{*2*−*4*} remained yellowish.

The alkyne was subsequently complexed with $Co_2(CO)_8$ to yield **6**, and upon this step, the polymer became dark red. Both the Sonogashira step and the complexation reaction were analyzed using IR spectroscopy. Disappearance of the alkyne C−H vibration at 3294 cm^{-1} after the Sonogashira coupling indicated a quantitative reaction. After formation of the dicobalt hexacarbonyl complex, a broad peak appeared around 2000 cm^{-1}(C≡O).

Our initial conditions for the Nicholas reaction involved the use of $BF_3{\cdot}OEt_2$ as the Lewis acid in CH_2Cl_2 and running the reaction for 1 h at −30 °C, wherupon the reaction vessel was left to warm overnight. Although a number of different Lewis acids have been applied in the Nicholas reaction, boron trifluoride is by far the most commonly used. A rapid screening of 21 different Lewis acids showed that $BF_3{\cdot}OEt_2$ was, indeed, a good choice, although similar results could be obtained with $TiCl_4$, $SiCl_4$, and $GeCl_4$. Milder Lewis acids, such as $MgBr_2$, LiCl, LiBr, and $ZnBr_2$, were not strong enough to catalyze the reaction. We could also see that no reaction occurred prior to addition of the nucleophile; i.e., the solution remained colorless, indicating that the reaction actually takes place on the polymer surface and not in solution.

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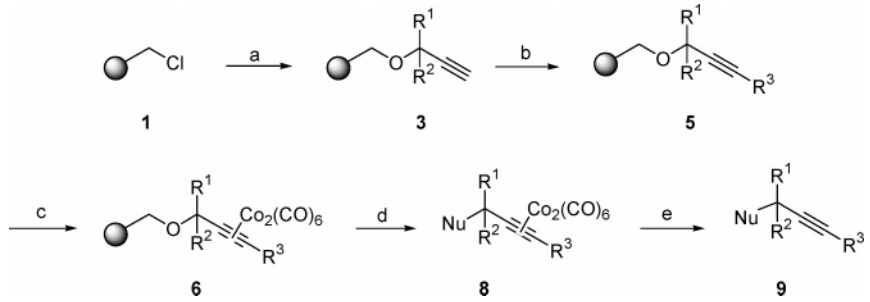
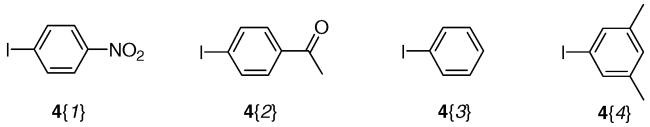
Scheme 1. The Sonogashira-Nicholas Sequence for the Solid-Phase Synthesis of Substituted Alkynes[a]

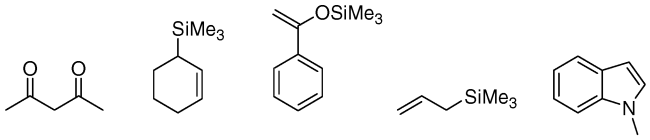


[a] Reagents and conditions: (a) alkynol (**2**), NaH, KI, DMF, room temperature, 18−48 h; (b) aryl halide (**4**), $Pd(PPh_3)_4$, CuI, piperidine, room temperature, 18 h; (c) $Co_2(CO)_8$, CH_2Cl_2, r.t., 3 h; (d) nucleophile (**7**), $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C to room temperature, 18 h; (e) $(NH_4)_2Ce(NO_3)_6$, THF/H_2O 9:1, 0 °C, 10−25 min.



4{*1*} **4**{*2*} **4**{*3*} **4**{*4*}

Figure 1. Aryl iodides **4**{*1*−*4*} used in the Sonogashira reaction in the first library.



7{*1*} **7**{*2*} **7**{*3*} **7**{*4*} **7**{*5*}

Figure 2. Carbon nucleophiles **7**{*1*−*5*} used as diversity reagents for the Nicholas reaction in library **9**.

We also looked briefly at the reaction time in the Nicholas step and found that the reaction was complete after 1 h at −30 °C followed by 1 h at room temperature; i.e., an overnight reaction was not necessary, and these conditions were adopted for subsequent reactions. The Nicholas reaction step was carried out according to these new conditions, and five different carbon nucleophiles **7**{*1*−*5*} (Figure 2) were used, forming chemset **8**{*1*−*4*,*1*−*5*}.

After quenching with triethylamine, the polymer was washed with CH_2Cl_2, and the dark red liquid was filtered through a short plug of silica. Oxidative decomplexation of library members **8**{*1*−*4*,*1*−*4*} was effected using cerium (IV) ammonium nitrate (CAN). Library members **8**{*1*−*4*,*5*} could not be oxidized with CAN, and the decomplexation was instead carried out with hydrogen peroxide in alkaline MeOH. The products were purified by flash chromatography, and the yields and purities of both crude and purified library compounds, that is, chemset **9**{*1*−*4*,*1*−*5*}, are summarized in Table 1.

Library members **9**{*1*−*4*,*4*}, in which trimethylallylsilane acted as a nucleophile, gave the best yields and products of high purity. Due to its volatility, the excess of the nucleophile could be easily removed by rotary evaporation. Compounds formed using *N*-methylindole as nucleophile, that is, **9**{*1*−*4*,*5*}, also gave products of high purity, although the yields were somewhat lower in these cases. Nucleophilic attack by cyclohex-2-enyl trimethylsilane can lead to diastereomeric products due to two adjacent stereogenic centers, and both HPLC and ^1H NMR showed that two similar products were, indeed, formed. The yields were rather modest, but library members **9**{*3*,*2*} and **9**{*4*,*2*} showed high purity. 1-Phenyl-1-(trimethylsilyloxy)-ethylene generated a ketone moiety in the products (library members **9**{*1*−*4*,*3*}). Apart from **9**{*3*,*3*}, the products were formed in relatively good yields, although the purities were low. Using 2,4-pentanedione as nucleophile only yielded product in two of the cases and in a very low yield (**9**{*2*,*1*} and **9**{*4*,*1*}). Although *β*-dicarbonyl substrates have been used earlier as nucleophiles in the Nicholas reaction,[5] they are sensitive compounds and probably undergo side reactions, such as the aldol condensation, under these reaction conditions.

Table 1. Overall Yields and Purities for the First Library (Chemset **9**)

		purity, %	
library member	yield, %	crude product	final product
9{*1*,*1*}	0		
9{*1*,*2*}	25	24	42
9{*1*,*3*}	36	27	66
9{*1*,*4*}	32	84	93
9{*1*,*5*}	19	56	96
9{*2*,*1*}	8	5	27
9{*2*,*2*}	37	54	64
9{*2*,*3*}	30	19	92
9{*2*,*4*}	41	92	97
9{*2*,*5*}	12	78	98
9{*3*,*1*}	0		
9{*3*,*2*}	37	96	99
9{*3*,*3*}	0		
9{*3*,*4*}	44	91	>99
9{*3*,*5*}	43	52	98
9{*4*,*1*}	10	52	90
9{*4*,*2*}	30	97	>99
9{*4*,*3*}	33	52	>99
9{*4*,*4*}	61	98	>99
9{*4*,*5*}	46	78	96

Although we had now verified that the reaction sequence could be carried out in a combinatorial format, there were, nevertheless, several aspects of the library procedure that we were not satsified with. The whole reaction sequence took a week to carry out, and chromatographic purification was necessary in most cases to give pure products. In addition, the oxidative decomplexation step involved an extraction to remove inorganic salts formed during the reaction. We thus set out to attend to these problems to make the reaction sequence more suitable for combinatorial purposes.

Optimization of the reaction sequence described in Scheme 1 started with the first step, that is, attachment of the alkynol to Merrifield resin. Our initial conditions involved the use of sodium hydride in DMF at room temperature for 24−48

Table 2. Results from the Microwave-Assisted Attachment of Alkynols to Merrifield Resin

entry[a]	alkynol	solvent	temp, °C	time, min	peak intensity ratio[d]
1	1-butyn-3-ol	DMF	130	6	m
2	1-butyn-3-ol	DMF	60	10	m
3	1-butyn-3-ol	THF/15-crown-5	60	10	s
4	1-butyn-3-ol[b]	THF	60	10	no reaction
5	1-butyn-3-ol	DMF	100	5	w
6	1-butyn-3-ol	THF/15-crown-5	100	5	w
7	1-butyn-3-ol	DMF	100	10	m
8	1-butyn-3-ol	THF/15-crown-5	100	10	m
9	1-butyn-3-ol	DMF	130	5	w
10	1-butyn-3-ol	THF/15-crown-5	130	5	w
11	1-butyn-3-ol	DMF	130	10	w
12	1-butyn-3-ol	THF/15-crown-5	130	10	w
13	3-phenyl-1-butyn-3-ol[b]	THF/15-crown-5	60	10	no reaction
14	3-phenyl-1-propyn-3-ol[b]	THF/15-crown-5	60	10	no reaction
15	1-butyn-3-ol[c]	DMF	20	840	s
16	1-butyn-3-ol[c]	THF/15-crown-5	20	840	s

[a] Sodium hydride was used as base in all reactions. [b] IR-spectrum showed no terminal alkyne peak at 3294 cm^{-1} [c] Reference reaction performed at room temperature without microwave heating. [d] The peak intensity of the terminal C−H bond was compared with the peak intensity of the peak induced by the solid support at ~1950 cm^{-1}: s = strong, m = medium, w = weak.

h, together with a catalytic amount of potassium iodide or tetrabutylammonium iodide, following an earlier published procedure.[6] Microwave heating has been increasingly used in solid-phase synthesis, and we decided to apply this technique to the alkylation step to see if the reaction time could be decreased.[7] We also tried another set of reaction conditions, that is, 15-crown-5 in THF together with sodium hydride, to see if the attachment of tertiary alkynols could be made more efficient. A series of different experiments was performed to find the optimal conditions for the microwave-assisted attachment step. The resulting polymers were subsequently analyzed by IR, where the terminal alkyne C−H vibration was compared to the signals from the polymer backbone and classified as strong, medium, or weak to give a crude estimate of the degree of attachment of the alkynol. The results are displayed in Table 2.

We found that running the reaction in THF in the presence of 15-crown-5 gave a significantly higher degree of attachment compared to using DMF as solvent, probably due to degradation of DMF under microwave heating. Mild conditions (entry 3) gave the best result, while high temperatures (entry 10) led to formation of byproducts even after a few minutes. If no crown ether was added (entry 4), no reaction occurred. Tertiary alkynols could not be attached using a microwave-assisted reaction (entries 13 and 14). Even an alkynol that earlier gave product at room temperature rendered only the corresponding ketone via elimination of acetylene under microwave conditions (entry 13). The corresponding reactions at room temperature were included for comparison (entries 15 and 16).

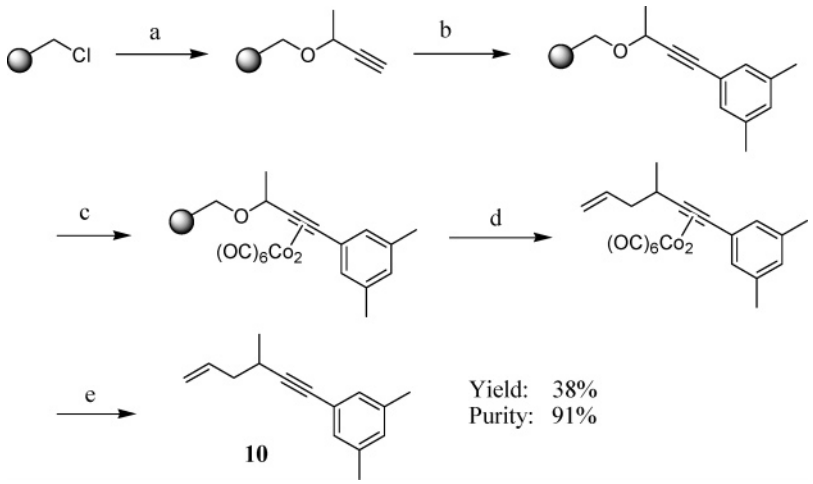
Sonogashira couplings also constitute a bottleneck in the reaction sequence in terms of reaction times. Gogoll et al. have described the microwave-assisted Sonogashira reaction,[8] and inspired by their report, we screened a set of different palladium catalysts and base/solvent systems for our reaction under microwave conditions. The reactions were performed according to the experimental procedure described by Gogoll, that is, at 120 °C for 15 min. The standard Sonogashira protocol used in our coupling reactions included the use of $Pd(PPh_3)_4$ as catalyst and piperidine as base. Nowadays, $Pd(PPh_3)_4$ is in many cases replaced by other less-air-sensitive catalysts, and we therefore tested some of these, $Pd_2(dba)_2$/PPh_3, $Pd(PPh_3)_2Cl_2$, $[(t\text{-Bu})_2P(OH)]_2PdCl_2$,[9] $[[(t\text{-Bu})_2PO\cdot\cdot H\cdot\cdot OP(t\text{-Bu})_2]PdCl]_2$, and $[(t\text{-Bu})_2P(OH)PdCl_2]_2$, in the microwave-assisted Sonogashira couplings. We also attempted exchanging piperidine for triethylamine, but only the original combination of $Pd(PPh_3)_4$ and piperidine gave complete disappearance of the terminal alkyne C−H stretch in IR, and we thus came to the conclusion that the reaction conditions used in our earlier sequence were the optimal ones, although the reaction time had now been decreased to 15 min.

An excess of nucleophile is used in order to get good yields in the Nicholas reaction step, and because cleavage occurs in this step, as well, this means that the product is contaminated by excess nucleophile. Volatile nucleophiles, such as allyltrimethylsilane, are easily removed by evaporation, but in other cases, the nucleophiles have to be removed by chromatography. To avoid this, polymer-bound scavengers were used instead, that is, PS-TsCl for oxygen nucleophiles, PS-isocyanate for nitrogen nucleophiles and MP-carbonate for sulfur nucleophiles. In all cases, the appropriate scavenger was added to the reaction vessel after the Nicholas reaction was complete without removing the Merrifield resin. The mixtures were stirred gently overnight, whereafter the polymer was removed by filtration and washed, leaving cobalt complexes of the desired products of high purity.

For carbon nucleophiles, a scavenger approach is not possible. Instead, we used a catch-and-release strategy. Polymer-bound triphenylphosphine was added to the reaction mixture dissolved in THF, and the slurry was heated at reflux until a color change of the solution from red to yellow indicated that the complex had been captured by the resin (normally after 1−3 h). The product was subsequently liberated from the polymer using the decomplexation method described below.

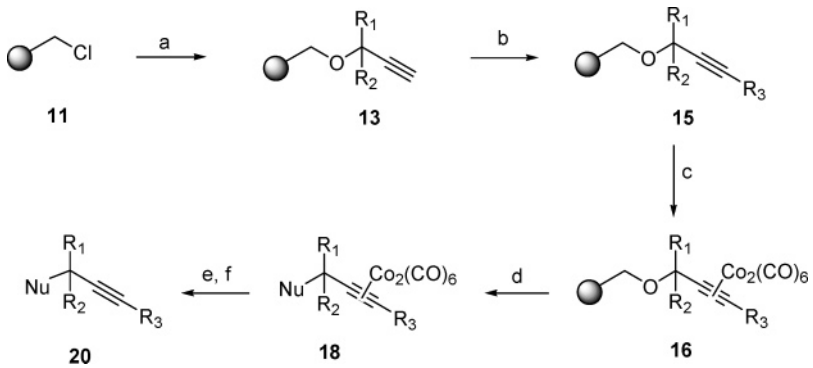
The last step to optimize was the cleavage of cobalt carbonyl complex. Our previous procedure was oxidative decomplexation using ammonium cerium(IV) nitrate (CAN). The major disadvantage of this method was the need for extractive workup and the fact that overoxidation could occur

Scheme 2.[a] The Optimized Reaction Sequence



[a] Reagents and conditions: (a) 3-butyn-2-ol, NaH, 15-crown-5, THF, MW 60 °C, 10 min; (b) 5-iodo-*m*-xylene, $Pd(PPh_3)_4$, CuI, piperidine, MW 120 °C, 15 min; (c) $Co_2(CO)_8$, CH_2Cl_2, room temperature, 3 h; (d) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, −30 °C for 1 h, then room temperature 1 h; (e) ethylenediamine, 65 °C, 30 min.

Scheme 3[a]



[a] Reagents and conditions: (a) 1-butyn-3-ol ($R^1 = CH_3$, $R^2 = H$), NaH, KI, DMF, room temperature, 48 h; (b) aryl halide (**14**), $Pd(PPh_3)_4$, CuI, piperidine, room temperature, 18 h; (c) $Co_2(CO)_8$, CH_2Cl_2, room temperature, 3 h; (d) nucleophile (**17**), $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C to room temperature, 2 h; (e) addition of scavenger or PS−PPh_3 (f) $H_2NCH_2CH_2NH_2$, THF, 65 °C, 10−40 min.

if the reaction was left for too long, causing degradation of the products. We performed several different experiments to find a mild and efficient decomplexation method, that is, using thiols,[10] iodine,[11] *N*-methylmorpholine *N*-oxide,[12] and ethylenediamine,[13] in which the latter method gave the best results. Refluxing the complex in a 2:1 mixture of THF and ethylenediamine gave pure product after nearly the same reaction time as oxidative cleavage by CAN, that is, 10−20 min. No extractive workup was needed because the excess diamine could be easily removed by eluting the mixture through an acidic ion-exchange resin.

It was of interest to implement all the optimization done so far to see if we could improve the yields. We resynthesized one of the compounds that we had prepared previously using our earlier methodology[4] (Scheme 2).

The MW-assisted attachment of the alkynol was performed in THF/15-crown-5 in 60 °C for 10 min. The polymer was washed and subjected to MW-assisted Sonogashira coupling in piperidine at 120 °C for 15 min with $Pd(PPh_3)_4$ as catalyst. After the polymer was washed and transferred to a solid-phase reaction vessel, dicobalt octacarbonyl was added to form the alkyne−cobalt carbonyl complex. The polymer was washed with CH_2Cl_2, whereupon the Nicholas reaction was performed with allyl trimethylsilane as nucleophile. Decomplexation with ethylenediamine gave **10** in 38% yield and 91% purity. Although the yield is roughly the same as when using the original conditions, the total reaction time is 1−2 days instead of 1 week, and chromatographic purification is no longer necessary.

We then set out to prepare a second library using the optimized reaction conditions. Because we did not have permanent access to a microwave reactor, the first two steps, that is, attachment to the resin and the Sonogashira reaction, were carried out at room temperature according to the original protocol, although we have shown that these two steps can be accelerated by microwave heating. We also expanded the scope of nucleophiles to include sulfur and nitrogen (Scheme 3). The results are summarized in Table 3.

As the table shows, using scavengers gave crude compounds of high purity. 1-Phenyl-1-(trimethylsilyloxy)-ethylene did not give any product when the alkyne had an *o*-tolyl substituent. Possible reasons for that may be the sensitivity of the product to Lewis acids or that such a bulky product could not be attached to PS-PPh_2.

There are two more heteroatoms which can act as nucleophiles, hydride and fluoride. The Nicholas reactions with both of these nucleophiles are described in the literature,[14,15] but all of our efforts to use them on solid phase

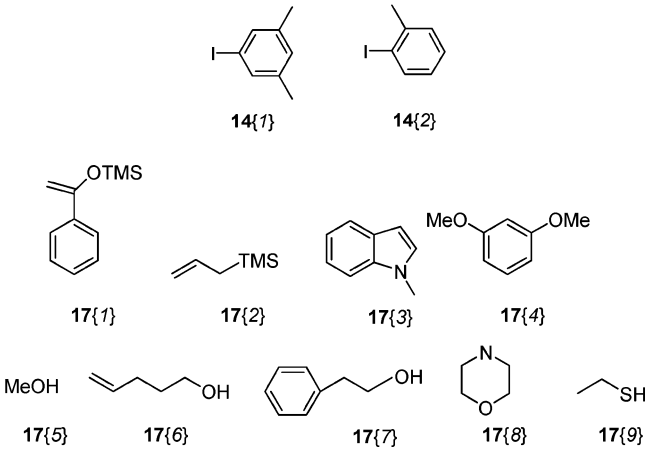


Figure 3. Aryl iodides **14**{*1*−*2*} used in the Sonogashira reaction and nucleophiles **17**{*1*−*9*} used in the Nicholas reaction in library 2.

Table 3. Overall Yields and Purities of the Members of Library **2**

library member	yield %	purity %	library member	yield %	purity %
20{*1,1*}	24	93	**20**{*2,1*}	0	
20{*1,2*}	51	80	**20**{*2,2*}	46	92
20{*1,3*}	25	91	**20**{*2,3*}	28	97
20{*1,4*}	15	90	**20**{*2,4*}	76	48
20{*1,5*}	37	77	**20**{*2,5*}	68	81
20{*1,6*}	34	81	**20**{*2,6*}	38	84
20{*1,7*}	24	92	**20**{*2,7*}	30	88
20{*1,8*}	22	89	**20**{*2,8*}	23	89
20{*1,9*}	0[a]		**20**{*2,9*}	21	50

[a] Some product was formed in this reaction according to ^{1}H NMR, but contamination by several byproducts made determination of the purity difficult.

Table 4. Different Hydride and Fluoride Nucleophiles Used in the Nicholas Reaction on Solid Phase

entry	nucleophile	Lewis acid
1	$NaBH_4$	$BF_3{\cdot}OEt_2$
2	$Na(OAc)_3BH$	$BF_3{\cdot}OEt_2$
3	$Na(CN)BH_3$	$BF_3{\cdot}OEt_2$
4	$Na(CN)BH_3$	CuCl
5	DAST	
6	DAST	$BF_3{\cdot}OEt_2$
7	DAST	$ZnCl_2$
8	HF	
9	TASF	CuCl

failed. Table 4 shows different nucleophile sources as well as different Lewis acids used in the reaction. Sodium borohydride (entry 1) led to elimination reaction and gave only conjugated alkene−alkyne product. The milder reagent sodium cyanoborohydride together with BF_3 (entry 3) caused discoloration of the polymer upon the reaction, but no product was isolated. To avoid any effect of the Lewis acid on the hydride, we used CuCl as the Lewis acid instead (entry 4), but still no product was formed.

Diethylaminosulfur trifluoride (DAST) does not have free fluorides and is easy to handle. It has been used in the fluorination of cobalt carbonyl complexes of propargylic alcohols.[15] Since DAST can act as a Lewis acid itself, we tried the fluorination without addition of external Lewis acid (entry 5). No reaction occurred. Addition of different Lewis acids (entries 6 and 7) did not change the reaction outcome, and we tried nucleophilic fluorination agents instead. However, strongly nucleophilic fluorination agents are known to induce cleavage of cobalt carbonyl complexes,[16] and we thus chose to use weakly to moderately nucleophilic fluoride carriers, that is, hydrogen fluoride (entry 8) and tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) together with CuCl as Lewis acid (entry 9). None of the reactions gave any product.

In summary, an efficient method for the solid-phase preparation of substituted alkynes using a combination of the Sonogashira and the Nicholas reactions has been developed. The five-step reaction sequence can be performed in 1 day by the use of microwave heating for two of the steps. The use of polymer-bound scavengers or a catch-and-release approach for the purification allows the preparation of target compounds of high purity. Carbon, oxygen, nitrogen, and sulfur nucleophiles could be used in the Nicholas step, while reactions with hydride and fluoride did not give any product.

Experimental Section

Materials. The library syntheses were carried out on Quest 210 from Argonaut Technologies. All procedures, excepting the oxidative decomplexation, were carried out under an atmosphere of argon or nitrogen. Commercially available chemicals were used without further purification unless stated otherwise. THF and CH_2Cl_2 were distilled prior to use; other solvents were used without purification. Merrifield resin was purchased from Novabiochem, and the yields are based on the initial loading of the resin. Scavengers were purchased from Argonaut Technologies. Cyclohex-2-enyl trimethylsilane was prepared according to Hitchcock et al.[17] Analytical data for compound **10** are in accordance with published data.[4] Microwave experiments were carried out on an Emrys Creator from Biotage. ^{1}H NMR spectra were recorded at room temperature on a Varian Unity-400 NMR spectrometer at 400 MHz in $CDCl_3$ with TMS as internal standard. Thin-layer chromatography was performed on silica gel plates (Merck, silica gel 60 F_{254}). Purification of the first library was performed on a Flash Master Lite from Jones Chromatography using silica gel from Matrex (grade 60 A, 35−70 μm). Purities were determined by HPLC on an Waters 996 photodiode array detector. Column: XTerra MS C8 4.6 × 50 mm 3.5 μm. Eluent: 0.1 M ammonium acetate in CH_3-CN/water gradient. HPLC/MS were recorded on an Agilent 1100 series module with a Waters ZQ 2000 mass spectrometer with pos/neg switch using ELS as primary detector and DAD as secondary detector. Column: Phenomenex Synergi MAX-RP 80A C12 50 × 3 mm 4 μm. Eluent: 10 mM ammonium acetate in CH_3CN/water gradient.

Library 1. General Procedure for Attachment of the Alkynol to the Solid Phase (Step A, Scheme 1). Merrifield resin (**1**) with the initial loading 0.84 mmol/g was used. To a suspension of Merrifield resin (1 or 2% DVB, 4 g, 3.36 mmol) in dry DMF (50 mL) in a fritted reaction vessel for solid-phase synthesis was added NaH (60% in mineral oil, 672 mg, 16.8 mmol) and KI (112 mg, 0.672 mmol). 1-Octyn-3-ol (16.8 mmol) was added dropwise, and the resulting

slurry was shaken for 2 days. The reaction was quenched with 2 mL of water. The polymer was filtered and washed (DMF/H_2O 1:1, THF, MeOH, CH_2Cl_2), then used directly in the next step.

A small sample was taken out, dried, and analyzed by IR (KBr pellet): 3294 cm^{-1}.

General Procedure for the Sonogashira Coupling (Step B, Scheme 1). To the reaction vessel containing a mixture of polymer **3** (200 mg, 0.168 mmol) and CuI (3.2 mg, 0.0168 mmol) was added $Pd(PPh_3)_4$ (9.7 mg, 0.0084 mmol), followed by 0.504 mmol of aryl iodide **4**{*1*−*4*} and 2 mL of degassed piperidine. The resulting mixture was agitated overnight and washed with DMF, MeOH, and CH_2Cl_2 to give polymer **5**{*1*−*4*}.

General Procedure for the Cobalt Carbonyl Complexation (Step C, Scheme 1). Polymer **5**{*1*−*4*} was swelled in CH_2Cl_2 for 15 min, and 0.336 mmol $Co_2(CO)_8$ in CH_2Cl_2 was added. The dark red mixture was agitated for 3 h, then washed with CH_2Cl_2.

General Procedure for the Nicholas Reaction and the Decomplexation (Step D, Scheme 1). Polymer **6**{*1*−*4*} was swelled in CH_2Cl_2 for 15 min and cooled to −30 °C. Boron trifluoride etherate (31 μL, 0.252 mmol) was added, followed by 0.504 mmol of nucleophile **7**{*1*−*5*}. The mixture was agitated at −30 °C for 1 h, and the temperature was then allowed to increase to ambient temperature over 1 h. The reaction was quenched with triethylamine (0.504 mmol, 70 μL), the polymer was washed with CH_2Cl_2 and concentrated, and the resulting dark red solution was eluted through a small plug of silica to remove the Lewis acid using pentane as the eluent and concentrated again.

General Procedure for the Decomplexation Step (Step E, Scheme 1). For compounds **9**{*1*−*4,5*}, decomplexation was effected with hydrogen peroxide according to the following protocol: The residue was dissolved in MeOH (1.4 mL) and cooled to 0 °C, and H_2O_2 (430 μL, 30%) was added, followed by NaOH (430 μL, 1 M in H_2O/MeOH). The reaction mixture was stirred for 5 min at 0 °C, diluted with ether (2 mL), and washed three times with brine. The organic phase was evaporated, and remaing cobalt byproducts were removed via elution through a small plug of silica gel with CH_2Cl_2 as eluent.

For the remaining library members, decomplexation was effected with CAN according to the following protocol: The residue was dissolved in 2 mL THF/H_2O (9/1) and cooled to 0 °C. A solution of 0.18 M cerium ammonium nitrate in THF/H_2O (9/1) was added dropwise until the dark red solution turned orange-yellow (the amount of CAN solution used corresponded to ∼2.5 equiv). The reaction mixture was diluted with 1 mL brine and 2 mL diethyl ether, the phases were separated, and the aqueous phase was extracted with 3 × 2 mL diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated by evaporation. The residue was purified by flash chromatography using FlashMaster Lite equipment and 1−10% ethyl acetate in pentane as eluent, depending on the polarity of the product.

Both crude and purified members of library **9**{*1*−*4,1*−*5*} were analyzed by HPLC. The reported yields of purified library members are based on the initial loading of Merrifield resin.

Data for Individual Library Members, Library 1. 9-{*1,2*}. Yield 12.8 mg (25%, yellow oil); purity: 42%. Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br d, J = 7.0 Hz, 2H), 7.60 (br d, J = 7.0 Hz, 2H), 5.85−5.50 (m, 2H), 3.90−3.70 (m, 1H), 2.05−1.95 (m, 1H), 1.90−1.20 (m, 14H), 0.98−0.88 (m, 3H); MS (ES) *m*/*z* 312.28 (MH^+).

9{*1,3*}. Yield 20.9 mg (36%, yellow oil); purity 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−7.94 (m, 3H), 7.62−7.54 (m, 2H), 7.52−7.42 (m, 4H), 3.29 (d, J = 11.9 Hz, 2H), 3.40−3.31 (m, 1H), 1.70−1.50 (m, 2H), 1.40−1.20 (m, 6H), 0.84 (t, J = 6.7 Hz, 3H); MS (ES) *m*/*z* 350.07 (MH^+).

9{*1,4*}. Yield 14.7 mg (32%, yellow oil); purity 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 5.96−5.84 (m, 1H), 5.09 (d, J = 17.1 Hz, 1H), 5.05 (d, 1H, J = 9.8 Hz, 1H,), 2.70−2.61 (m, 1H), 2.32 (t, J = 7.0 Hz, 2H), 1.60−1.40 (m, 2H), 1.40−1.20 (m, 6H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 146.52, 135.65, 132.27, 131.10, 123.44, 116.86, 99.39, 80.74, 39.09, 34.18, 32.42, 31.60, 27.03, 22.58, 14.07.

9{*1,5*}. Yield 11.7 mg (19%, orange solid); purity 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.3 (dd, J = 8.8, 7.6 Hz, 1H), 7.07 (dd, J = 8.8, 6.7 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.56 (s, 1H), 3.27 (t, J = 7.6 Hz, 1H), 3.27 (s, 3H), 1.80−1.20 (m, 8H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.19, 142.59, 135.37, 131.94, 129.41, 128.93, 128.47, 127.12, 123.01, 122.68, 121.87, 107.61, 102.35, 93.27, 32.47, 31.58, 28.65, 26.74, 25.76, 22.60, 14.08.

9{*2,1*}. Yield 4.3 mg (8%, yellow oil); purity 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.70 (m, 2 H), 7.54−7.52 (m, 2H), 5.43 (d, J = 4.9 Hz, 1H), 3.90−3.84 (m, 1H), 2.60 (s, 1H), 2.01 (s, 6H), 1.42−1.22 (m, 8H), 0.96 (t, J = 7.4 Hz, 1H); MS (ES) *m*/*z* 325.86 $(M - 1)^-$.

9{*2,2*}. Yield 19.0 mg (37%, yellow oil); purity 64%. Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 5.82−5.60 (m, 2H), 2.59 (s, 3H), 2.24−2.14 (m, 1H), 2.06−1.96 (m, 1H), 1.60−1.20 (m, 14H), 0.85 (t, J = 7.1 Hz, 3H); MS (ES) *m*/*z* 309.18 (MH^+).

9{*2,3*}. Yield 17.7 mg (30%, yellow oil); purity 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.48 (dd, J = 7.6, 7.3 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 3.34 (d, J = 9.5 Hz, 2H), 3.19−3.10 (m, 1H), 2.58 (s, 3H), 1.66−1.20 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H); MS (ES) *m*/*z* 347.10 (MH^+).

9{*2,4*}. Yield 18.4 mg (41%, yellow oil); purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 5.99−5.86 (m, 1H), 5.12 (d, 1H, J = 17.4 Hz), 5.09 (d, J = 10.4 Hz, 1H), 2.70−2.60 (m, 1H), 2.59 (s, 3H), 2.32 (dd, 2H, J = 7.02 Hz), 1.58−1.42 (m, 2H), 1.40−1.20 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H); MS (ES) *m*/*z* 269.14 (MH^+).

9{*2,5*}. Yield 6.9 mg (11%, orange solid); purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 7.0 Hz, 2H), 7.68 (d, J = 7.0 Hz, 2H), 7.30

(dd, $J = 7.9$, 7.6 Hz, 1H), 7.06 (dd, $J = 7.6$, 7.3 Hz, 1H), 6.82 (d, $J = 7.9$ Hz, 1H), 3.22 (s, 3H), 3.21 (t, $J = 7.7$ Hz, 1H), 2.63 (s, 3H), 1.80−1.20 (m, 8H), 0.91 (t, $J = 6.9$ Hz, 3H), one proton in the aromatic area overlaps with chloroform; ^{13}C NMR (500 MHz, $CDCl_3$) δ 197.12, 167.19, 142.59, 136.97, 135.37, 131.94, 129.40, 128.47, 127.11, 123.00, 122.67, 121.86, 107.60, 102.34, 93.26, 32.50, 31.57, 29.70, 28.64, 26.72, 25.75, 22.58, 14.06.

9{***3,2***}**.** Yield 16.7 mg (37%, colorless oil); purity 98%. Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.36 (m, 2H), 7.32−7.23 (m, 3H), 5.80−5.62 (m, 2H), 2.20−2.12 (m, 1H), 2.05−1.95 (m, 1H), 1.65−1.50 (m, 6H), 1.50−1.20 (m, 8H), 0.89 (t, $J = 7.3$ Hz, 3H); MS (ES) *m*/*z* 267.33 (MH^+).

9{***3,4***}**.** Yield 16.7 mg (44%, yellow oil); purity >99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2H), 7.30−7.24 (m, 3H), 6.05−5.88 (m, 1H), 5.12 (d, $J = 17.9$ Hz, 1H), 5.09 (d, $J = 10.2$ Hz, 1H), 2.61 (m, 1H), 2.31 (t, $J = 7.3$, 6.8 Hz, 2H), 1.60−1.20 (m, 8H), 0.91 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) 136.24, 131.61, 128.13, 127.43, 124.20, 116.36, 93.17, 82.11, 39.49, 34.55, 32.31, 31.71, 27.01, 22.59, 14.01.

9{***3,5***}**.** Yield 22.9 mg (43%, yellow oil); purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, $J = 7.9$ Hz, 1H), 7.49−7.43 (m, 2H), 7.34−7.22 (m, 5H), 7.14 (dd, $J = 7.9$, 7.0 Hz, 1H), 7.08 (s, 1H), 4.18−4.13 (m, 1H), 3.77 (s, 3H), 2.06−1.90 (m, 2H), 1.66−1.50 (m, 2H), 1.40−1.25 (m, 4H), 0.92 (t, $J = 6.71$ Hz, 3H); MS (ES) *m*/*z* 316.15 (MH^+).

9{***4,1***}**.** Yield 5.4 mg (10%, yellow oil); purity 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 2H), 6.96 (s, 1H), 5.03 (d, $J = 4.4$ Hz, 1H), 3.39−3.37 (m, 1H), 2.26 (s, 6H), 2.00 (s, 6H), 1.35−1.22 (m, 8H), 0.91 (t, $J = 7.1$ Hz, 1H); MS (ES) *m*/*z* 311.74 $(M - 1)^-$.

9{***4,2***}**.** Yield 14.8 mg (30%, yellow oil); purity >99%. Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 6.92 (s, 1H), 5.69−5.66 (m, 2H), 2.28 (s, 6H), 2.19−2.12 (m, 1H), 2.03−1.97 (m, 1H), 1.91−1.75 (m, 2H), 1.60−1.32 (m, 12H), 0.85 (t, 3H, $J = 7.2$ Hz); MS (ES) *m*/*z* 295.24 (MH^+).

9{***4,3***}**.** Yield 18.5 mg (33%, pale yellow oil); purity >99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−7.96 (m, 2H), 7.60−7.44 (m, 3H), 6.95 (s, 2H), 6.88 (s, 1H), 3.33 (d, $J = 6.7$ Hz, 2H), 3.28 (m, 1H), 2.24 (s, 6H), 1.68−1.46 (m, 2H), 1.38−1.25 (m, 2H), 0.9 (t, $J = 7.0$ Hz, 3H); MS (ES) *m*/*z* 333.25 (MH^+).

9{***4,4***}**.** Yield 25.9 mg (61%, pale yellow oil); purity >99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 2H), 6.90 (s, 1H), 6.00−5.88 (m, 1H), 5.16−5.00 (m, 2H), 2.60−2.50 (m, 1H), 2.31 (t, $J = 6.8$ Hz, 2H), 2.29 (s, 6H), 1.2−1.6 (m, 8H), 0.90 (t, $J = 6.8$ Hz, 3H); MS (ES) *m*/*z* 255.12 (MH^+).

9{***4,5***}**.** Yield 26.5 mg (46%, pale yellow oil); purity 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J = 7.9$ Hz, 1H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.24 (dd, $J = 8.2$, 6.7 Hz, 1H), 7.13 (dd, $J = 7.9$, 6.7 Hz, 1H), 7.1 (s, 2H), 7.07 (s, 1H), 6.93 (s, 1H), 4.16−4.10 (m, 1H), 3.77 (s, 3H), 2.29 (s, 6H), 2.04−1.86 (m, 2H), 1.64−1.48 (m, 2H), 1.38−1.26 (m, 4H), 0.91 (t, $J = 6.7$ Hz, 3H); MS (ES) *m*/*z* 344.24 (MH^+).

Library 2. General Procedure for Attachment of the Alkynol to the Solid Phase (Step A, Scheme 3). Merrifield resin (**11**) with the initial loading 0.84 mmol/g was used. To a suspension of Merrifield resin (1 or 2% DVB, 3 g, 2.52 mmol) in dry DMF (30 mL) in a fritted reaction vessel for solid-phase synthesis was added NaH (60% in mineral oil, 504 mg, 12.6 mmol) and KI (84 mg, 0.504 mmol). 1-Butyn-3-ol (988 μL, 12.6 mmol) was added dropwise, and the resulting slurry was shaken for 2 days. The reaction was quenched with 1 mL of water. The polymer was filtered and washed (DMF/H_2O 1:1, THF, MeOH, CH_2Cl_2) and then used directly in the next step. A small sample was taken out, dried, and analyzed by IR (KBr pellet): 3294 cm^{-1}.

General Procedure for the Sonogashira Coupling (Step B, Scheme 3). To the reaction vessel containing a mixture of polymer **13** (700 mg, 0.588 mmol) and CuI (11.2 mg, 0.059 mmol) was added $Pd(PPh_3)_4$ (34 mg, 0.029 mmol), followed by 1.76 mmol of aryl iodide **14**{*1*−*2*} and 5 mL of degassed piperidine. The resulting mixture was agitated overnight and washed with DMF, MeOH, and CH_2Cl_2 to give polymer **15**{*1*−*2*}.

General Procedure for the Cobalt Carbonyl Complexation (Step C, Scheme 3). Polymer **15**{*1*−*2*} was swelled in CH_2Cl_2 for 15 min, and 689 mg (2.02 mmol) of $Co_2(CO)_8$ in CH_2Cl_2 was added. The dark red mixture was agitated for 3 h, then washed with CH_2Cl_2.

General Procedure for the Nicholas Reaction (Step D, Scheme 3). Polymer **16**{*1*−*4*} (100 mg, 0.084 mmol) was swelled in CH_2Cl_2 for 15 min and cooled to −30 °C. Boron trifluoride etherate (31 μL, 0.252 mmol) was added, followed by 0.252 mmol of nucleophile **17**{*1*−*5*}. The mixture was agitated at −30 °C for 1 h, and the temperature was then allowed to increase to ambient over 2 h. The reaction was quenched with triethylamine (0.252 mmol, 35 μL), whereupon the polymer was washed.

General Procedure for Scavenging Oxygen Nucleophiles (Step E, Scheme 3). To the dark red solution obtained after the Nicholas reaction, 330 mg (0.756 mmol) polymer-bound tosyl chloride and 211 μL (1.51 mmol) triethylamine were added. The mixture was stirred at room temperature for 5 h, whereupon an additional 330 mg of PS-TsCl was added. The mixture was stirred for another 7 h. The polymer was separated by filtration and washed with CH_2Cl_2. After the solvent was removed, library members **19**{*1*−*2,6*−*7*} were obtained as dark red oils.

General Procedure for Scavenging Nitrogen Nucleophiles (Step E, Scheme 3). To the dark red solution obtained after the Nicholas reaction, polymer-bound isocyanate (319 mg, 0.504 mmol) was added. The mixture was stirred at room temperature for 12 h. The polymer was separated by filtration and washed with CH_2Cl_2. After the solvent was removed, library members **19**{*1*−*2,8*} were obtained as dark red oils.

General Procedure for Scavenging Sulfur Nucleophiles (Step E, Scheme 3). To the dark red solution obtained after the Nicholas reaction, polymer-bound carbonate (397 mg, 1.01 mmol) was added. The mixture was stirred at room temperature for 12 h. The polymer was separated by filtration and washed with CH_2Cl_2. After the solvent was removed, library members **19**{*1*−*2,9*} were obtained as dark red oils.

General Procedure for Trapping the Products on-Polymer after the Reaction with Carbon Nucleophiles (Step E, Scheme 3). The solvent was removed after the

Nicholas reaction. The resulting dark red oil was dissolved in distilled THF, and polymer-bound triphenylphosphine (115 mg, 0.252 mmol) was added. The mixture was refluxed for 1−3 h or until decoloration of the solution indicated that the reaction was complete. The polymer, which became dark red, was separated from the solution by filtration and washed with THF and CH_2Cl_2. Library members **19**{*1−2,1*} and **19**{*1−2,3−4*} were obtained.

General Procedure for Decomplexation of the Cobalt Carbonyl (Step F, Scheme 3). Library members **19**{*1−2,2*} and **19**{*1−2,5−9*} were dissolved in 2 mL of distilled THF, and 1 mL ethylenediamine was added. The mixture was refluxed until the color changed from dark red to yellow (10−20 min). The solution was allowed to cool and eluted through a plug of acidic ion-exchange resin (SCX-2 from Argonaut Technologies). The solvent was removed, giving library members **20**{*1−2,2*} and **20**{*1−2,5−9*}.

Library members **19**{*1−2,1*} and **19**{*1−2,3−4*} were swelled in 2 mL of distilled THF, and 1 mL ethylenediamine was added. The mixture was refluxed until the polymer color changed from dark red to yellowish and the solution became yellow (20−40 min). The mixture was allowed to cool and eluted through a plug of acidic ion-exchange resin (SCX-2 from Argonaut Technologies). The solvent was removed, giving library members **20**{*1−2,1*} and **20**{*1−2,3−4*}.

Library members **20**{*1−2,1−9*} were analyzed by HPLC. The reported yields are based on the initial loading of Merrifield resin.

Data for the Individual Library Members. 20{***1,1***}**.** Yield 5.6 mg (24%, yellow oil); purity 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H) 6.97 (s, 2H), 6.89 (s, 1H), 3.43−3.33 (m, 2H), 3.16−3.07 (m, 1H), 2.25 (s, 6H), 1.35 (d, J = 6.8 Hz, 3H); MS (ES) *m*/*z* 277.64 (MH^+).

20{***1,2***}.** Yield 8.5 mg (51%, yellow oil); purity 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 2H), 6.90 (s, 1H), 5.93 (ddt, J = 17.1, 10.2, 7. 0 Hz, 1H), 5.10 (dd, J = 17.0, 9.9 Hz, 2H), 2.71 (q, J = 6.8 Hz, 1H), 2.38−2.28 (m, 2H), 2.27 (s, 6H), 1.24 (d, J = 6.9 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) 137.66, 136.07, 129.40, 129.26, 127.85, 123.52, 116.56, 114.75, 93.25, 81.29, 41.18, 31.06, 26.46, 21.05, 20.55.

20{***1,3***}.** Yield 6.1 mg (25%, yellow oil); purity 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 8.4, 6.8 Hz, 1H), 7.09 (dd, J = 8.0, 6.8 Hz, 1H), 7.04 (s, 2H), 7.03 (s, 1H), 6.88 (s, 1H), 4.21 (q, J = 6.9 Hz, 1H), 3.73 (s, 3H), 2.24 (s, 6H), 1.64 (d, J = 7.2 Hz, 3H).

20{***1,4***}.** Yield 3.8 mg (15%, yellow oil); purity 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 1H), 7.08 (s, 2H), 6.91 (s, 1H), 6.50 (dd, J = 8.4, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 4.27 (q, J = 7.2 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.28 (s, 6H), 1.46 (d, J = 6.8 Hz, 3H); MS (ES) *m*/*z* 295.65 (MH^+).

20{***1,5***}.** Yield 5.8 mg (37%, yellow oil); purity 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 2H), 6.95 (s, 1H), 4.29 (q, J = 6.4 Hz, 1H), 3.46 (s, 3H), 2.28 (s, 6H), 1.50 (d, J = 6.6 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) 137.80, 130.17, 129.36, 127.83, 122.27, 114.68, 88.01, 85.39, 67.30, 56.32, 22.01, 21.25, 21.08.

20{***1,6***}.** Yield 6.9 mg (34%, yellow oil); purity 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 6.94 (s, 1H), 5.83 (ddt, J = 16.9, 10.1, 6.6 Hz, 1H), 5.03 (br d, J = 17.2 Hz, 1H), 4.95 (br d, J = 10.0 Hz, 1H), 4.34 (q, J = 6.6 Hz, 1H), 3.81−3.71 (m, 1H), 3.47−3.40 (m, 1H), 2.27 (s, 6H), 2.18−2.10 (m, 2H), 1.75−1.63 (m, 2H), 1.49 (d, J = 6.6 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) 138.33, 137.78, 130.10, 129.37, 127.84, 126.49, 118.67, 117.46, 114.67, 88.75, 84.96, 68.12, 65.73, 30.35, 28.94, 22.27, 21.05 (two carbons overlap).

20{***1,7***}.** Yield 5.5 mg (24%, yellow oil); purity 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.22 (m, 5H), 7.05 (s, 2H), 6.94 (s, 1H), 4.39 (q, J = 6.8 Hz, 1H), 4.04−3.95 (m, 1H), 3.70−3.62 (m, 1H), 2.87 (t, J = 6.6 Hz, 2H), 2.27 (s, 6H), 1.50 (d, J = 6.6 Hz, 3H); MS (ES) *m*/*z* 279.64 (MH^+).

20{***1,8***}.** Yield 4.5 mg (22%, yellow oil); purity 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 6.94 (s, 1H), 3.90−3.63 (m, 5H), 2.79−2.72 (m, 2H), 2.60−2.54 (m, 2H), 2.28 (s, 6H), 1.42 (d, J = 7.1 Hz, 3H); MS (ES) *m*/*z* 244.63 (MH^+).

20{***2,2***}.** Yield 7.1 mg (46%, yellow oil); purity 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.3 Hz, 1H), 7.19−7.07 (m, 3H), 5.94 (ddt, J = 17.1, 10.0, 7.0 Hz, 1H), 5.17−5.06 (m, 2H), 2.82−2.73 (m, 1H), 2.40 (s, 3H), 2.34−2.28 (m, 2H), 1.27 (d, J = 6.9 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) 139.88, 136.04, 131.72, 129.22, 127.49, 125.35, 123.60, 116.64, 98.10, 79.85, 45.79, 41.25, 26.66, 20.75.

20{***2,3***}.** Yield 25.8 mg (28%, yellow oil); purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.24 (dd, J = 4.2, 2.9 Hz, 1H), 7.20−7.10 (m, 4H), 7.07 (s, 1H), 4.32−4.28 (m, 1H), 3.76 (s, 3H), 2.44 (s, 3H), 1.71 (d, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) 141.06, 139.99, 131.93, 129.27, 127.56, 125.75, 125.38, 123.82, 121.68, 119.44, 118.84, 109.75, 109.32, 99.38, 97.37, 79.84, 32.61, 24.17, 23.10, 20.77.

20{***2,4***}.** Yield 18 mg (76%, yellow oil); purity 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.04 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.50 (dd, J = 7.6 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.22 (s, 1H), 7.17 (m, 1H), 7.12 (dd, J = 8 Hz, 1H), 4.35 (q, J = 7 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.46 (s, 3H), 1.51 (d, J = 6.99 Hz, 3H).

20{***2,5***}.** Yield 9.9 mg (68%, yellow oil); purity 81%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.3 Hz, 1H), 7.22−7.10 (m, 3H), 4.35 (q, J = 6.6 Hz, 1H), 3.48 (s, 3H), 2.43 (s, 3H), 1.54 (d, J = 6.6 Hz, 3H). Anal. Calcd. For $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.62; H, 7.97.

20{***2,6***}.** Yield 7.3 mg (38%, yellow oil); purity 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.6 Hz, 1H), 7.24−7.16 (m, 2H), 7.15−7.10 (m, 1H), 5.84 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.04 (ddt, J = 17.2, 2.0, 1.6 Hz, 1H), 4.96 (br d, J = 10.4 Hz, 1H), 4.41 (q, J = 6.6 Hz, 1H), 3.82 (dt, J = 9.1, 6.7 Hz, 1H), 3.47 (dt, J = 9.1, 6.5 Hz, 1H), 2.42 (s, 3H), 2.16 (app q, $J \approx 7$ Hz, 2H), 1.73 (app br pent, $J \approx 7$ Hz, 2H), 1.54 (d, J = 6.8 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) 140.32, 138.50, 132.18, 129.55, 128.38, 125.65, 122.93, 114.85, 93.78, 83.76, 68.32, 66.04, 30.57, 29.20, 22.58, 20.82.

20{***2,7***}**.** Yield 6.7 mg (30%, yellow oil); purity 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $J = 7.5$ Hz, 1H), 7.34−7.10 (m, 8H), 4.45 (q, $J = 6.6$ Hz, 1H), 4.08−4.00 (m, 1H), 3.72−3.65 (m, 1H), 2.96 (t, $J = 7.3$ Hz, 2H), 2.41 (s, 3H), 1.54 (d, $J = 6.5$ Hz, 3H); MS (ES) *m*/*z* 265.63 (MH^+).

20{***2,8***}**.** Yield 4.5 mg (23%, yellow oil); purity 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, $J = 7.4$ Hz, 1H), 7.22−7.18 (m, 2H), 7.16−7.09 (m, 1H), 3.80−3.62 (m, 4H), 3.32−3.24 (m, 1H), 2.80−2.73 (m, $J = 9.3$ Hz, 2H), 2.62−2.55 (m, $J = 9.4$ Hz, 2H), 2.48 (s, 3H), 1.45 (d, $J = 6.9$ Hz, 3H); MS (ES) *m*/*z* 230.63 (MH^+).

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