A New Germanium-Based Linker for Solid Phase Synthesis of Aromatics: Synthesis of a Pyrazole Library

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An efficient synthesis of chlorogermane linker **12** is described. Economic introduction of germanium into this linker is accomplished by insertion of dichlorogermylene [from germanium(IV) chloride] into the homobenzylic C−Cl bond of 4-(2-chloroethyl)phenol **1**. Using linker **12**, transmetalation with lithiated 4-acetophenone, 3-acetophenone, and 4-(4′methoxy)biphenyl followed by Mitsunobu-type coupling to Argogel gives functionalized resins **14**, **16**, and **18**, respectively. Treatment of resin **18** with TFA, ICl, Br_2, or NCS effects clean *ipso*-degermylation releasing biphenyls **19**−**22**, respectively. Resins **14** and **16** are employed for the parallel synthesis of a library of pyrazoles by enaminone formation (using Bredereck's reagent), condensative ring-closure (using a series of monosubstituted hydrazines), and cleavage (using TFA and Br_2). Analysis of this library reveals the influence of the hydrazine substituent on both the regioselectivity of ring-closure and the propensity for electrophilic substitution at the 4-position of the pyrazoles during *ipso*-degermylative cleavage.

Introduction

Group 14 metals form the cornerstone of a number of linker strategies in solid-phase organic synthesis (SPOS),[1] and as such have been utilized for the immobilization of a diverse array of molecules onto the solid phase.[2] Silicon in particular commands a pre-eminent position by virtue of its incorporation into both silyl ether-based linkers (for the immobilization of alcohols)[3,4] and arylsilane-based linkers (for the immobilization of aromatics).[5] Mirroring the versatility of silyl ether-protecting groups in solution,[6] silyl ether-based linkers are stable to a relatively wide range of reaction conditions and are readily cleaved with acid (e.g., TFA)[7] or fluoride (e.g., HF)[8] to liberate alcohols. Aryl silane-based linkers are also stable to a relatively wide range of reaction conditions and can be cleaved via *ipso*-protodesilylation with acid (e.g., TFA)[7] to liberate aromatics in a "traceless" fashion.[5,9−18] Cleavage with concomitant diversification has also been achieved via *ipso*-halodesilylation using Br_2 and ICl (liberating arylbromides and iodides, respectively).[13,19,20]

However, one limitation to the use of arylsilane-based linkers for SPOS is the necessity for harsh conditions (e.g., neat HF) when cleaving electron-deficient aromatics.[10] One tactic that addresses this problem involves the utilization of anchimeric assistance of, for example, a β-amide carbonyl, to increase the reactivity of arylsilanes toward *ipso*-protiodesilylative cleavage.[15,16,20,21] Alternatively, susceptibility toward electrophilic *ipso*-demetalation can been increased by exchanging silicon for germanium[17,22] or tin.[23−25] This is because these Group 14 elements exert a greater β-effect in the rate-determining

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† Single-crystal X-ray analysis.

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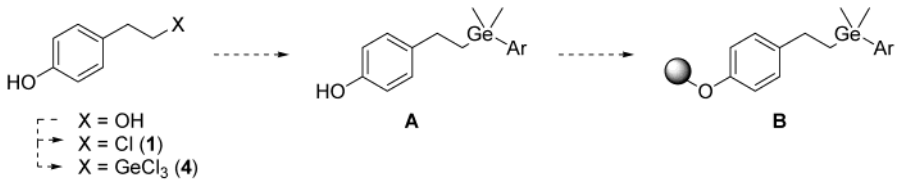
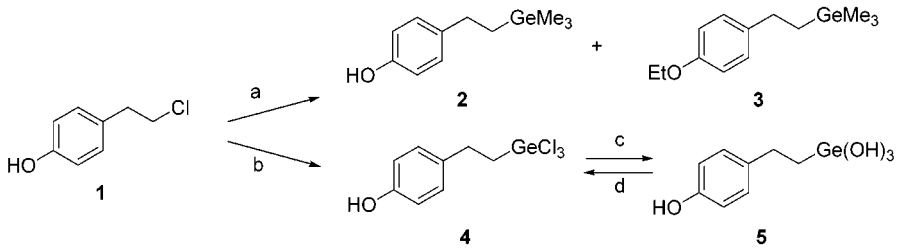
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) (i) $HGeCl_3 \cdot 2Et_2O$, Et_2O, 40 °C, 5 days, (ii) MeMgBr, Et_2O, 1 h, [→ **2** (75%) + **3** (4%) + **1** (8%)]; (b) $GeCl_2 \cdot C_4H_8O_2$, 1,4-dioxane, 140 °C, 16 h; (c) H_2O and wash; (d) HCl, CH_2Cl_2, [→ **4** (91% from **1**)]

electrophilic *ipso*-addition step (Sn ≫ Ge > Si).[23,26,27] Although aryltin-based linkers potentially offer the mildest cleavage conditions, their extreme lability toward acidic/electrophilic conditions, coupled with toxicity concerns, seriously limits their versatility for library construction. Arylgermane-based linkers however can be viewed as offering an appealing compromise: they display intermediate susceptibility to electrophilic cleavage relative to their arylsilane and aryltin analogues, with the additional and significant advantage of enhanced stability toward bases and nucleophilies.[28,29] Aryl and alkylgermanes also generally display comparably low toxicity to their silane counterparts.[30] This is gratifying during synthesis and crucial should trace quantities leach into biological assays. The development of useful germanium-based linker strategies however has been restricted by the high cost of small partially akylated germyl halides, analogous to those used in the synthesis of silicon-based linkers.

Cognisant of this situation, we embarked upon the development of a novel SPOS immobilization strategy for aromatics based around a 4-(2-dimethylgermylethyl)-phenol unit.[22] It was envisaged that this could be attached under Mitsunobu conditions[31] to commercial hydroxy-functionalized resins, e.g., Argogel,[32,33] via the phenolic hydroxyl group (Scheme 1).We selected 4-(2-chloroethyl)phenol **1**[34] as our starting material because this homobenzylic chloride was anticipated to allow facile insertion of dichlorogermylene into its C−Cl bond to give trichlorogermane **4** as the result of precedented $Ar_1^{\ominus}$-3 neighboring group participation by the phenolic ring.[35] Furthermore, the homobenzylic C−Ge bond thus formed was anticipated to be stable towards electrophiles, thereby preventing leaching of germanium-containing material during electrophilic *ipso*-degermylative library cleavage. It was initially envisaged that trichlorogermane/diethyl etherate complex[36,37] would be employed as the source of dichlorogermylene because of its simple preparation from inexpensive germanium(IV) chloride by reduction with tetramethyldisiloxane (TMDS).[38,39] Selective "capping"[40,41] of trichlorogermane **4** by careful control of the stoichiometry in reaction with a methyl Grignard reagent and the desired arylmetal "library precursor" (e.g., MeMgBr/ArLi, 2:1) would give arylgermane **A** and set the stage for Mitsunobu-type coupling to the resin (→ **B**) (Scheme 1).

Results and Discussion

4-(2-Chloroethyl)phenol[34] **1,** and trichlorogermane/diethyl etherate complex,[38] were prepared following literature one-step procedures from 4-(2-hydroxyethyl)phenol (90%) and germanium(IV) chloride (82%), respectively. However, dichlorgermylene insertion into chloride **1** using trichlorogermane/diethyl etherate complex was very sluggish. Even after 5 days at reflux in Et_2O,[42] and following exhaustive methylation with MeMgBr to facilitate purification by chromatography, 4-(2-trimethylgermylethyl)phenol **2** was isolated in variable yield (28−75%) accompanied by its ethyl ether **3** (4−20%) and recovered chloride **1** (4−10%) (Scheme 2). Formation of ether **3** was attributed to the strong acidity of trichlorogermane/diethyl etherate complex, probably exacer-

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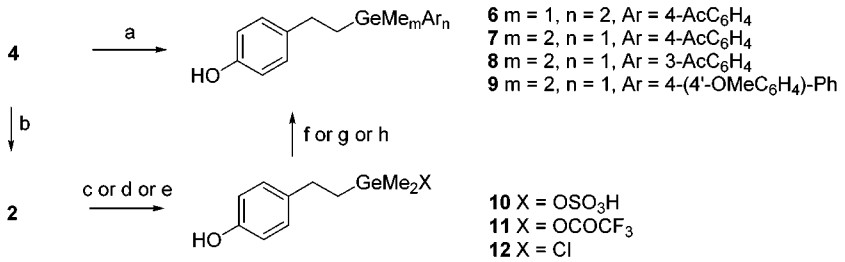
(42) Trichlorogermane/diethyl etherate complex decomposes rapidly in other solvents preventing its use in higher boiling solvents.

Scheme 3[a]



[a] Reagents and conditions: (a) (i) MeMgBr (3 equiv), Et_2O, -78 °C, 30 min, (ii) *n*-BuLi/2-(4-bromophenyl)-2-methyl-1,3-dioxolane, THF, hexane, −78 → 20 °C, 16 h, (iii) PPTS, acetone, H_2O, 67 °C, 16 h, [→ **6** (37%) + 7 (17%) + **2** (28%)]; (b) MeMgBr (6 equiv), Et_2O, toluene, 110 °C, 16 h, 82%; (c) H_2SO_4, (→ **10**; see text); (d) TFA, reflux, (→ 11, see text); (e) $SnCl_4$, $MeNO_2$, 50 °C, 16 h, [→ **12** (99%)]; (f) (i) *n*-BuLi/2-(4-bromophenyl)-2-methyl-1,3-dioxolane, THF, hexane, −78 → 110 °C, 16 h, (ii) PPTS, acetone, H_2O, 67 °C, 16 H, [**12** → **7** (86%)]; (g) (i) *n*-BuLi/2-(3-bromophenyl)-2-methyl-1,3-dioxolane, THF, hexane, −78 → 110 °C, 16 h, (ii) PPTS, acetone, H_2O, 67 °C, 16 h, [**12** → **8** (43%)]; (h) *n*-BuLi/4-bromo-4′-methoxy biphenyl, THF, hexane, −78 → 110 °C, 22 h, [**12** → **9** (85%)].

bated by its degradation at elevated temperature.[43] To circumvent this, we turned our attention to the air-stable and crystalline dichlorogermylene/1,4-dioxane complex ($GeCl_2 \cdot C_4H_8O_2$).[44−47] This complex, like the diethyl etherate, is prepared by reduction[48,49] of germanium(IV) chloride with TMDS.[38] However, employing refluxing 1,4-dioxane (bp 102 °C) in place of refluxing Et_2O (bp 35 °C) leads to in situ α-elimination of HCl, from the initially formed trichlorogermane, to give the essentially neutral dichlorogermylene complex. This beautiful white crystalline compound was routinely obtained in good yield (75%) by simple suction filtration of the crude reaction mixture in air.

Dichlorogermylene insertion into chloride **1** using dichlorogermylene/1,4-dioxane complex was much more rapid, resulting in the formation of 4-(2-trichlorogermylethyl)phenol **4** in excellent yield after just 16 h as judged by crude ^{1}H NMR (Scheme 2).[50] Unfortunately, we were unable to purify this compound by either chromatography or distillation, and so, a two-step chemical purification had to be developed.[51] Thus, hydrolysis of trichlorogermane **4** resulted in precipitation of the uncharacterized germyl oxide **5** as an amorphous polymer. This was washed with CH_2Cl_2 (to remove any traces of starting material) and water (to remove water-soluble monomeric germanium oxide impurities resulting from hydrolysis of any excess dichlorogermylene complex). After drying, the solid was dissolved in concentrated HCl, thereby regenerating trichlorogermane **4**, which could be obtained in 91% yield, analytically pure, following re-extraction into CH_2Cl_2.[52]

With trichlorogermane **4** in hand, we were in a position to investigate introduction of an aromatic library precursor onto the germanium. We chose initially to investigate 3- and 4-acetophenones as we envisaged that these would provide versatile functional handles for library construction. Despite precedent for the selective capping of trihalogermanes with aryl and alkyl organometallics[40,41] repeated attempts to cap trichlorogermane **4** using various combinations of MeMgBr with either the lithium or Grignard[53] derivatives of 2-(4-bromphenyl)-2-methyl-1,3-dioxolane[53] proved unsatisfactory in our hands (Scheme 3). Despite extensive experimentation using a variety of solvents, temperatures and stoichiometries a roughly statistical distribution of diarylmethylgermane **6**, aryldimethylgermane **7**, and trimethylgermane **2** resulted following dioxolane deprotection. For example, treatment of trichlorogermane **4** with MeMgBr (3 equiv) in Et_2O at −78 °C for 30 min followed by addition of lithiated 2-(4-bromophenyl)-2-methyl-1,3-dioxolane and allowing to warm to room temperature afforded diarylmethylgermane **6** (37%), desired aryldimethylgermane **7** (17%), and an inseparable mixture of trimethylgermane **2** (∼28% by ^{1}H NMR) and acetophenone following dioxolane deprotection.

It was apparent that a new strategy was required, and we elected to investigate mono-demethylation of trimethylgermane **2**,[54] as this derivative could be prepared in 82% yield by exhaustive methylation of trichlorogermane **4** using excess MeMgBr (Scheme 3). Provided chemoselective mono-demethylation could be achieved, subsequent capping with our metalated 3- and 4-acetophenone library precursors would give us the desired aryldimethylgermanes **7**/**8** with the advantage that this capping reaction would not be constrained by the need for exact stoichiometry. Of the various methods that have been reported for mono-dealkylation/heterofunctionalization of alkylgermanes,[55−63] we chose initially to inves-

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(50) Interestingly, 2-phenethyl chloride underwent dichlorogermylene insertion much more slowly giving 2-phenethyltrichlorogermane in just 16% yield after 16 h under identical conditions and lending credence to the involvement of neighboring group participation by the phenolic ring in reaction with chloride **1**.
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(52) Use of CH_2Cl_2 is important. When $CHCl_3$ was employed, a trace of the corresponding dichlorogermanium oxide was also re-extracted.
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(54) Commercially available from AFChemPharm Ltd., Unit C14, Alison Centre, Alison Cresent, Sheffield, S2 1AS, U.K.
(55) Mono-dealkylation (as opposed to poly-dealkylation) usually occurs in this type of electrophilic substitution reaction because the heteroatom introduced strongly inductively deactivates the product towards further substitutive dealkylation. Forcing conditions however can lead to preparatively useful di-dealkylation in certain cases. See Bulten and Dreneth.[67]
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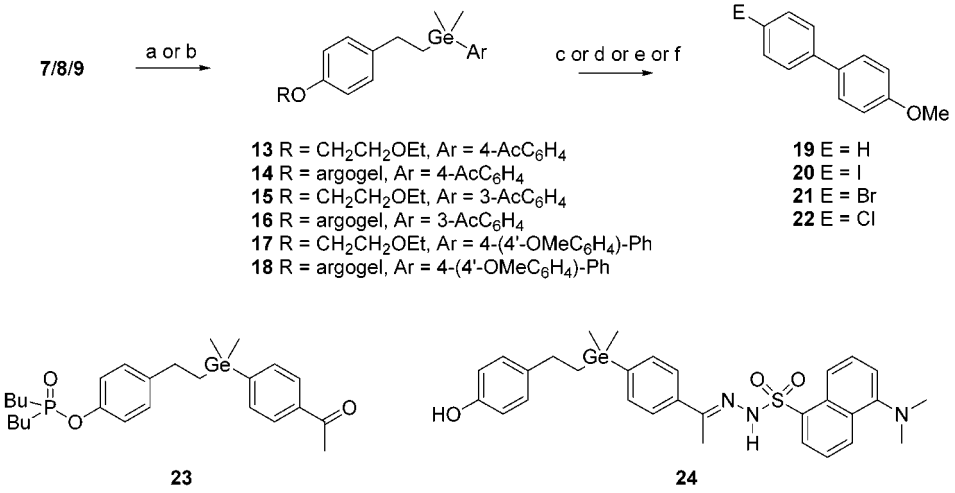
Scheme 4[a]



[a] Reagents and conditions: (a) ethoxy ethanol, TMAD, PBu_3, benzene, 16 h, [**7** → **13** (87%), **8** → **15** (90%), **9** → **17** (99%)]; (b) Argogel (0.49 mmol g^{-1}), TMAD, PBu_3, PhH, 16 h, [**7** → **14** (0.43 mmol g^{-1}), **8** → **16** (0.44 mmol g^{-1}), **9** → **18** (0.47 mmol g^{-1})]; (c) TFA, 16 h, [**17** → **19** (98%)]; (d) ICl, CH_2Cl_2, 15 min, [**17** → **20** (98%)]; (e) Br_2, CH_2Cl_2, 15 min, [**17** → **21** (93%)]; (f) NCS, THF, 70 °C, 14 h, [**17** → **22** (62%)].

tigate monosulfodemethylation using neat concentrated H_2SO_4.[64,65] Although promising in so much as methane was evolved as required, these experiments were thwarted by our inability to recover any sulfogermane **10** from the reaction mixture. To circumvent this problem, we replaced H_2SO_4 with refluxing TFA.[66] This allowed isolation of product simply by evaporation. However, under these conditions, undesired mono-dephenethylation was competitive with demethylation as revealed by ^{1}H NMR which showed a ~1:3 mixture of trifluoroacetoxygermane **11** and 4-ethylphenol. In response to this lack of selectivity, we turned to Lewis acid mediated mono-halodemethylation as Bulten and Noltes have shown that $SnCl_4$ in $MeNO_2$ effects totally chemoselective mono-chlorodemethylation of a number of methyl trialkylgermanes containing Et, Pr, and Bu groups.[67,68] Gratifyingly, we were able to reproduce this selectivity using our linker precursor **2**. Thus, using their conditions, 4-chlorodimethylgermane **12** could be isolated in quantitative yield following removal of $MeNO_2$, any excess $SnCl_4$, and $MeSnCl_3$ in vacuo (Scheme 3). As expected, reactions of chlorodimethylgermane linker **12** with excess lithiated 2-(4-bromophenyl)-2-methyl-1,3-dioxolane, and 2-(3-bromophenyl)-2-methyl-1,3-dioxolane (i.e., our library precursors) were uneventful and led, following dioxolane deprotection, to the isolation of aryldimethylgermanes **7** and **8** in 86% and 43% yields, respectively.

Optimization of Mitsunobu-type coupling to Argogel was carried out initially with aryldimethylgermane **7**, using ethoxy ethanol as a soluble surrogate for the PEG-based resin. Use of the standard REDOX system [DEAD/PPh_3] failed to produce any coupled product **13**. However, Castro's betaine[69] and Tsunoda's 1,1′-(azodicarbonyl)-dipiperidine[70] (ADDP)/PBu_3 REDOX systems resulted in modest conversions (32% and 42%, respectively) to coupled product **13**. Unexpectedly, dibutylphosphonate **23** (10%) was isolated as a byproduct from the ADDP reaction, possibly as the result of a rearrangement around a pentavalent phosphorus intermediate on the reaction pathway.[71] Eventually, Tsunoda's *N*,*N*′,*N*,*N*′-tetramethylazocarboxamide[72] (TMAD)/PBu_3 REDOX system was found to be optimal giving 87% coupled product **13** for the model system and a loading level of 0.43 mmol g^{-1} for functionalized Argogel resin **14**.[73] Similarly, aryldimethylgermane **8** was coupled to ethoxy ethanol (→ **15**) in 90% yield and to Argogel (→ **16**)[73] with a loading level of 0.44 mmol g^{-1} (Scheme 4). Functionalized resin **14** was characterized by magic angle spinning (MAS) ^{1}H NMR and IR. The loading level was determined by mass balance for introduction of the arylated linker (and corroborated following *ipso*-degermylative cleavage).[74] We also attempted to verify the loading level fluorimetrically after derivatization with dansyl hydrazine.[75] However, significant degradation of the dansyl hydrazine solution occurred over the 5 h period required for complete hydrazone formation even with model aryldimethylgermane **7** (→ hydrazone **24**). This precluded quantitative interpretation of the fluorescence spectra.

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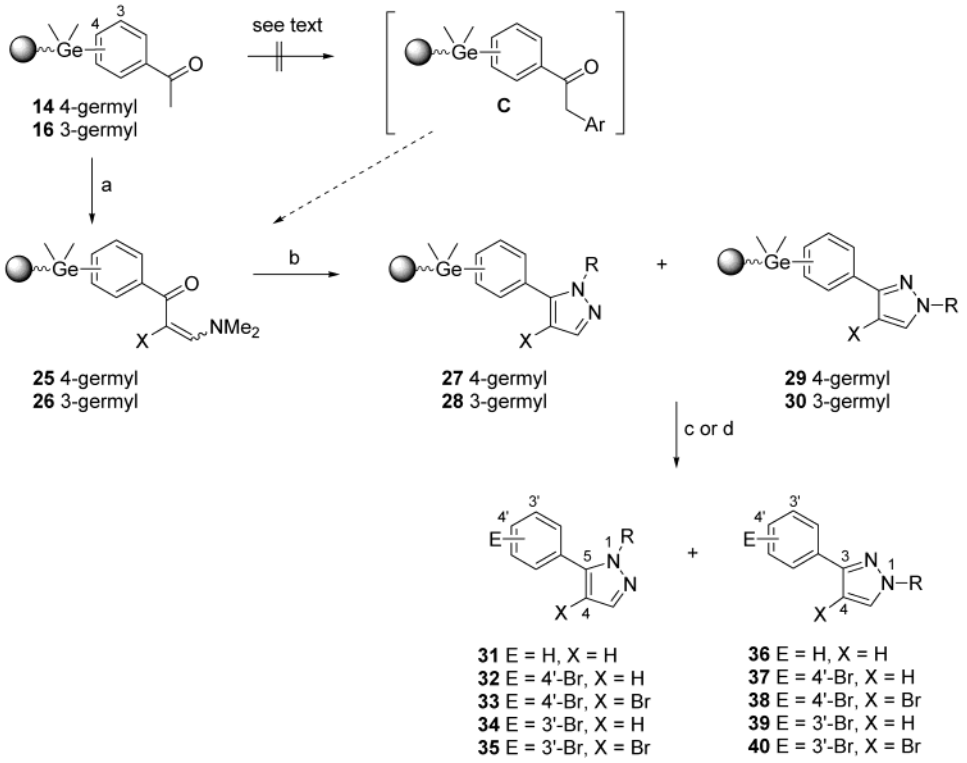
Scheme 5[a]



[a] Reagents and conditions: (a) Bredereck's reagent, THF, 70 °C, 3 h; (b) $RNHNH_2 \cdot HCl$, *n*-BuOH/AcOH (50:1), 100 °C, 1 h; (c) TFA, 16 h; (d) Br_2, CH_2Cl_2, 15 min.

We decided to optimize the conditions for *ipso*-degermylative cleavage from the linker using a different immobilized aromatic: 4-(4′-methoxy)biphenyl. This compound was chosen because the ortho positions on the constituent anisole ring were expected to be highly susceptible to standard electrophilic substitution and we wanted to determine whether the required *ipso*-degermylative cleavage would prevail in the face of such competition. Again we opted to employ a soluble model system for our initial studies, and so, biaryldimethylgermane **17** was synthesized in an analogous fashion to linker models **13** and **15** by treatment of chlorodimethylgermane **12** with lithiated 4-bromo-4′-methoxy biphenyl [→ **9** (85%)] followed by TMAD/PBu_3-mediated coupling to ethoxy ethanol [→ **17** (99%)] (Scheme 4).[76] Treatment with TFA, ICl, and Br_2 at room temperature led to cleavage of the aryl−germanium bond, yielding proto-, iodo-, and bromobiaryl products **19** (98%), **20** (98%), and **21** (93%), respectively. No traces of products resulting from competitive electrophilic substitution on the anisole ring could be detected. Use of Cl_2 resulted in the formation of a mixture of polychlorinated biaryl derivatives, but chlorobiaryl **22**, resulting from selective *ipso*-degermylation, could be obtained cleanly using either *N*-chlorosuccinimide (NCS, 62%), or dichloroamine-T (65%) in refluxing THF, with the mass balance being recovered starting material in both cases. These results were mirrored when using the corresponding biaryl-functionalized resin **18**[73] (loading level of 0.47 mmol g^{-1}, from aryldimethylgermane **9** and Argogel using TMAD/PBu_3) Pleasingly, the same proto-, iodo-, bromo-, and chlorobiaryl products **19**−**22** could be released into solution with >98% purity as determined by analytical HPLC of the crude washings.[22]

Having established that our linker could be cleaved with concomitant functionalization in this manner, and that this *ipso*-degermylation occurred more rapidly than ortho-substitution of an anisole ring, we embarked upon the parallel synthesis of a library of arylpyrazoles. Although a number of approaches have been employed for SPOS of pyrazoles,[77−82] we opted to investigate a hitherto unreported (on the solid phase) acetophenone (**14**/**16**) → enaminone (**25**/**26**) → pyrazole (**27**/**28** and **29**/**30**) sequence (Scheme 5).[83,84] We were attracted to such a strategy because enaminones **25** and **26** should also be versatile intermediates for the preparation of a range of other azole and azine derivatives.[83,84]

Our original aim was to initiate the sequence with Pd(0)-mediated α-arylation[85−89] of the immobilized acetophenones **14** and **16** with a series of aryl iodides to give

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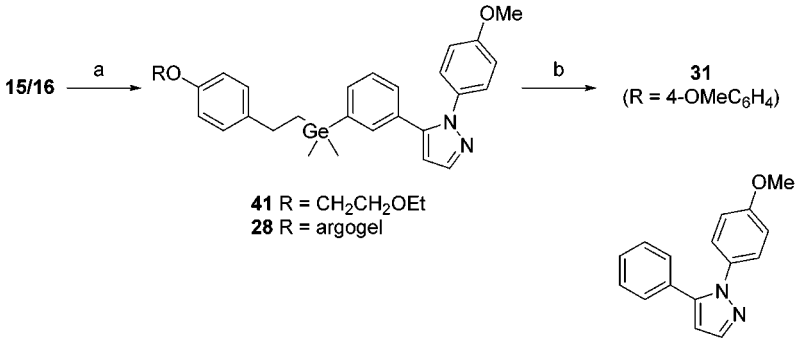
(85) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478.
(86) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383.
(87) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109.

Scheme 6[a]



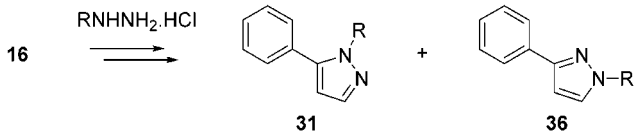
[a] Reagents and conditions: (a) (i) Bredereck's reagent, THF, 70 °C, 3 h, (ii) 4-$MeOC_6H_4NHNH_2$·HCl, *n*-BuOH/AcOH (50:1), 100 °C, 1 h, [**15** → **41** (88%)]; (b) TFA, 16 h, [41 → 31 (87%)].

germyldeoxybenzoins **C** prior to enaminone formation [→ **25**/**26** (X = Ar)] thereby accessing diarylpyrazoles [**27**/**28** and **29**/**30** (X = Ar)]. However, ^{1}H NMR and HPLC-MS monitoring of exploratory reactions between soluble model **15** and phenyliodide indicated that although 3-germyldeoxybenzoin (cf. **C**, Ar = Ph) was formed it was unstable to the reaction conditions[90] and underwent rapid decomposition. Consequently, this diversification step was omitted. The other steps however were efficient as evidenced in preliminary runs also using soluble model **15**. Thus, successive treatment of 3-acetophenone **15** with Bredereck's reagent[91,92] and 4-methoxyphenylhydrazine hydrochloride gave germylpyrazole **41** in 88% yield. TFA-mediated *ipso*-degermylation gave pyrazole **31** (R = 4-$OMeC_6H_4$) in 87% yield.[93] This success was mirrored on a test run using resin **16**, when 100 mg of resin gave 6 mg of the same pyrazole (55%, based on a loading level of 0.44 mmol g^{-1}) using the same reagents (Scheme 6). It is noteworthy that no products of *ipso*-protodegermylation were detected following the condensative ring-closure step which was performed in 50:1 BuOH/AcOH at 100 °C.

By employing the conditions delineated in this test run and starting with 3-acetophenone resin **16**, a library of resin-bound pyrazoles (**28**/**30**) was constructed using a series of 31 commercially available monosubstituted hydrazine salts[94] (27 aryl and 4 alkyl, Table 1). Cleavage from the resin using TFA, and analysis of the crude washings by ^{1}H NMR and HPLC-MS revealed that the unsubstituted (entry **1**) and all monosubstituted aryl hydrazines (entries **2**−**15**) that had cyclized gave 1,5-disubstituted pyrazoles **31** in >89% purity.[95] The situation for disubstituted aryl hydrazines (entries **16**−**25**) was less clear-cut. Although 1,5-disubstituted pyrazoles **31** were again the major products (>90%) for most of these, 2,5- and 3,4-disubstituted aryl hydrazines gave significant proportions of 1,3-diaryl pyrazoles **36** (entries **20**−**22** and **24**). The two trisubstituted aryl hydrazines (entries **26**−**27**) and the alkyl hydrazines (entries **28**−**31**) also gave mixtures of isomers.

By analogy with the work of Penning et al.,[96] we expected 1,5-disubstituted pyrazoles **31** to be the predominant products when using aryl hydrazines. In

Table 1.



		HPLC-MS purity[a]	
entry	R	31	36
1	Ph	94	
2	2-BrC_6H_4	92	
3	2-ClC_6H_4	95	
4	2-$CF_3C_6H_4$	92	
5	2-MeC_6H_4	99	
6	3-BrC_6H_4	89	
7	3-ClC_6H_4	97	
8[b]	3-$OMeC_6H_4$		
9	4-BrC_6H_4	94	
10	4-ClC_6H_4	95	
11	4-FC_6H_4	95	
12	4-$OCF_{3C}H_4$	93	
13	4-$OMeC_6H_4$	92	
14	4-$(SO_2NH_2)C_6H_4$	90	
15[b]	4-$(SO_2NMe_2)C_6H_4$		
16	2,3-$Cl_2C_6H_3$	93	
17	2,4-$Cl_2C_6H_3$	93	
18	2,4-$F_2C_6H_3$	94	
19	2,4-$Me_2C_6H_3$	98	
20	2,5-$Cl_2C_6H_3$[c]	34	42
21	2,5-$F_2C_6H_3$	77	20
22	2-Cl-5-$CF_3C_6H_3$	83	12
23	2,6-$Cl_2C_6H_3$	92	
24	3-F-4-ClC_6H_3	54	44
25	3-Me-4-FC_6H_3	96	
26	2,4,6-$Cl_3C_6H_2$	58	22
27	2,6-Cl_2-4−$CF_3C_6H_2$	77	16
28	Et[d]	43	25
29	Pr[d]	61	18
30	Bu[d]	58	15
31	$PhCH_2CH_2$[e]	85	

[a] Calculated as area/area percentage. [b] No products eluted from HPLC. [c] As free hydrazine. [d] As oxalate salt. [e] As sulfonate salt.

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(90) Typical conditions: PhI (1.2 equiv), BINAP (10 mol %), $Pd_2(dba)_3$ (5 mol %), KHMDS (2.2 equiv), toluene, 90 min, 110 °C. Interestingly, reaction of soluble model **13** with 2-bromo toluene under these conditions led to the unexpected isolation of the corresponding 4-carboxylic acid derivative presumably as the result of a haloform-type reaction.

(91) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffman, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41−50.

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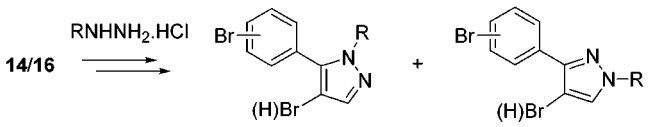
(93) 1,5-Diaryl substitution was confirmed by a single-crystal X-ray structure determination in this case. See Supporting Information.

(94) Interestingly, hydrazine salts invariably performed much better than the corresponding free hydrazines for pyrazole formation.

(95) Purity is based on area/area integration of HPLC peaks (220 nm detection) with no correction for response factors.

Table 2.



32/34 and 33/35 37/39 and 38/40

			HPLC-MS purity[a]			
entry	resin	R	32/34	33/35	37/39	38/40
32	14	4-OMeC_6H_4		95		
33	16	4-OMeC_6H_4		89		
34	14	Ph		99		
35	16	Ph		80		
36	14	2-ClC_6H_4		95		
37	16	2-ClC_6H_4		87		
38	14	3-ClC_6H_4		88		
39	16	3-ClC_6H_4		96		
40	14	4-ClC_6H_4		95		
41	16	4-ClC_6H_4		90		
42	16	2,3-$Cl_2C_6H_3$	8	72	5	10
43	16	2,4-$Cl_2C_6H_3$	3	78	4	8
44	16	2,5-$Cl_2C_6H_3$[b]	10	56	8	23
45	16	2,6-$Cl_2C_6H_3$	2	63	6	17
46	16	3,5-$Cl_2C_6H_3$	1	79	2	10
47	16	2,4,6-$Cl_3C_6H_2$	5	71	9	13

[a] Calculated as area/area percentage. [b] As free hydrazine.

related cyclizations, Tupper et al. have attributed such selectivity to conjugate addition by the unsubstituted hydrazine nitrogen to the enaminone followed by condensative ring-closure.[97] The detection of both 1,5- and 1,3-isomers when employing alkyl hydrazines is precedented[98] and may reflect similarity in nucleophilicity (vis-à-vis conjugate addition) between the hydrazine nitrogens.[99] However, the detection of 1,3-disubstituted pyrazoles when employing highly electron-deficient aryl hydrazines was unexpected and may well indicate that the mechanistic situation is more complex.

A subset of the initial resin-bound pyrazoles (**28**/**30**), along with some of the corresponding 4-acetophenone-derived pyrazoles (**27/29**) were also subject to cleavage with bromine (Table 2). Analysis of the crude washings by ^{1}H NMR and HPLC-MS revealed that, in contrast to our earlier studies using biaryl anisole resin **18**, bromination at C-4 of the pyrazole ring was clearly competitive with *ipso*-bromodegermylative cleavage as dibrominated pyrazoles **33/38** and **35/40** were the major products in all cases. The susceptibility of pyrazoles toward electrophilic substitution at C-4 is well documented,[100] but it is interesting to note the influence of the *N*-aryl substituent on the reactivity of this position. For both the 3- (**28/30**) and 4-germyl (**27/29**) systems, C-4 pyrazole bromination becomes less competitive with *ipso*-degermylation the more electron deficient the *N*-aryl substituent (entries **42**−**47;** cf. entries **32**−**41**). This trend was also seen following cleavage of the same series of resin-bound pyrazoles with ICl and NCS (data not shown). In all cases, mixtures of mono- and dihalogenated pyrazoles formed.

Conclusions

We have developed an efficient four-step synthesis of germyl linker **12** and demonstrated that it can be used to immobilize lithiated aromatic derivatives onto hydroxy-functionalized Argogel resin using a simple two-step protocol involving transmetalation and Mitsunobu-type coupling. Treatment of a biarylanisole-functionalized resin **18** (incorporating this linker) with TFA, ICl, Br_2, or NCS has been shown to result in *ipso*-degermylative cleavage releasing biphenyls **19**−**22** cleanly into solution. A library of pyrazoles has also been prepared from acetophenone-functionalized resins **14** and **16** by parallel synthesis. The arylgermane linkage was sufficiently robust to survive 50:1 BuOH/AcOH at 100 °C during condensative ring-closure. Analysis of the isomeric ratios of 1,5- and 1,3-disubstituted pyrazoles **31/36** isolated following release into solution with TFA revealed the influence of the hydrazine substituent on the regioselectivity of this condensative ring-closure process. Similarly, analysis of the mixtures of mono- and dibrominated pyrazoles following release into solution with bromine illuminated the close competition between *ipso*-degermylation and electrophilic substitution at C-4 of the pyrazole ring. The convenience of parallel synthesis for the qualitative delineation of reactivity patterns such as these is noteworthy.

Experimental Section

General Methods. All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in oven-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to known procedures.[101] Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230−400 mesh) silica gel. Only distilled solvents were used as eluents. Thin-layer chromatography (TLC) was performed on Merck DC-Alufolien or glass plates precoated with silica gel 60 F_{254} which were visualized either by quenching of ultraviolet fluorescence (λ_{max} = 254 nm) or by charring with 10% $KMnO_4$ in 0.1 M H_2SO_4. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over calcium hydride. Anhydrous THF and Et_2O were obtained by distillation, immediately before use, from sodium/benzophenone ketyl under an atmosphere of nitrogen. Anhydrous DMF was obtained by distillation from magnesium sulfate under reduced pressure. Petrol refers to the fraction of light petroleum boiling between 40 and 60 °C. High-resolution mass spectrometry (HRMS) measurements are reported on M^+ unless otherwise indicated and are valid to ±5 ppm. ^{31}P NMR were recorded with H_3PO_4 as internal standard.

Trichlorogermane/diethyl etherate complex,[38] 2-(4-bromphenyl)-2-methyl-1,3-dioxolane,[53] 2-(3-bromphenyl)-2-methyl-1,3-dioxolane,[53] and triphenyl phosphine 3,3-dimethyl-1,2,5-thiadiazolidine 1,1-dioxide[69] were prepared according to literature procedures.

4-(2-Chloroethyl)phenol 1.[34] 4-(2-hydroxy-ethyl)phenol (498 mg, 3.60 mmol) and concentrated HCl (3 mL) were heated

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in a Carius tube at 103 °C for 3 h. After being cooled, the reaction mixture was poured into H_2O (30 mL) and extracted with Et_2O (3 × 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Purification by flash chromatography (CH_2Cl_2) gave the title compound **1** as a pale brown oil (505 mg, 90%). ^{1}H NMR ($CDCl_3$) δ 2.99 (t, J = 7.6, 2H), 3.67 (t, J = 7.3, 2H) 4.89 (s, 1H), 6.78 (d, J = 8.6, 2H), 7.09 (d, J = 8.6, 2H); ^{13}C NMR ($CDCl_3$) δ 38.3 (t), 45.3 (t), 115.5 (d), 130.1 (d), 130.4 (s), 154.4 (s); IR (neat) 3355 cm^{-1}; MS (FAB+) m/z 156 (M^+). HRMS calcd for C_8H_9OCl 156.0342, found 156.0349.

4-(2-Trimethylgermylethyl)phenol 2 and 4-(2-Trimethylgermylethyl)phenyl ethyl ether 3. 4-(2-Chloroethyl)-phenol **1**[34] (60 mg, 0.38 mmol) and trichlorogermane/diethyl etherate complex[38] (0.1 mL, 0.38 mmol) were refluxed at 40 °C for 5 days. The resultant mixture was dissolved in Et_2O (3.8 mL), MeMgBr (2.6 mL, 3.0M, 7.8 mmol) in Et_2O was added dropwise, and the resulting solution was stirred for 1 h at room temperature. The reaction mixture was quenched with H_2O (30 mL) and extracted with Et_2O (3 × 30 mL). The organic fractions were collected, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 9/1) gave phenol **2** as white plates (86 mg, 75%). Mp 47−48 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 9H), 0.98−1.04 (m, 2H), 2.58−2.64 (m, 2H), 4.72 (s, 1H), 6.74 (d, J = 8.9, 2H), 7.06 (d, J = 9.0, 2H); ^{13}C NMR ($CDCl_3$) δ −2.4 (q), 18.8 (t), 30.2 (t), 115.1 (d), 128.9 (d), 137.3 (s), 153.3 (q); IR (neat) 3333 cm^{-1}; MS (EI+) m/z 240 (M^+); HRMS calcd for $C_{11}H_{18}Ge^{74}O$ 240.0569, found 240.0559; ether **3** as a colorless oil (4 mg, 4%).^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.89−0.95 (m, 2H), 1.29 (t, J = 7.0, 3H), 2.48−2.55 (m, 2H), 3.90 (q, J = 7.0, 2H), 6.69 (d, J = 8.6, 2H), 7.00 (d, J = 8.9, 2H); ^{13}C NMR ($CDCl_3$) δ −2.4 (q), 14.9 (q), 18.8 (t), 30.2 (t), 63.4 (t), 114.3 (d), 128.7 (d), 137.0 (s), 156.9 (q); IR (neat) 1511, 1243, 820 cm^{-1}; MS (EI+) m/z 268 (M^+); HRMS calcd for $C_{13}H_{22}Ge^{74}O$ 268.0882, found 268.0874; chloride **1** as a light brown oil (5 mg, 8%). Spectroscopic data as above.

Dichlorogermylene/1,4-Dioxane Complex ($GeCl_2$·$C_4H_8O_2$).[38,48] Tetramethyldisiloxane (0.59 g, 4.4 mmol), germanium(IV) chloride (0.94 g, 4.4 mmol), and dioxane (2 mL) were refluxed at 100 °C for 3 h. After being cooled to 0 °C, the suspended white crystals were isolated by filtration and washed with cold chloroform (3 × 30 mL). The crystals were then dried under vacuum to give the title complex (0.76 g, 75%). Mp 179−182 °C (decomp.) (cf. 178−180 °C[48]); IR (Nujol) 1369, 1284, 1250, 1101, 1072, 1034, 894, 838, 668, 619 cm^{-1}; MS (EI+) m/z 144 ($GeCl_2^+$), 88 ($C_4H_8O_2^+$).

4-(2-Trichlorogermylethyl)phenol 4. 4-(2-Chloroethyl)-phenol **1**[34] (507 mg, 3.2 mmol), and dichlorogermylene/1,4-dioxane complex[48] (140 mg, 0.606 mmol) were heated in a Carius tube at 140 °C for 16 h. After being cooled, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and added dropwise to H_2O (50 mL). The resulting white precipitate was collected by filtration, washed with H_2O (3 × 50 mL) and then CH_2Cl_2 (3 × 50 mL), and dried under suction. The dried precipitate was dissolved in concentrated HCl (37% w/v) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give trichlorogermane **4** as a colorless oil (975 mg, 91%). ^{1}H NMR ($CDCl_3$) δ 2.27−2.33 (m, 2H), 2.94−3.01 (m, 2H), 5.09 (s, 1H), 6.79 (d, J = 9.2, 2H), 7.10 (d, J = 9.0, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2 (t), 34.2 (t), 115.7 (d), 129.4 (d), 131.9 (s), 154.4 (s); IR (neat) 3340, 1448, 1173, 831 cm^{-1}; MS (EI+) m/z 300 (M^+); HRMS calcd for $C_8H_9Cl^{35}{}_3Ge^{70}O$ 295.8961, found 295.8951.

4-{2-[(Phenyl-4-ethanone)dimethy1germyl]ethyl}-phenol 7 and 4-{2-[Di(phenyl-4-ethanone)methy1germyl]-ethyl}phenol 6. A solution of MeMgBr (0.47 mL, 3.0M, 1.4 mmol) in Et_2O was added dropwise over 50 min. to a solution of trichlorogermane **4** (142 mg, 0.47 mmol) in THF (1 mL) at −78 °C. A solution of 2-(4-lithiophenyl)-2-methyl-1,3-dioxalane was then prepared [in a separate flask, by dropwise addition of *n*-BuLi (1.3 mL, 1.8 M, 2.37 mmol) in hexanes to a solution of 2-(4-bromphenyl)-2-methyl-1,3-dioxolane[53] (575 mg, 2.37 mmol) in THF (1 mL) at −78 °C] and added by cannula at −78 °C. The resulting mixture was allowed to warm slowly to room temperature with stirring over 14 h before being quenched by addition of H_2O (50 mL), followed by Et_2O (50 mL), and filtered through a pad of Celite. After being partitioned with further Et_2O (3 × 50 mL), the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil (446 mg). To this oil was added acetone (10 mL), H_2O (0.5 mL), and PPTS, (30 mg) and the mixture was refluxed for 16 h at 67 °C before being concentrated in vacuo. The resulting yellow paste was dissolved in EtOAc (20 mL) and washed successively with H_2O (10 mL), 10% $NaHCO_3$ (10 mL), and H_2O (10 mL). The organic layer was dried ($MgSO_4$) prior to dry-loading onto flash silica gel for purification by flash chromatography (petrol/EtOAc, 4/1 → 2/1) to give aryldimethylgermane **7** as a yellow oil (27 mg, 17%). ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 6H), 1.24−1.31 (m, 2H), 2.59−2.68 (m, 2H), 2.62 (s, 3H), 4.68 (s, 1H), 6.72 (d, J = 8.5, 2H), 7.01 (d, J = 8.6, 2H), 7.54 (d, J = 6.4, 2H), 7.91 (d, J = 6.4, 2H); ^{13}C NMR ($CDCl_3$) δ −3.8 (q), 18.0 (t), 26.7 (q), 30.1 (t), 115.2 (d), 127.5 (d), 128.9 (d), 133.5 (d), 136.1 (s), 136.7 (s), 149.1 (s), 154.0 (s), 199.4 (s); IR (neat) 3406, 1670, 1236, 820 cm^{-1}; MS (EI+) m/z 344 (M^+); HRMS calcd for $C_{18}H_{22}Ge^{70}O_2$ 340.0862, found 340.0850; diarylmethylgermane **6** as a yellow oil (78 mg, 37%). ^{1}H NMR ($CDCl_3$) δ 0.65 (s, 3H) 1.57−1.65 (m, 2H), 2.60 (s, 6H), 2.65−2.72 (m, 2H), 4.71 (s, 1H), 6.71 (d, J = 8.6, 2H), 6.99 (d, J = 8.6, 2H), 7.54 (d, J = 8.2, 4H), 7.94 (d, J = 8.2, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 16.6 (t), 26.6 (q), 29.9 (t), 115.2 (d), 127.6 (d), 128.8 (d), 134.1 (d), 135.5 (s), 137.2 (s), 145.5 (s), 154.0 (s), 198.5 (s); IR (neat) 3356, 1681, 1275, 819 cm^{-1}; MS (EI+) m/z 448 (M^+); HRMS calcd for $C_{25}H_{26}Ge^{74}O_3$ 448.1093, found 448.1098; an inseparable mixture of trimethylgermane **2** (∼28% by ^{1}H NMR) and acetophenone.

4-(2-Trimethylgermylethyl)phenol 2. Method II. A solution of MeMgBr (32 mL, 3.0M, 96 mmol) in Et_2O was added to a solution of trichlorogermane **4** (4.78 g, 16 mmol) in toluene (20 mL). The mixture was then refluxed at 110 °C for 16 h before partitioning between 1 M HCl (100 mL) and Et_2O (100 mL). After being extracted further with Et_2O (2 × 100 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a brown oil (1.3 g). Purification by flash chromatography (petrol/EtOAc, 9/1) gave the title compound **2** as a white solid (2.54 g, 82%). Spectroscopic data as above.

4-[2-(Chlorodimethylgermyl)ethyl]phenol 12. Tin(IV) chloride (0.1 mL, 0.86 mmol) was added dropwise to a solution of trimethylgermane **2** (205 mg, 0.86 mmol) in $MeNO_2$ (2 mL) at room temperature, and then the reaction mixture was heated at 50 °C for 16 h. Volatiles were then removed by distillation (90 °C, 0.5 mmHg) to leave chlorodimethylgermane **12** as a brown oil (220 mg, 99%). ^{1}H NMR ($CDCl_3$) δ 0.60 (s, 6H), 1.46−1.52 (m, 2H), 2.76−2.82 (m, 2H), 4.57 (s, 1H), 6.76 (d, J = 8.5, 2H), 7.08 (d, J = 8.9); ^{13}C NMR ($CDCl_3$) δ 3.5 (q), 23.6 (t), 29.1 (t), 115.4 (d), 129.1 (d), 135.2 (s), 153.7 (s); IR (neat) 3405, 1241, 821 cm^{-1}, MS (FAB+) m/z 260 (M^+); HRMS calcd for $C_{10}H_{15}Cl^{35}Ge^{70}O$ 256.0054, found 256.0034.

4-{2-[(Phenyl-4-ethanone)dimethylgermyl]ethyl}-phenol 7. Method II. A solution of *n*-BuLi (9.5 mL, 2.0M, 19 mmol) in hexanes was added dropwise to a solution of 2-(4-bromphenyl)-2-methyl-1,3-dioxolane[53] (4.6 g, 19 mmol) in THF/toluene (40 mL, 1/1) at −78 °C. After being stirred for 20 min, the mixture was transferred by cannula to a solution of chlorodimethylgermane **12** (985 mg, 3.8 mmol) in toluene (10 mL) at −78 °C. The mixture was then refluxed at 110 °C for 16 h. The sample was then quenched with 1 N HCl (50 mL) and extracted with Et_2O (3 × 100 mL). The organic fractions were collected, dried ($MgSO_4$), and concentration in vacuo to give a yellow oil (446 mg). To this oil was added acetone (50 mL), H_2O (2.5 mL), and PPTS, (100 mg), and the mixture was refluxed for 16 h at 67 °C before being concentrated in vacuo. The resulting yellow paste was dissolved in EtOAc (50 mL) and washed successively with H_2O (50 mL), 10% $NaHCO_3$ (50 mL), and H_2O (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 4/1) gave aryldimethylgermane **7** as a yellow oil (1.101 g, 86%). Spectroscopic data as above.

4-{2-[(Phenyl-3-ethanone)dimethylgermyl]ethyl}-phenol 8. A solution of *n*-BuLi (34.4 mL, 1.6M, 55 mmol) in hexanes was added dropwise to a solution of 2-(3-bromphenyl)-2-methyl-1,3-dioxolane[53] (13.5 g, 55 mmol) in THF (100 mL) at −78 °C. After being stirred for 20 min, the mixture was transferred by cannula to a solution of chlorodimethylgermane **12** (2.85 g, 11 mmol) in toluene (50 mL) at −78 °C. The mixture was then refluxed at 110 °C for 3 h. The sample was then quenched with 1 N HCl (100 mL) and extracted with Et_2O (3 × 100 mL). The organic fractions were collected, dried ($MgSO_4$), and concentration in vacuo to give a yellow oil. To this oil was added acetone (100 mL), H_2O (5 mL), and PPTS, (200 mg), and the mixture was refluxed for 16 h at 67 °C before being concentrated in vacuo. The resulting yellow paste was dissolved in EtOAc (100 mL) and washed successively with H_2O (100 mL), 10% $NaHCO_3$ (100 mL), and H_2O (100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 4/1) gave aryldimethylgermane **8** as a yellow oil (1.62 g, 43%). ^{1}H NMR ($CDCl_3$) δ 0.39 (s, 6H), 1.26−1.31 (m, 2H), 2.61−2.68 (m, 2H), 2.61 (s, 3H), 4.72 (s, 1H), 6.71 (d, J = 8.4, 2H), 7.01 (d, J = 8.4, 2H), 7.43 (t, J = 7.2, 1H), 7.91 (d, J = 7.5, 1H), 7.89 (d, J = 7.5, 1H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 3.7 (q), 18.0 (t), 26.7 (q), 30.1 (t), 115.3 (d), 128.1 (d), 128.5 (d) 128.9 (d), 132.9 (d), 136.0 (s), 136.2 (s), 138.2 (d) 142.5 (s), 154.1 (s), 199.7 (s); IR (neat) 3390, 1680, 1260 cm^{-1}; MS (TSP+) 362 (MNH_4^+); HRMS calcd for (MNa^+) $C_{18}H_{22}Ge^{70}O_2Na$ 363.0760, found 363.0768.

4-Bromo-4′-methoxy Biphenyl 21.[102] Dimethyl sulfate (1.7 mL, 18 mmol), 4-bromo-4′-hydroxybipenyl (3.028 g, 12 mmol), and $LiOH\cdot H_2O$ (765 mg, 18 mmol) were suspended in THF (20 mL) and heated at 70 °C for 1 h. The resulting mixture was partitioned between 1 M KOH and Et_2O. The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the resulting white solid was recrystallized (CH_2Cl_2/petrol) to give methyl ether **21** as white needles (3.06 g, 97%). Mp 142−145 °C (CH_2Cl_2/petrol) [cf. 144−145 °C (EtOH−benzene)[102]]; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 6.97 (d, J = 8.9, 2H), 7.39−7.55 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 55.4 (q), 114.3 (d), 120.8 (s), 128.0 (d), 128.3 (d), 131.8 (d), 132.5 (s), 139.7 (s), 159.4 (s); MS (EI+) m/z 262 (M^+).

4-[2-Dimethyl-(4,4′-biphenylmethoxy)germylethyl]phenol 9. A solution of *n*-BuLi (3.9 mL, 2.0M, 8.2 mmol) in hexanes was added dropwise to a solution of biphenyl **21** (2.141 g, 8.14 mmol) in THF (20 mL) at −78 °C. This solution was transferred by cannula to a solution of chlorodimethylgermane **12** (0.422 g, 1.63 mmol) in toluene (15 mL) at −78 °C. The resulting mixture was warmed to room temperature and stirred for 16 h at this temperature before being refluxed for 6 h at 110 °C. After being quenched with 1 N HCl (100 mL), the mixture was extracted with Et_2O (3 × 200 mL), and the combined organic extracts were dried ($MgSO_4$). Purification by flash chromatography (CH_2Cl_2) gave aryldimethylgermane **9** as a white solid (0.562 g, 85%). Mp 86−87 °C (petrol/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.42 (s, 6H), 1.28−1.35 (m, 2H), 2.66−2.73 (m, 2H), 3.83 (s, 3H), 5.03 (s, 1H), 6.75 (d, J = 8.5, 2H), 7.00−7.10 (m, 4H), 7.52−7.60 (m, 6H); ^{13}C NMR ($CDCl_3$) δ −3.6 (q), 18.1 (t), 30.2 (t), 55.4 (q), 114.3 (d), 115.2 (d), 126.3 (d). 128.2 (d), 129.0 (d), 133.7 (d), 136.9 (s), 139. (s), 140.8 (s), 153.5 (s), 159.1 (s); IR (Nujol) 3334, 1253, cm^{-1}; MS (FAB+) m/z 408 (M^+); HRMS calcd for $C_{23}H_{26}Ge^{74}O_2$ 408.1144, found 408.1150.

4-{2-[(Phenyl-4-ethanone)dimethylgermyl]ethyl}-phenyl Ethoxyethyl Ether 13 and 4-{2-[(Phenyl-4-ethanone)dimethylgermyl]ethyl}phenyl Dibutyl Phosphonate 23. A solution of ADDP (366 mg, 1.45 mmol) in benzene (2 mL) was added dropwise to a solution of ethoxy ethanol (30 mg, 0.29 mmol), phenol **7** (96 mg, 0.29 mmol), and PBu_3 (0.35 mL, 1.5 mmol) in benzene (1 mL) at 0 °C over 10 min. After being stirred for a further 30 min at 0 °C, the solution was allowed to warm to room temperature and was stirred at this temperature for a further 3 h, after which time the white precipitate was removed by filtration and the filtrate was concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 9/1) gave ethoxyethyl ether **13** as a colorless oil (59 mg, 42%). ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 6H), 1.24 (t, J = 7.2, 3H), 1.25−1.32 (m, 2H), 2.60 (s, 3H), 2.60−2.67 (m, 2H), 3.59 (q, J = 7.0, 2H), 3.77 (t, J = 5.2, 2H), 4.08 (t, J = 5.2, 2H), 6.96 (d, J = 8.9, 2H), 7.05 (d, J = 9.0, 2H), 7.55 (d, J = 8.3, 2H), 7.89 (d, J = 8.2, 2H); ^{13}C NMR ($CDCl_3$) δ -3.8 (q), 15.2 (q), 17.9 (t), 26.6 (q), 30.1 (t), 66.8 (t), 67.5 (d), 69.0 (d), 114.6 (d), 127.4 (d), 128.7 (d), 133.5 (d), 136.5 (s), 148.7 (s), 157.0 (s), 198.4 (s); IR (neat) 1684, 1245 cm^{-1}; MS (CI+) m/z 417 (MH^+). HRMS calcd for (MH^+) $C_{22}H_{31}Ge^{74}O_3$ 417.1485, found 417.1502; and dibutylphosphonate **23** as a colorless oil (15 mg, 10%). ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 6H), 0.90 (t, J = 7.0, 6H), 1.23−1.32 (m, 2H), 1.35−1.47 (m, 4H), 1.54−1.68 (m, 4H), 1.75−1.88 (m, 4H), 2.60 (s, 3H), 2.61−2.68 (m, 2H), 7.08 (s, 4H), 7.55 (d, J = 8.2, 2H), 7.90 (d, J = 8.3, 2H); ^{13}C NMR ($CDCl_3$) δ −4.0 (q), 13.4 (q), 17.6 (t), 23.8 (t), 26.6 (q), 26.7 (t), 28.5 (t), 31.0 (t), 120.3 (d), 127.2 (d), 128.8 (d), 133.3 (d), 137.1 (s), 138.0 (s), 139.9 (s), 148.2 (s), 198.1 (s); ^{31}P NMR ($CDCl_3$) δ 58.54 (s); MS (FAB+) m/z 505 (MH^+); HMRS calcd for (MH^+) $C_{26}H_{40}Ge^{74}O_3P$ 505.1927, found 505.1939.

4-{2-[(Phenyl-4-ethanone)dimethylgermyl]ethyl}-phenyl Ethoxyethyl Ether 13. Method II. A solution of TMAD (520 mg, 2.86 mmol) in benzene (10 mL) was added dropwise to a solution of ethoxy ethanol (30 mg, 0.29 mmol), phenol **7** (96 mg, 0.29 mmol), and PBu_3 (0.35 mL, 1.5 mmol) in benzene (15 mL). After being stirred for 16 h, the resulting gel was diluted with EtOAc/CH_2Cl_2 (1/1) whereupon a white precipitate formed. This precipitate was removed by filtration, and the filtrate was concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 9/1) gave ethoxyethyl ether **13** as a colorless oil (343 mg, 87%). Spectroscopic data as above.

4-{2-[(Phenyl-4-ethanone)dimethylgermyl]ethyl}-phenyl Ether Resin 14. A solution of TMAD (270 mg, 1.5 mmol) in benzene (10 mL) was added dropwise to a mixture of Argogel (735 mg, 0.36 mmol),[73] phenol **7** (370 mg, 1.1 mmol), and PBu_3 (0.45 mL, 1.8 mmol) in benzene (20 mL). After being stirred for 16 h, the resulting gel was diluted with EtOAc/CH_2Cl_2 (1/1), and the resin was separated by filtration and washed with DMF (3 × 30 mL), MeOH (3 × 30 mL), THF (3 × 30 mL), Et_2O (3 × 30 mL), and CH_2Cl_2 (3 × 30 mL). The resin was then dried under high vacuum (0.7 mmHg, 80 °C) for 3 days to give a free-flowing yellow resin **14** (835 mg, ∼0.43 mmol g^{-1}; N.B.: loading was determined by mass balance of acetophenone following cleavage using TFA).^{1}H MAS NMR (CH_2Cl_2) δ 0.41 (s, 6H), 1.30−1.38 (m, 2H), 2.59 (s, 3H), 2.62−2.66 (m, 2H), 3.42−3.79 (polymer CHs), 6.91 (d, J = 8.9, 2H), 7.10 (d, J = 9.0, 2H), 7.60 (d, J = 8.3, 2H), 7.93 (d, J = 8.2, 2H); IR (Nujol) 1682, 1511 cm^{-1}.

Dansyl Hydrazone of 4-{2-[(Phenyl-4-ethanone)dimethylgermyl]ethyl}phenol (24). Aryldimethylgermane **7** (37 mg, 0.11 mmol) and dansyl hydrazine (31 mg, 0.12 mmol) were dissolved in DMF/AcOH (1.0 mL, 1/1) and the resulting solution stirred for 5 h. The solvent was then removed in vacuo and the resulting oily residue purified by flash chromatography (petrol/EtOAc, 1/1) to yield dansyl hydrazone **24** as a fluorescent yellow oil (51 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 0.31 (s, 6H), 1.17−1.24 (m, 2H), 2.11 (s, 3H), 2.53−2.60 (m, 2H), 2.87 (s, 6H), 5.28 (s, 1H), 6.68 (d, J = 8.5, 2H), 6.94 (d, J = 8.5, 2H), 7.18 (d, J = 7.6, 1H), 7.31 (d, J = 8.2, 2H), 7.44 (d, J = 8.2, 2H), 7.58 (t, J = 8.5, 2H), 8.14 (s, 1H), 8.46 (d, J = 7.3, 1H), 8.55 (t, J = 8.2, 2H); ^{13}C NMR ($CDCl_3$) δ −3.8 (q), 13.2 (q). 18.0 (t), 30.1 (t), 45.5 (q), 115.1 (d), 115.3 (d), 119.3 (d), 123.5 (d), 125.6 (d), 128.4 (d), 128.9 (d), 129.7 (s), 129.9 (s), 131.1 (d), 131.3 (d), 133.1 (d), 133.7 (s), 136.4 (s), 137.0 (s), 143.5 (s), 152.0 (s), 153.7 (s); MS (FAB+) m/z 592 (MH^+). HRMS calcd for (MH^+) $C_{30}H_{36}Ge^{70}N_3O_3S$ 588.1720, found 588.1675.

4-{2-[(Phenyl-3-ethanone)dimethylgermyl]ethyl}-phenyl Ethoxyethyl Ether 15. A solution of TMAD (510 mg, 3.0 mmol) in toluene (20 mL) was added dropwise to a solution of ethoxy ethanol (270 mg, 3.0 mmol), phenol **8** (684 mg, 2.0 mmol), and PBu_3 (0.7 mL, 3.0 mmol) in toluene (20 mL). After being stirred for 16 h, the mixture was diluted with EtOAc/

(102) Harley-Mason, J.; Mann, F. G. *J. Chem. Soc.* **1940**, 1379−1385.

CH_2Cl_2 (1/1) whereupon a white precipitate formed. This precipitate was removed by filtration, and the filtrate was concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 9/1) gave ethoxyethyl ether **15** as a yellow oil (746 mg, 90%). ^{1}H NMR ($CDCl_3$) δ 0.39 (s, 6H), 1.24 (t, J = 6.9, 3H), 1.28−1.34 (m, 2H), 2.61 (s, 3H), 2.63−2.68 (m, 2H), 3.60 (t, J = 6.9, 2H), 3.77 (t, J = 4.8, 2H), 4.09 (t, J = 5.1, 2H), 6.82 (d, J = 8.4, 2H), 7.06 (d, J = 9.0, 2H), 7.43 (t, J = 7.2, 1H), 7.63 (d, J = 7.2, 1H, 7.89 (d, J = 7.5, 1H), 8.03 (s, 1H); ^{13}NMR ($CDCl_3$) δ_C −3.7 (q), 15.2 (t), 17.9 (t), 26.6 (q), 30.1 (t), 66.8 (t), 67.5 (t), 69.0 (t), 114.6 (d), 128.0 (d), 128.3 (d) 128.7 (d), 132.8 (d), 136.5 (s), 137.9 (d), 142.3 (s), 157.0 (s), 198.5 (s); IR (neat) 3390, 1680, 1260 cm^{-1}; MS (TSP+) m/z 439 (MNa^+). HRMS calcd for (MNa^+) $C_{22}H_{30}Ge^{70}NaO_3$ 435.1333, found 435.1329.

4-{2-[(Phenyl-3-ethanone)dimethylgermyl]ethyl}-phenyl Ether Resin 16. TMAD (1.9 g, 11 mmol) was added to a mixture of Argogel (4.5 g, 2.2 mmol),[73] phenol **8** (2.26 g, 6.6 mmol), and PBu_3 (2.6 mL, 11.0 mmol) in toluene (50 mL). After being stirred for 16 h, the resin was separated by filtration and washed with DMF (3 × 30 mL), MeOH (3 × 30 mL), THF (3 × 30 mL), Et_2O (3 × 30 mL), and CH_2Cl_2 (3 × 30 mL). The resin was then dried under high vacuum (0.7 mmHg, 80 °C) for 3 days to give a free-flowing yellow resin **16** (5.2 g, ∼0.44 mmol g^{-1}; N.B.: loading was determined by mass balance of acetophenone following cleavage using TFA).

4-[2-Dimethyl-(4,4′-biphenylmethoxy)germylethyl]-phenyl Ethoxyethyl Ether 17. A solution of TMAD (295 mg, 1.7 mmol) in benzene (10 mL) was added dropwise to a solution of aryldimethylgermane **9** (465 mg, 1.1 mmol), PBu_3 (0.42 mL, 1.7 mmol), and ethoxy ethanol (0.11 mL, 1.1 mmol). After being stirred for 14 h, the mixture was triturated with CH_2Cl_2/petrol (20 mL, 1/1) and filtered, and the filtrate was concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 9/1) gave ethoxyethyl ether **17** as a white solid (543 mg, 99%). Mp 53−55 °C (petrol); ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 6H), 1.26 (t, J = 7.0, 3H), 1.26−1.35 (m, 2H), 2.66−2.73 (m, 2H), 3.61 (t, J = 7.0, 2H), 3.79 (t, J = 4.9, 2H), 3.86 (s, 3H), 4.11 (t, J = 4.9, 2H), 6.85 (d, J = 8.9, 2H), 7.00 (d, J = 8.9, 2H), 7.11 (d, J = 8.9, 2H), 7.51−7.58 (m, 6H); ^{13}C NMR ($CDCl_3$) δ −3.6 (q), 15.2 (q), 18.1 (t), 30.2 (t), 55.4 (q), 66.9 (t), 67.5 (t), 69.1 (t), 114.2 (d), 114.5 (d), 126.3 (d), 128.2 (d), 128.7 (d), 133.7 (d), 137.0 (s), 139.5 (s), 140.8 (s), 156.9 (s), 159.1 (s); IR (Nujol) 1253, 816 cm^{-1}; MS (FAB+) m/z 480 (M^+); HRMS calcd for $C_{27}H_{34}Ge^{74}O_3$ 480.172, found 480.173.

4-[2-Dimethyl-(4,4′-biphenylmethoxy)germylethyl)-phenyl Ether Resin 18. A solution of TMAD (110 mg, 0.64 mmol) in benzene (10 mL) was added dropwise to a suspension of Argogel (250 mg, 0.12 mmol),[73] phenol **9** (260 mg, 0.64 mmol), and PBu_3 (0.16 mL, 0.64 mmol) in benzene (20 mL). After being stirred for 16 h, the resulting gel was diluted with EtOAc/CH_2Cl_2 (1/1), and the resin was separated by filtration and washed with DMF (300 mL), MeOH (300 mL), THF (300 mL), Et_2O (300 mL), and CH_2Cl_2 (300 mL). The resin was then dried under high vacuum (0.7 mmHg) for 3 days to give a free-flowing white resin **18** (295 mg, ∼0.47 mmol g^{-1}; N.B.: loading was determined by mass balance of 4-methoxy biphenyl **19** following cleavage using TFA; see below).

Procedure for TFA-Mediated Cleavage from Soluble Model System 17. A solution of aryldimethylgermane **17** (77 mg, 0.42 mmol) in freshly distilled TFA (3 mL) was stirred at room temperature for 16 h. The TFA was then removed in vacuo, and the crude material was purified by flash chromatography (CH_2Cl_2) to give 4-methoxybiphenyl **19**[103] as a white solid (29 mg, 98%). Mp 86−87 °C (petrol) (cf. 84.5−85.5 °C[103]); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.98 (d, J = 8.9, 2H), 7.31 (d, J = 7.3, 1H), 7.43 (t, J = 7.6, 2H), 7.52−7.59 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 55.4 (q), 114.2 (d), 126.7 (d), 126.8 (d), 128.2 (d), 128.7 (d), 133.8 (s), 140.8 (s), 159.2 (s); MS (EI+) m/z 184 (M^+).

Procedure for TFA-Mediated Cleavage from Resin 18. A suspension of resin **18** (27 mg, 13 μmol) in freshly distilled TFA (2 mL) was stirred for 16 h. The resin was separated by filtration and washed extensively with CH_2Cl_2. The organic washings were concentrated in vacuo to give 4-methoxy biphenyl **19**[103] as a white solid (2.3 mg, equivalent to a loading level of resin **18** of ∼0.47 mmol g^{-1}). The purity of the crude mixture was determined to be >98% by HPLC, and its identity was established by co-injection with an authentic sample.

Procedure for ICl-Mediated Cleavage from Soluble Model System 17. To a solution of aryldimethylgermane **17** (75 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) at room temperature was added iodine monochloride (25 mg, 0.16 mmol) dropwise, and the resulting solution was stirred for 15 min. The mixture was then quenched with 1 M $Na_2S_2O_3$ and extracted repeatedly with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2) gave 4-iodo-4′-methoxy biphenyl **20**[102] as a white solid (48 mg, 98%). Mp 180−183 °C [cf. 182−183 °C (EtOH−benzene)[102]]; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.96 (d, J = 8.9, 2H), 7.27 (d, J = 8.6, 2H), 7.48 (d, J = 8.5, 2H), 7.72 (d, J = 8.5, 2H); ^{13}C NMR ($CDCl_3$) δ 55.4 (q), 92.1 (s), 114.3 (d), 127.9 (d), 128.6 (d), 132.5 (s), 137.8 (d), 140.3 (s), 159.5 (s); MS (EI+) m/z 310 (M^+).

Procedure for ICl-Mediated Cleavage from Resin 18. To a suspension of resin **18** (19 mg, 8.5 μmol) in CH_2Cl_2 (1 mL) at room temperature was added a solution of iodine monochloride (3 mg, 18 μmol) in CH_2Cl_2 (1 mL) dropwise, and the resulting suspension was stirred for 40 min. The resin was separated by filtration and washed extensively with CH_2Cl_2. The organic washings were quenched with 1 M $Na_2S_2O_3$, the phases were separated, and the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give 4-iodo-4′-methoxy biphenyl **20**[102] as a white solid (2 mg). The purity of crude mixture was determined to be >98% by HPLC, and its identity was established by co-injection with an authentic sample and by ^{1}H NMR and MS.

Procedure for Bromine-Mediated Cleavage from Soluble Model System 17. To a solution of aryldimethylgermane **17** (84 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) at room temperature was added bromine (28 mg, 0.18 mmol) dropwise, and the resulting solution was stirred for 20 min. The mixture was then concentrated in vacuo, and the remaining residue was purified by flash chromatography (CH_2Cl_2) to give 4-bromo-4′-methoxy biphenyl **21**[102] as a white solid (43 mg, 93%). Spectoscopic data as above.

Procedure for Bromine-Mediated Cleavage from Resin 18. To a suspension of resin **18** (35 mg, 15μmol) in CH_2Cl_2 (2 mL) at room temperature was added a solution of bromine (4 mg, 26μmol) in CH_2Cl_2 (0.25 mL) dropwise, and the resulting suspension was stirred for 40 min. The resin was separated by filtration and washed extensively with CH_2Cl_2. The organic washings were concentrated in vacuo to give 4-bromo-4′-methoxy biphenyl **21**[102] as a white solid (4 mg). The purity of the crude mixture was determined to be >98% by HPLC, and its identity was established by co-injection with an authentic sample and by ^{1}H NMR and MS.

Procedure for NCS-Mediated Cleavage from Soluble Model System 17. To a solution of aryldimethylgermane **17** (78 mg, 0.16 mmol) in THF (2 mL) at room temperature was added *N*-chlorosuccinimide (22 mg, 0.16 mmol), and the resulting solution was refluxed for 14 h at 70 °C. The solvent was then removed in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2) to yield 4-chloro-4′-methoxy biphenyl **22**[104] as a white solid (22 mg, 62%). Mp 111−113 °C (cf. 110−111 °C[104]); ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 1H), 6.97 (d, J = 8.9, 2H), 7.37 (d, J = 8.9, 2H), 7.45−7.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 55.4 (q), 114.3 (d), 127.9 (d), 128.0 (d), 128.8 (d), 132.5 (s), 133.0 (s), 139.5 (s), 158.6 (s); MS (EI+) 218 (M^+).

Procedure for Dichloramine-T-Mediated Cleavage from Soluble Model System 17. To a solution of aryldimethylgermane **17** (67 mg, 0.14 mmol) in THF (2 mL) at room temperature was added dichloroamine-T (34 mg, 0.14 mmol),

(103) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266−3270.

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and the resulting solution was refluxed for 14 h at 70 °C. The solvent was then removed in vacuo, and the residue was purified by flash chromatography (petrol/EtOAc, 9/1) to yield chlorobiaryl **22**[104] as a white solid (22 mg, 65%). Spectroscopic data as above.

Procedure for NCS-Mediated Cleavage from Resin 18. To a suspension of resin **18** (37 mg, 16 μmol) in THF (3 mL) at room temperature was added *N*-chlorosuccinimide (11 mg, 79 μmol), and the resulting suspension was refluxed for 16 h at 70 °C. The resin was separated by filtration and washed extensively with CH_2Cl_2. The organic washings were concentrated in vacuo to give 4-chloro-4′-methoxy biphenyl **22**[104] as a white solid (2 mg). The purity of crude mixture was determined to be >98% by HPLC, and its identity was established by co-injection with an authentic sample and by ^{1}H NMR and MS. N.B.: Neither *N*-chlorosuccinimide nor succinimide elute from the HPLC column under the conditions used (see Supporting Information).

1-(2-Ethoxyethoxy)-4-(3-germa-3-{3-[1-(4-methoxyphenyl)pyrazol-3-yl]phenyl}-3-methylbutyl)benzene 41. Brederecks reagent[91] (1 mL, 4.8 mmol) was added dropwise to a solution of aryldimethylgermane **15** (75 mg, 0.18 mmol) in THF (1 mL) at room temperature and then heated to 70 °C for 3 h. The volatiles were then removed in vacuo, and the crude mixture was dissolved in *n*-BuOH (5 mL). 4-Methoxyphenylhydrazine hydrochloride (0.5 g, 2.9 mmol) and AcOH (0.1 mL) were added to this solution at room temperature and then heated at 100 °C for 3 h. After being cooled, the mixture was concentrated in vacuo and purified by flash chromatography (hexane/EtOAc, 1/1) to give pyrazole **41** as a brown oil (72 mg, 88%). ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 6H), 1.12−1.18 (m, 2H), 1.25 (t, J = 6.9, 3H), 2.51−2.57 (m, 2H), 3.60 (t, J = 6.9, 2H), 3.74 (s, 3H), 3.78 (t, J = 5.4, 2H), 4.09 (t, J = 5.1, 2H), 6.51 (d, J = 1.5, 1H), 6.64 (d, J = 9.0, 1H), 6.75 (d, J = 8.9, 1H), 6.81−6.86 (m, 4H), 7.03 (d, J = 8.4, 2H), 7.20−7.38 (m, 4H), 7.70 (d, J = 1.5, 1H); ^{13}C NMR ($CDCl_3$) δ −3.9 (q), 15.2 (q), 17.8 (t), 30.1 (t), 55.4 (q), 66.8 (t), 67.6 (t), 69.0 (t), 107.0 (d), 114.1 (d), 114.6 (d), 114.8 (d), 116.4 (d), 126.8 (d), 127.9 (d), 128.5 (d), 128.6 (d). 129.6 (d), 128.7 (d), 133.7 (d), 137.0 (s), 139.5 (s), 140.8 (s), 156.9 (s), 159.1 (s); IR (Nujol) 1610, 1514, 1247 cm^{-1}; MS (TSP+) 547 (MH^+). HRMS calcd for (MH^+) $C_{30}H_{37}Ge^{70}N_2O_3$ 543.2034, found 543.2041.

4-Methoxy-1-(5-phenylpyrazolyl)benzene 31 (R = 4-OMeC$_6$H$_4$). A solution of pyrazole **41** (72 mg, 0.13 mmol) in freshly distilled TFA (4 mL) was stirred at room temperature for 16 h. The TFA was then removed in vacuo, and the crude material was purified by flash chromatography (hexane/EtOAc, 7/3) to give pyrazole **31** (R = 4-OMeC$_6$H$_4$) as a white solid (20 mg, 87%). Mp 93−95 °C (MeOH); ^{1}H NMR (MeOD) δ 3.62 (s, 3H), 6.56 (d, J = 1.8, 1H), 6.91 (d, J = 9.3, 2H), 7.14−7.30 (m, 7H), 7.67 (d, J = 1.8, 1H); ^{13}C NMR ($CDCl_3$) δ 55.5 (q), 107.3 (d), 114.0 (d), 126.6 (d), 128.1 (d), 128.4 (d), 128.7 (d), 130.6 (s), 133.4 (s), 139.5 (d), 142.9 (s), 158.8 (s); IR (Nujol) 1517, 1247 cm^{-1}; MS (TSP+) 251 (MH^+). HRMS calcd for (MH^+) $C_{16}H_{15}N_2O$ 251.1184, found 251.1178.

General Procedure for the Preparation of Resin-Bound Pyrazoles 27/29 and 28/30. To a suspension of acetophenone resin **14** or **16** (5 g) in THF (50 mL) was added Brederecks reagent[91] (50 mL) dropwise, and the resulting suspension was refluxed at 70 °C for 3 h. The resin was separated by filtration, washed repeatedly with THF, and then dried under suction. The dried resin was partitioned into 100 mg batches and suspended in *n*-BuOH (5 mL), and the hydrazine hydrochloride (500 mg) was added, followed by AcOH (0.1 mL). This mixture was heated at 100 °C for 30 min before being cooled to room temperature. The resin was then separated by filtration, washed with H_2O, MeOH, EtOH, DMF, THF, Et_2O, and CH_2Cl_2 and then dried under high vacuum (1 mmHg).

4-Methoxy-1-(3-phenylpyrazolyl)benzene 31 (R = 4-OMeC$_6$H$_4$). Method II. A suspension of resin **28** (X = H, R = 4-OMeC$_6$H$_4$) (100 mg, 44 μmol) in freshly distilled TFA (4 mL) was stirred at room temperature for 16 h. The resin was separated by filtration and washed extensively with CH_2Cl_2. The organic washings were concentrated in vacuo to give pyrazole **31** (R = 4-OMeC$_6$H$_4$) as a white solid (6.0 mg, 55%). The purity of the crude mixture was determined to be 94% by HPLC, and its identity was established by co-injection with an authentic sample. Spectroscopic data as above.

General Procedure for TFA-Mediated Cleavage of Pyrazoles from Resins 27/29 and 28/30. (See Table 1, entries 1−32). A suspension of resin (100 mg) in freshly distilled TFA (1 mL) was stirred for 16 h. The resin was separated by filtration and washed with CH_2Cl_2. The organic washings were concentrated in vacuo to give the crude pyrazoles which were subject to ^{1}H NMR and HPLC-MS analysis (see Supporting Information).

General Procedure for Bromine-Mediated Cleavage of Pyrazoles from Resins 27/29 and 28/30. (See Table 2, entries 33−48). To a suspension of resin (100 mg) in CH_2Cl_2 (2 mL) was added bromine (8 mg) dropwise, and the resulting mixture was stirred for 30 min at room temperature in an Isolute syringe filter. After addition of 1 M $Na_2S_2O_3$ (2 mL), the mixture was stirred until complete decolorization was observed. The CH_2Cl_2 was then allowed to pass through the filter under atmospheric pressure to separate it from the aqueous layer; further CH_2Cl_2 was added, and the process was repeated. The combined organic washings were concentrated in vacuo to give the crude pyrazoles which were subject to ^{1}H NMR and HPLC-MS analysis (see Supporting Information).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all nonlibrary compounds, HPLC data for cleavage of biaryls **19**−**22** and pyrazole **31** (R = 4-OMeC$_6$H$_4$), single-crystal X-ray data for pyrazole **31** (R = 4-OMeC$_6$H$_4$), and HPLC retention times, MS and ^{1}H NMR data for library pyrazoles **1**−**47**. This material is available free of charge via the Internet at http://pubs.acs.org.

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