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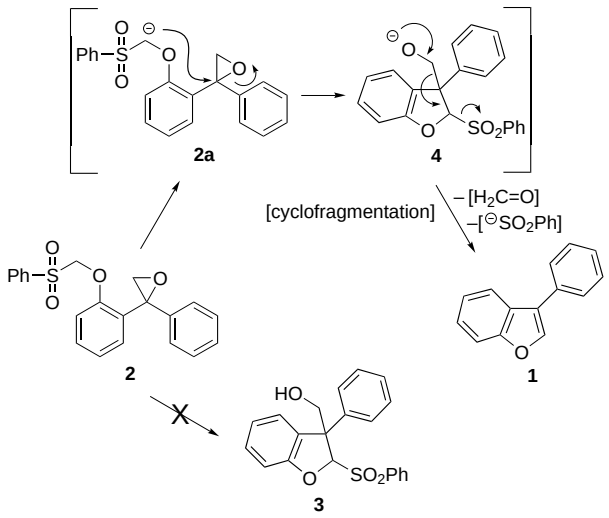
[10] Yields from the solid-support synthesis were determined from the weight of cleaved product and are reported as an overall yield for the sequence based upon the initial loading of the selenium bromide resin (see ref. [4]).
[11] All new compounds exhibited satisfactory spectral and exact mass data.



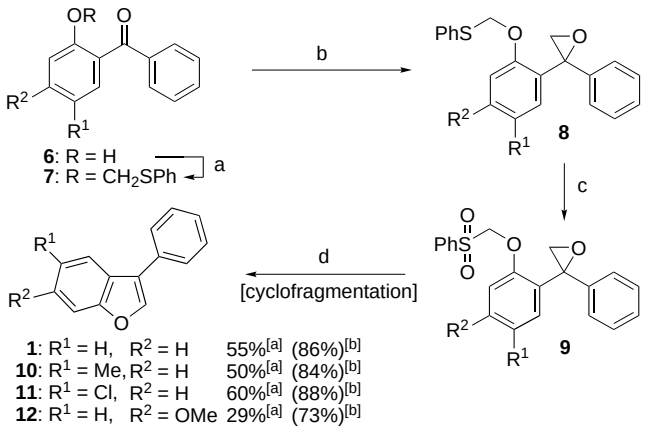
Scheme 1. The cyclofragmentation pathway to 3-arylbenzofurans (**1**).

Solution and Solid-Phase Synthesis of Functionalized 3-Arylbenzofurans by a Novel Cyclofragmentation – Release Pathway**

K. C. Nicolaou,* Scott A. Snyder, Antony Bigot, and Jeffrey A. Pfefferkorn

The 3-arylbenzofuran nucleus is a central component of a diverse class of heterocyclic natural and synthetic products that possess a broad range of biological activities.[1] During the course of recent synthetic investigations we discovered a novel reaction cascade leading to 3-phenylbenzofuran (**1**, Scheme 1), the core structure of the 3-arylbenzofuran class. This serendipitous observation occurred as a result of attempts to convert epoxide **2** (see Scheme 2 for its preparation) into **3** by deprotonation of the methylene group adjacent to the sulfone followed by selective opening of the epoxide ring.[2] Surprisingly, rather than providing the desired system **3**, the only product observed was benzofuran **1**. The proposed mechanism for this transformation, a novel cyclofragmentation pathway, is outlined in Scheme 1, in which after the initial generation of the alkoxide intermediate **4** from a 5-*exo*-trig cyclization, collapse to **1** occurs by the concomitant expulsion of both formaldehyde and a phenylsulfinate anion.[3, 4] Given the importance of 3-arylbenzofurans in biology and medicine, we sought to test the generality of this reaction cascade for the preparation of more highly functionalized systems. Herein, we report the exploration of the scope of this technology, both in solution and on solid support, which led to the generation of a diverse family of 3-arylbenzofurans and the streamlining of the method for use in combinatorial chemistry.

We initially alkylated three commercially available 2-hydroxybenzophenones (**6**) with chloromethylphenyl sulfide to generate **7** (Scheme 2). Subsequent epoxidation with trimethylsulfonium iodide[5] followed by *m*CPBA-mediated oxidation of the sulfide gave **9** in high overall yields. Gratifyingly, treatment of these sulfones with either KO*t*Bu in DMF (–57 °C or 0 °C) or LDA in THF (–78 °C) resulted in the exclusive formation of the desired 3-arylbenzofurans **10** – **12**,[6] thereby establishing the potential of this reaction to generate substituted benzofurans.



Scheme 2. Synthesis of 3-arylbenzofurans (**1**, **10** – **12**) from 2-hydroxybenzophenones. a) $ClCH_2SPh$ (1.3 equiv), K_2CO_3 (1.5 equiv), DMF, 50 °C, 5 h; b) trimethylsulfonium iodide (1.5 equiv), KO*t*Bu (1.0 M in THF, 1.5 equiv), DMSO, 0 °C, 10 min; c) *m*CPBA (2.5 equiv), $NaHCO_3$ (2.5 equiv), CH_2Cl_2, 25 °C, 2 h; d) KO*t*Bu (1.0 M in THF, 2.5 equiv), DMF, 0 °C, 5 min. *m*CPBA = *meta*-chloroperbenzoic acid. [a] Overall yield after four steps. [b] Average yield per step.

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[**] Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), doctoral fellowships from the National Science Foundation (S.A.S.) and the Department of Defense (J.A.P.), and grants from Abbott, Amgen, Boehringer – Ingelheim, Glaxo, Hoffmann – La Roche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

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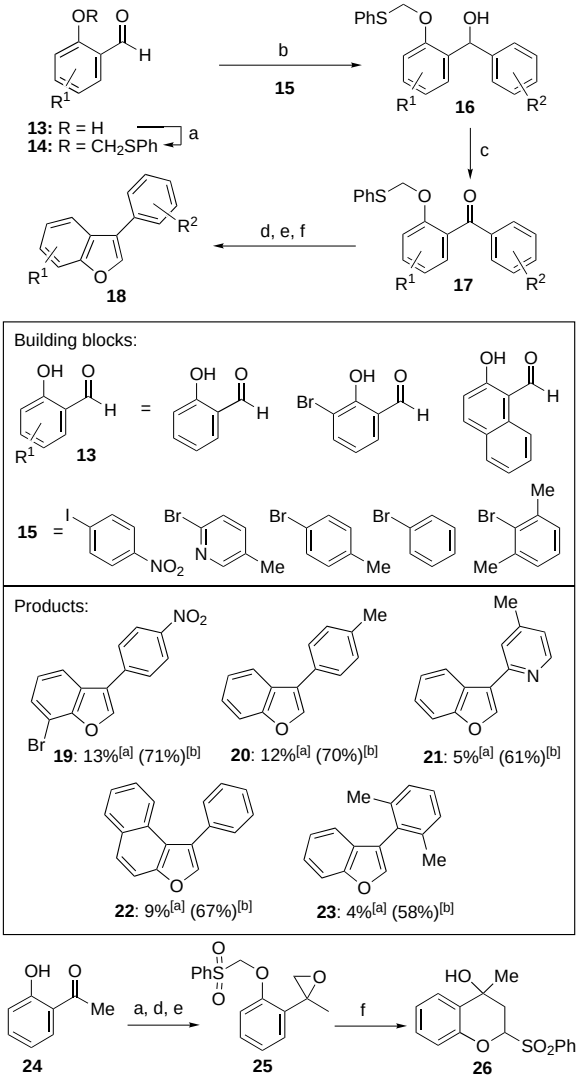
We next undertook a more generalized approach to the construction of the requisite benzophenone precursor so that further diversity could be introduced onto the 3-phenylbenzofuran scaffold (Scheme 3). Initial alkylation of 2-hydroxybenzaldehydes (**13**) with chloromethylphenyl sulfide

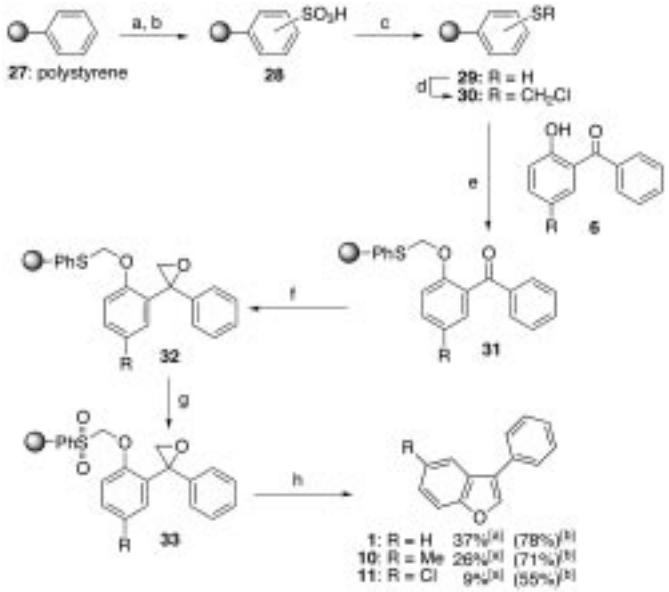


Scheme 3. Synthesis of 3-arylbenzofurans (**19**–**23**). a) $ClCH_2SPh$ (1.3 equiv), K_2CO_3 (1.5 equiv), DMF, 50 °C, 5 h; b) aryl halide (1.1 equiv), *n*BuLi (1.6 M in hexanes, 1.1 equiv), THF, −78 °C; then **14**, −78 °C, 5 min; c) MnO_2 (10.0 equiv), CH_2Cl_2, 25 °C, 12 h; d) trimethylsulfonium iodide (1.5 equiv), KO*t*Bu (1.0 M in THF, 1.5 equiv), DMSO, 0 °C, 10 min; e) *m*CPBA (2.5 equiv), $NaHCO_3$ (2.5 equiv), CH_2Cl_2, 25 °C, 2 h; f) KO*t*Bu (1.0 M in THF, 2.5 equiv), DMF, 0 °C, 5 min. [a] Overall yield after four steps. [b] Average yield per step.

followed by nucleophilic attack or the aldehyde using an aryl lithium species afforded benzhydrols **16**. Subsequent selective oxidation of the bisbenzylic secondary alcohol with MnO_2 provided the desired functionalized benzophenones (**17**), which were then transformed to 3-arylbenzofuran derivatives **19**–**23** by using the protocol described above. Rather than performing a serial coupling of each benzaldehyde and aryl lithium building block, we instead sought to test only the diversity that could be incorporated onto the final scaffold. Not only were both electron-withdrawing and electron-donating groups tolerated, but pyridyl (**21**),[7] naphthyl (**22**), and sterically hindered analogues such as xylene derivative **23** were also readily obtained.

To verify that both aryl groups were required for regioselective epoxide opening, an attempt was made to generate 3-methylbenzofuran starting from 2-hydroxyacetophenone (**24**, Scheme 3). As expected, after elaboration to the corresponding sulfone (**25**), base treatment led solely to **26** (as a diastereomeric mixture at the quaternary center), the exclusive product of a 6-*endo*-trig cyclization. The only other instance in which such a product was observed was during the final reaction to generate naphthyl analogue **22**, where intramolecular nucleophilic attack at the quaternary carbon center of the epoxide is conformationally less favored than in other cases, and resulted in the formation of equal amounts of both **22** and the 6-*endo*-trig congener.

Given the generality of this method for the construction of 3-arylbenzofurans in solution, we hoped to adapt the strategy to a solid-phase approach, thereby facilitating its use in combinatorial synthesis.[8] Examination of the proposed cyclofragmentation mechanism (Scheme 1) suggested that the requisite solid support might be tethered to the scaffold through the thiophenyl functionality. The advantage of such a strategy would be threefold: 1) linking at this position allows for incorporation of full diversity on either aromatic ring; 2) since the phenylsulfinate moiety is ultimately expelled



Scheme 4. Preparation of the chloromethyl sulfide resin and preliminary studies on the loading and cyclofragmentation release of 3-arylbenzofurans. a) *n*BuLi (1.2 equiv), polystyrene (1.0 equiv, 1 % DVB cross-linked, 100–200 mesh), TMEDA (1.0 equiv), cyclohexane, 65 °C, 4 h; b) $SO_3 \cdot NMe_3$ (1.5 equiv), THF, 0 → 25 °C, 8 h; c) I_2, (5.0 equiv), Ph_3P (15.0 equiv), benzene, 80 °C, 8 h; d) DBU (3.0 equiv), $BrCH_2Cl$, 25 °C, 12 h; e) benzophenone **6** (10.0 equiv), Cs_2CO_3 (5.0 equiv), DMF, 95 °C, 12 h; f) trimethylsulfonium iodide (10.0 equiv), KO*t*Bu (1.0 M in THF, 10.0 equiv), THF:DMSO (1:1), 0 → 25 °C, 2 h; g) *m*CPBA (10.0 equiv), $NaHCO_3$ (15.0 equiv), CH_2Cl_2, 25 °C, 12 h; h) KO*t*Bu (1.0 M in THF, 10.0 equiv), DMF, 0 → 25 °C, 15 min. DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene, DVB = divinylbenzene; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. [a] Overall yield of isolated product based on a resin loading of 0.21 mmol g^{-1}. [b] Average yield per step.

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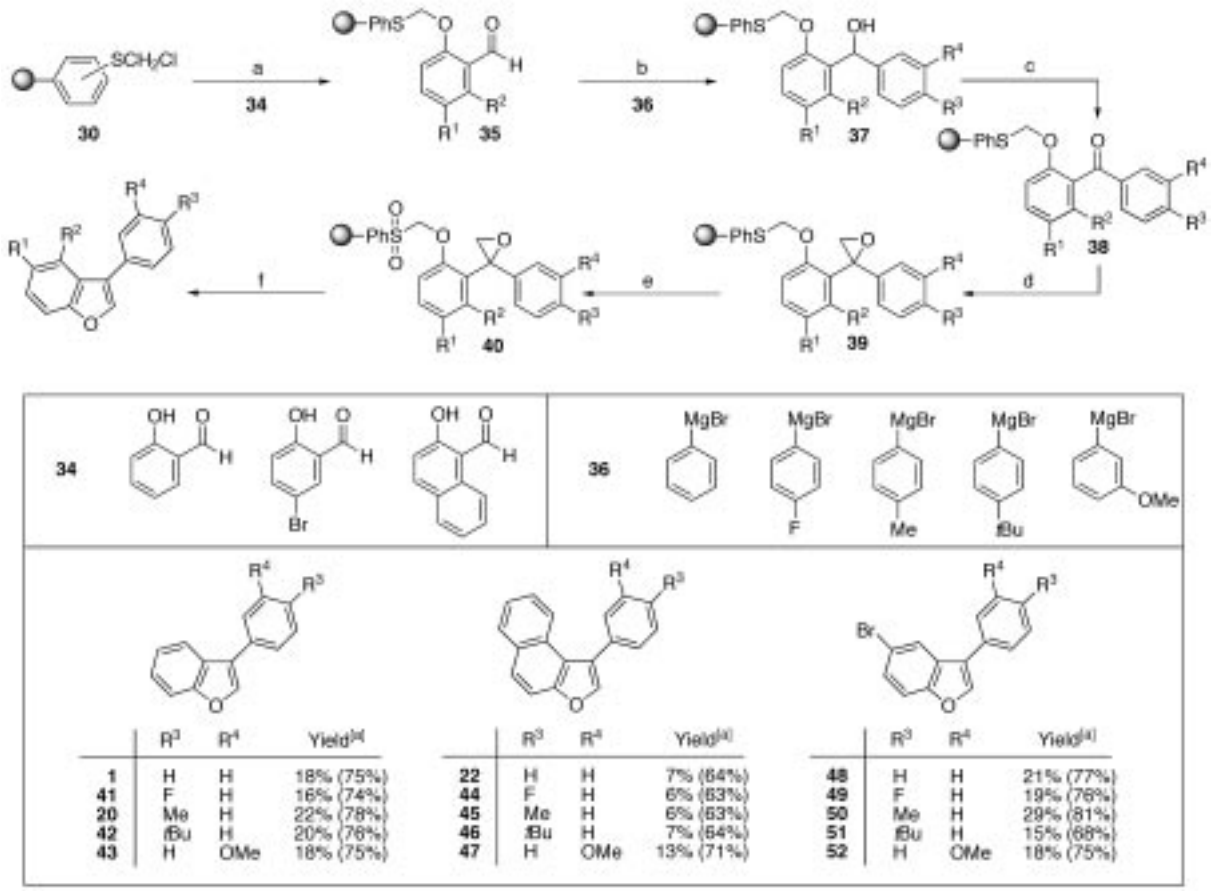
during product formation, substrates will undergo traceless release; 3) linking through the aryl sulfone imparts a fail-safe feature to the cleavage step, since only the desired benzofuran skeleton can undergo release, thereby ensuring that the final products will be isolated in high purity.[9, 10]

To test this solid-phase strategy we required the polymer-bound equivalent of the previously used chloromethylphenyl sulfide, which we envisaged could be constructed from a polymeric phenylthiol.[11] Thus, polystyrene was lithiated[12] and then quenched with $SO_3 \cdot NMe_3$[13] to provide sulfonic acid resin[14] **28** (Scheme 4, see page 1094), which was subsequently reduced to the free thiol resin **29** upon treatment with I_2/Ph_3P.[15] Resin **29** became dark orange upon standing in air for two hours, presumably as a result of oxidative cross-linking; therefore, freshly prepared **29** was immediately alkylated with $ClCH_2Br$ in the presence of DBU[16] to provide **30** as a stable resin that could be stored under ambient conditions. To confirm the viability of our linking/cleavage strategy, we loaded the previous 2-hydroxybenzophenones (**6**) onto the chloromethylsulfide resin to give structures **31**, which were subsequently elaborated to sulfones **33** by utilizing the same methodology as described above. Gratifyingly, the 3-phenylbenzofurans **1**, **10**, and **11** were cleanly released from the solid support in greater than 95% purity upon treatment with KO*t*Bu, with no other side-products observed.

With the fidelity of the tethering strategy confirmed, we sought to generalize this method to accommodate greater structural diversity. Hence, a series of functionalized salicylaldehydes (**34**) were loaded onto resin **30** (Scheme 5). The resulting resin-bound aldehydes were then treated with a series of arylmagnesium bromides (**36**) to give **37** and subsequently selectively oxidized with IBX[8e] to afford benzophenones **38**. Interestingly, although the controlled use of an aryllithium reagent in solution readily provided benzhydrols such as **16** (Scheme 3), large excess of the lithium reagent failed to generate **37** (Scheme 5). On the basis of additional solution studies, the extra base probably deprotonates the methylene group adjacent to the sulfide moiety, leading to several rearrangement side-products. With **38** in hand, sulfur ylide epoxidation followed by *m*CPBA oxidation gave resin-bound sulfones **40** via **39** as before, which provided 3-arylbenzofurans **1**, **20**, **22**, and **41**–**52** upon treatment with KO*t*Bu. As expected, all cleavage products were remarkably clean, presumably since the product of any structures other than **40** remained bound to the resin.

In conclusion, a novel synthetic methodology leading to 3-arylbenzofurans has been developed both in solution and on solid support. The cascade pathway for the generation of the benzofuran system is particularly well-suited to solid-phase synthesis, which permits the efficient generation of a large



	R^3	R^4	Yield[a]
1	H	H	18% (75%)
41	F	H	16% (74%)
20	Me	H	22% (78%)
42	*t*Bu	H	20% (76%)
43	H	OMe	18% (75%)

	R^3	R^4	Yield[a]
22	H	H	7% (64%)
44	F	H	6% (63%)
45	Me	H	6% (63%)
46	*t*Bu	H	7% (64%)
47	H	OMe	13% (71%)

	R^3	R^4	Yield[a]
48	H	H	21% (77%)
49	F	H	19% (76%)
50	Me	H	29% (81%)
51	*t*Bu	H	15% (68%)
52	H	OMe	18% (75%)

Scheme 5. Solid-phase parallel synthesis of 3-arylbenzofurans (**1**, **20**, **22**, **41**–**52**). a) **34** (10.0 equiv), Cs_2CO_3 (5.0 equiv), DMF, 95 °C, 12 h; b) **36** (10.0 equiv), −20 → 0 °C, 3 h; c) IBX (10.0 equiv), THF:DMSO (1:1), 25 °C, 2 h; d) trimethylsulfonium iodide (10.0 equiv), KO*t*Bu (1.0 M in THF, 10.0 equiv), THF:DMSO (1:1), 0 → 25 °C, 2 h; e) *m*CPBA (10.0 equiv), $NaHCO_3$ (15.0 equiv), CH_2Cl_2, 25 °C, 12 h; f) KO*t*Bu (1.0 M in THF, 10.0 equiv), DMF, 0 → 25 °C, 15 min. IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one. [a] Overall isolated yield based on a resin-loading of 0.21 mmol g^{-1}; average yield per step is given in parentheses.

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number of compounds in high purity for potential applications in chemical biology and medicinal chemistry. Continuing efforts are aimed towards the development of additional carbonyl-based coupling strategies to extend the scope of this method into new structural classes.

Received: October 11, 1999 [Z14139]

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[2] Although nucleophiles typically open epoxides at the less substituted carbon atom, we envisaged that this steric bias could be overcome by the electron-donating effect of the two aryl rings, which would sufficiently stabilize any cationic character at the quaternary center to facilitate preferential nucleophilic opening at that site. In general, Lewis acid catalysts are required to direct the attack of the nucleophile preferentially at such a position (see A. Mordini, S. Bindi, S. Pecchi, A. Capperucci, A. Degl'Innocenti, G. Reginato, *J. Org. Chem.* **1996**, *61*, 466 – 468).

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[4] Although the mechanism drawn in Scheme 1 proceeds by a putative S_N2 pathway, one could envision sufficient generation of cationic character at the quaternary carbon atom of the epoxide to permit a competitive S_N1 reaction leading to the formation of **4** from **2a**.

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[6] In the case of **12**, some rearrangement of the epoxide to the corresponding aldehyde was noted prior to cyclization, which accounts for the lower yield observed (see A. Kumar, R. Singh, A. K. Mandal, *Synth. Commun.* **1982**, *12*, 613 – 619).

[7] Pyridines are readily *N*-oxidized when exposed to *m*CPBA; however, in this case we found that sulfide oxidation occurred in preference to *N*-oxide formation as long as only 2.0 equivalents of *m*CPBA were utilized at 0 °C.

[8] For previous solid-phase syntheses of benzofurans, see a) A. Routledge, C. Abell, S. Balasubramanian, *Synlett* **1997**, 61 – 62; b) D. Fancelli, M. C. Fagnola, D. Severino, A. Bedeschi, *Tetrahedron Lett.* **1997**, *38*, 2311 – 2314; c) H.-C. Zhang, B. E. Maryanoff, *J. Org. Chem.* **1997**, *62*, 1804 – 1809; d) X. Du, R. W. Armstrong, *J. Org. Chem.* **1997**, *62*, 5678 – 5679; e) T. L. Boehm, H. D. H. Showalter, *J. Org. Chem.* **1996**, *61*, 6498 – 6499. For the use of polymer-supported reagents in the synthesis of 3-arylbenzofurans, see f) J. Habermann, S. V. Ley, R. Smits, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2421 – 2423.

[9] For example, in solution studies neither the sulfide nor the sulfoxide congeners of **2** underwent the desired cyclofragmentation upon treatment with base to give 3-phenylbenzofuran (**1**); thus, generation of the sulfone activated the resin for cleavage. Moreover, a failure in any previous step (Grignard addition, alcohol oxidation, or epoxidation) would result in a structure incapable of undergoing the cyclofragmentation – release cascade.

[10] Our laboratory has been engaged for several years in the development of novel resins and improved linking and release strategies, see a) K. C. Nicolaou, N. Winssinger, J. Pastor, F. Murphy, *Angew. Chem.* **1998**, *110*, 2677 – 2680; *Angew. Chem. Int. Ed.* **1998**, *37*, 2534 – 2537; b) K. C. Nicolaou, J. Pastor, N. Winssinger, F. Murphy, *J. Am. Chem. Soc.* **1998**, *120*, 5132 – 5133; c) K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268 – 272; d) K. C. Nicolaou, N. Winssinger, D. Vourloumis, T. Oshima, S. Kim, J. Pfefferkorn, J.-Y. Xu, T. Li, *J. Am. Chem. Soc.* **1998**, *120*, 10814 – 10826; e) K. C. Nicolaou, N. Winssinger, J. Pastor, D. Frederik, *J. Am. Chem. Soc.* **1997**, *119*, 449 – 450; f) K. C. Nicolaou, J. A. Pfefferkorn, G.-Q. Cao, S. Kim, J. Kessabi, *Org. Lett.* **1999**, *1*, 807 – 810; g) K. C. Nicolaou, J. A. Pfefferkorn, G.-Q. Cao, *Angew. Chem.* **2000**, *112*, 750 – 755; *Angew. Chem. Int. Ed.* **2000**, *39*, 734 – 739; h) K. C. Nicolaou, G.-Q. Cao, J. A. Pfefferkorn, *Angew. Chem.* **2000**, *112*, 755 – 759; *Angew. Chem. Int. Ed.* **2000**, *39*, 739 – 743.

[11] To the best of our knowledge, most previously described polystyrene thiophenol resins contain an aliphatic amide spacer between the polymer backbone and the thiophenol moiety (see I. Parrot, C.-G. Wermuth, M. Hibert, *Tetrahedron Lett.* **1999**, *40*, 7975 – 7978). Since the abstraction of protons adjacent to the amide functionality during the KO*t*Bu cleavage step might interfere with product release, we sought to prepare a spacerless resin.

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[13] K. Smith, D. Hou, *J. Org. Chem.* **1996**, *61*, 1530 – 1532.

[14] While numerous polystyrene sulfinic acid resins are available, most are used as scavenger resins (for example, Dowex WX4 – 50), and hence are too highly loaded to be practical for solid-phase organic synthesis.

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[16] N. Ono, H. Miyake, T. Saito, A. Kaji, *Synthesis* **1980**, 952 – 953.

Novel Ruthenium Building Blocks for the Efficient Modular Construction of Heterobimetallic Molecular Squares of Porphyrins**

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The construction of structurally well defined, highly ordered supramolecular systems containing porphyrins and metalloporphyrins is of prime interest. By virtue of the

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[**] This work was supported by the Italian MURST. We thank Prof. L. G. Marzilli (Emory University, Atlanta, USA) for helpful discussions, and Johnson Matthey for a loan of $RuCl_3 \cdot x H_2O$. The CNR staff at ELETTRA is acknoweldged for help in the use of the facility supported by CNR and Elettra Scientific Division.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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