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Modular Synthesis

Modular Generation of (Iodinated) Polyarenes Using Triethylgermane as Orthogonal Masking Group

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Abstract: While the modular construction of molecules from suitable building blocks is a powerful means to more rapidly generate a diversity of molecules than through customized syntheses, the further evolution of the underlying coupling methodology is key to realize widespread applications. We herein disclose a complementary modular coupling approach to the widely employed Suzuki coupling strategy of boron containing precursors, which relies on organogermane containing building blocks as key orthogonal functionality and an electrophilic (rather than nucleophilic) unmasking event paired with air-stable Pd^{I} dimer based bond construction. This allows to significantly shorten the reaction times for the iterative coupling steps and/or to close gaps in the accessible compound space, enabling straightforward access also to iodinated compounds.

Introduction

Polyarenes are privileged motifs within pharmaceuticals, materials and agrochemicals.[1] Their function is directly correlated with their substitution pattern. Owing to the vast potential chemical space in this context, there is significant interest in devising synthetic methods that allow for an accelerated construction of diversely substituted polyarenes via modular syntheses from pre-defined building blocks (Figure 1). This approach offers the opportunity to reach molecular diversity faster, and consequently increases the likelihood of discovery of new drugs, materials and agrochemicals.[2] If the methodology is robust, practical and general, it will potentially also allow for automation of chemical synthesis, which is considered key to further enhance the molecule output.[3–5] Modularity is achieved through selective coupling at a single molecular handle, and further functionalization can then be achieved through subsequent selective functionalization at other potential reactive sites (sequential coupling) or upon introduction of repeat units (iterative couplings).[4,6–8] The latter strategy was successfully applied by Burke and co-workers in automated small molecule synthesis, relying on MIDA-protected (*N*-methyliminodiacetic acid) boronates as building blocks, which are introduced by Pd^{0}-catalyzed Suzuki couplings with aryl bromides.[4] The sequence then requires "deprotection" of the BMIDA unit to release a free boronic acid for the next iteration (see Figure 1).[9] While the development of this approach and alternative modular strategies, have greatly progressed in recent years,[7,8] there is a need for additional methods to further increase the speed of compound synthesis and expand the scope. For example, Burke's method relies on 16–24 h Suzuki coupling steps at elevated temperature for each iteration.[4] The scope is inherently dependent on the coupling ability of the unprotected boronic acid and its potential instability as well as the ability to deprotect BMIDA, which requires basic conditions.[4,9] For example, fluorinated aryl boronic acids have only a millisecond stability in basic media.[10]

Moreover, a functionality which cannot readily be tolerated in such modular constructions of molecules is

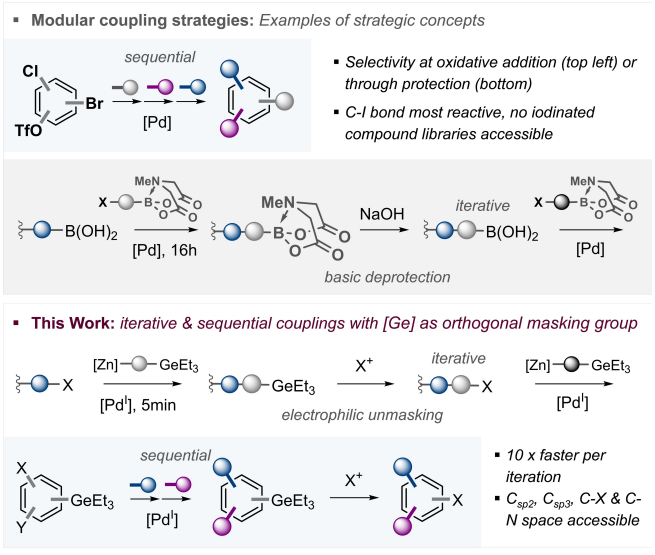

Figure 1. State-of-the-art for modular synthesis and this work; aryl germanes as masking groups in modular cross-coupling.

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iodine owing to the inherently high reactivity of $C_{(sp2)}$–I bonds (relative to alternative halogen sites) in oxidative addition with Pd, making it the site of preferential coupling.[11] Such compounds are of importance however in a medicinal chemistry context as well as in radio imaging,[12] supramolecular[13] and materials chemistry.[14] Facile and modular access to diverse iodinated molecules would therefore be greatly enabling. The halogenation of the boron moiety is relatively harsh and not necessarily amenable to a broad functional group compatibility, which makes the BMIDA iterative approach less suitable.[15] The direct iodination of C–H bonds is an alternative, but site-selectivity is an issue and certain sites are inaccessible (e.g. meta-C–H iodination).[16,17] There is hence the need for an alternative approach.

We recently introduced aryl germanes as orthogonal functional handles which can be selectively coupled in the presence of other readily functionalizable moieties (i.e. C–Br, C–Cl, C–OTf, C–$B(OR)_2$, C–SiR_3) under Pd-nanoparticle,[18] Au-catalysis[19] or with electrophilic halogenation[20] (Figure 1, bottom).[21]

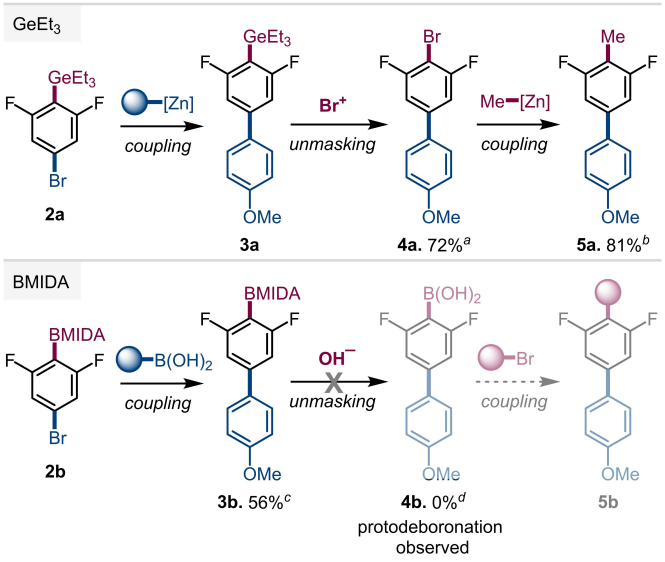
The non-toxic,[22] and easily installed $GeEt_3$ functionality[23] offers high stability to a range of reaction conditions including air, moisture, as well as acidic and basic media.[18] Since the [Ge]-transmetalation is associated with an unsurmountable activation barrier as well as lack of driving force on [L_nPd^{II}(Ar)] intermediates,[18] the [$GeEt_3$] unit is unreactive in homogeneous L_nPd^0/L_nPd^{II} cross-couplings. We therefore hypothesized that it could be harnessed in sequential and iterative couplings, instead of e.g. BMIDA. This approach could be advantageous, as [Ge] could be unmasked in a complementary electrophilic rather than nucleophilic (basic) manner.[20] Moreover, it would allow for facile iodination and, as such, unlock modular access to iodinated compounds.

In this context, the wider chemical stability is key: clearly, a masking or protecting group is optimal if it is inert to a large number of chemical transformations, while being the sole reactant in the specific deprotection or unmasking event. This report describes our investigation in this context and examines $GeEt_3$ as masking group for iterative and/or sequential couplings and diverse chemical transformations.

Results and Discussion

Building on our previous developments of rapid Pd^I dimer-enabled cross-couplings of aryl bromides with organometallic reagents,[8] we first set out to investigate whether such couplings could be achieved in the presence of the robust and readily installable aryl germane ($GeEt_3$) functionality, i.e. whether $GeEt_3$ would truly function as a non-reactive masking group (Scheme 1).

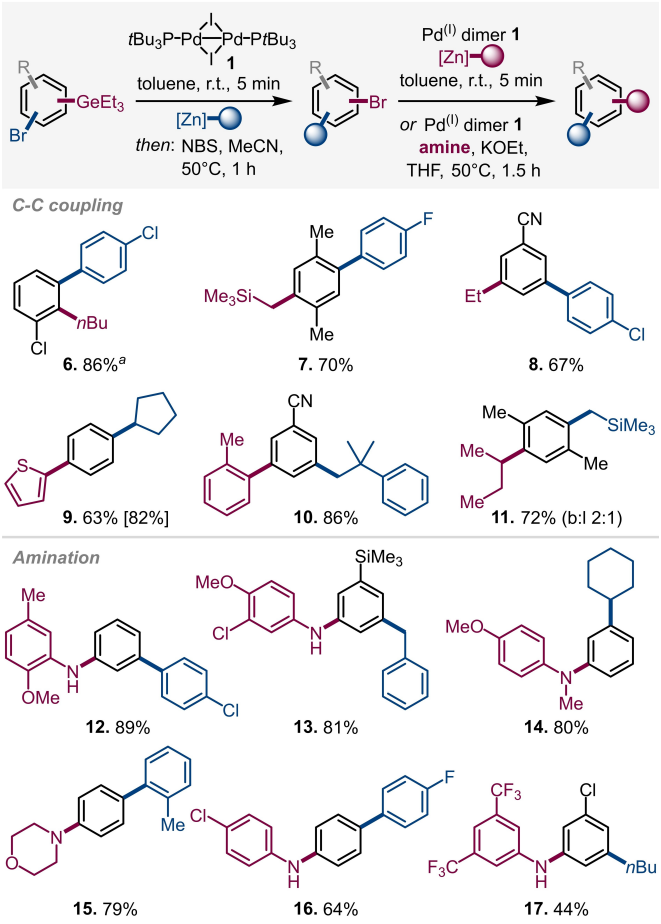
To this end, we subjected 4-methoxyaryl zincate to bromoaryl germane **2a** and indeed observed selective coupling at the bromide to yield biaryl germane **3a** in less than 15 min at room temperature. The $GeEt_3$ functionality remained fully untouched. We subsequently set out to unmask C–$GeEt_3$ via bromination, which proceeded readily in 72 % (over two steps, see Scheme 1), creating another C–Br site for further rapid Pd^I-based alkylation or arylation. Simple filtration through a silica plug was sufficient purification between these steps. As such, the modular diversification at single arene units appears indeed viable via this approach and compound **5a** was obtained in 90 min. As a direct comparison to the established BMIDA approach,[4] the first coupling step of **2b** required 24 hours at 55 °C. However, the deprotection of BMIDA under basic conditions to release the free boronic acid **4b** led to protodeboronation as a consequence of the low stability of such fluorinated boronic acids, clearly showing that a complementary electrophilic deprotection approach is of value.



Scheme 1. Cross-coupling in the presence of aryl germane and unmasking by bromination. Reaction conditions: a) **1** (2.5 mol%), **2a** (0.2 mmol), RZnCl (0.3 mmol), toluene (2 mL), argon, r.t., 5 min; filtration, then NBS (0.24 mmol), MeCN (2 mL), 60 °C, 1 h. b) **1** (2.5 mol%), **4a**, RZnCl (0.4 mmol), toluene (2 mL), argon, r.t., 5 min. c) ArBMIDA **2b** (0.33 mmol), XPhosPd-G2 (5 mol%), K_3PO_4 (1 mmol), THF (3 mL), $RB(OH)_2$ (0.11 mmol) in THF (10 mL), 55 °C, 24 h. d) NaOH (0.12 mmol), THF/H_2O (7:1, 1 mL), r.t., 20 min.

We subsequently set out to showcase the diversity that can be reached with additional examples. Both sp^2–sp^2 and sp^2–sp^3 couplings could rapidly be achieved in this manner and the cross-coupling reaction was not sensitive to the electronic nature of arylzinc reagents, with methyl bearing **7** and **11**, fluorine/chlorine bearing **7** and **8** or heterocyclic motif **9** formed in good to excellent yields (Scheme 2).

Carbon–heteroatom bond formation, especially amination reactions,[25] are of significant importance and we therefore investigated if such a transformation could also be possible with the air-stable iodide-bridged Pd^I dimer **1**. We found that the Br-site created in the unmasking from [Ge] was also readily aminated at 50 °C within 1.5 h (**12**–**17**). While aminations of aryl bromides using the labile and air-sensitive [Pd(μ-Br)($PtBu_3$)]$_2$ dimer have previously



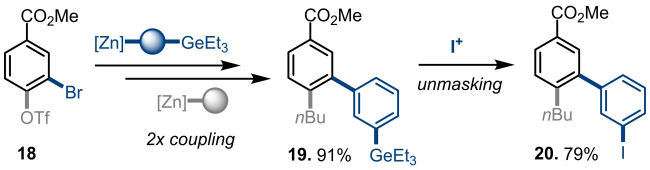
Scheme 2. Demonstration of germane as a masking group for bromine in sequential couplings. Reaction conditions: *1st coupling*: **1** (2.5 mol%), ArBr (0.2 mmol), RZnCl (0.3 mmol), toluene (2 mL), argon, r.t., 5 min; filtration, then NBS (0.24 mmol), MeCN (2 mL), 60 °C, 1 h. *2nd coupling*: **1** (2.5 mol%), ArBr, RZnCl (0.4 mmol), toluene (2 mL), argon, r.t., 15 min. *Amination*: **1** (5 mol%), ArBr, THF (1 mL), amine (0.3 mmol), KOEt (0.8 mmol), 50 °C, 1.5 h. Isolated yields over three steps. a) 6 h reaction time for bromination. b) Quantitative ^{1}H NMR yield of the crude. c) Branched:linear ratio.[24]

been reported,[26] this constitutes the first rapid amination using the air-stable and more robust iodide-bridged Pd^I dimer $[Pd(\mu\text{-}I)(P\mathit{t}Bu_3)]_2$ **1**. Upon completion of an initial C–C bond coupling, and subsequent halogenation of the aryl germane, anilines and secondary amines were successfully coupled at 50 °C in 1.5 hours. Both electron-rich (**12**–**14**) as well as electron-deficient anilines (**17**) were incorporated efficiently. Secondary amine morpholine also furnished the cross-coupled product in a good yield of 79 %. The amination protocol also tolerated other potentially reactive functional handles such as Ar–Cl (**13**, **16**–**17**) and Ar–$SiMe_3$ (**13**). These examples illustrate that starting from a bifunctional arene bearing both a C–Br and a C–Ge functionality (which can be readily accessed from a commercial bromo arene via C–H germylation),[23] it is possible to sequentially arylate/alkylate within a few minutes, followed by halogenation as unmasking event (1 hour for bromination). Subsequently, yet another arylation/alkylation can be done in a short time frame (5–15 minutes) at room temperature. Alternatively, amination within 90 minutes at 50 °C can also be performed. It is therefore possible to undertake the coupling/unmasking/coupling strategy in less than 3 hours, compared to the previous BMIDA approach which requires 32–48 hours.[4] Moreover, an additional advantage is the ability to introduce a carbon-heteroatom coupling in the sequence via amination in a site selective manner using the same air-stable Pd^I dimer catalyst **1**. Importantly, owing to the generality and selectivity of the Pd^I-based coupling, the strategy is compatible with alternative (pseudo)halogens, e.g. C–Cl and C–OTf, which can be utilized in further derivatizations.

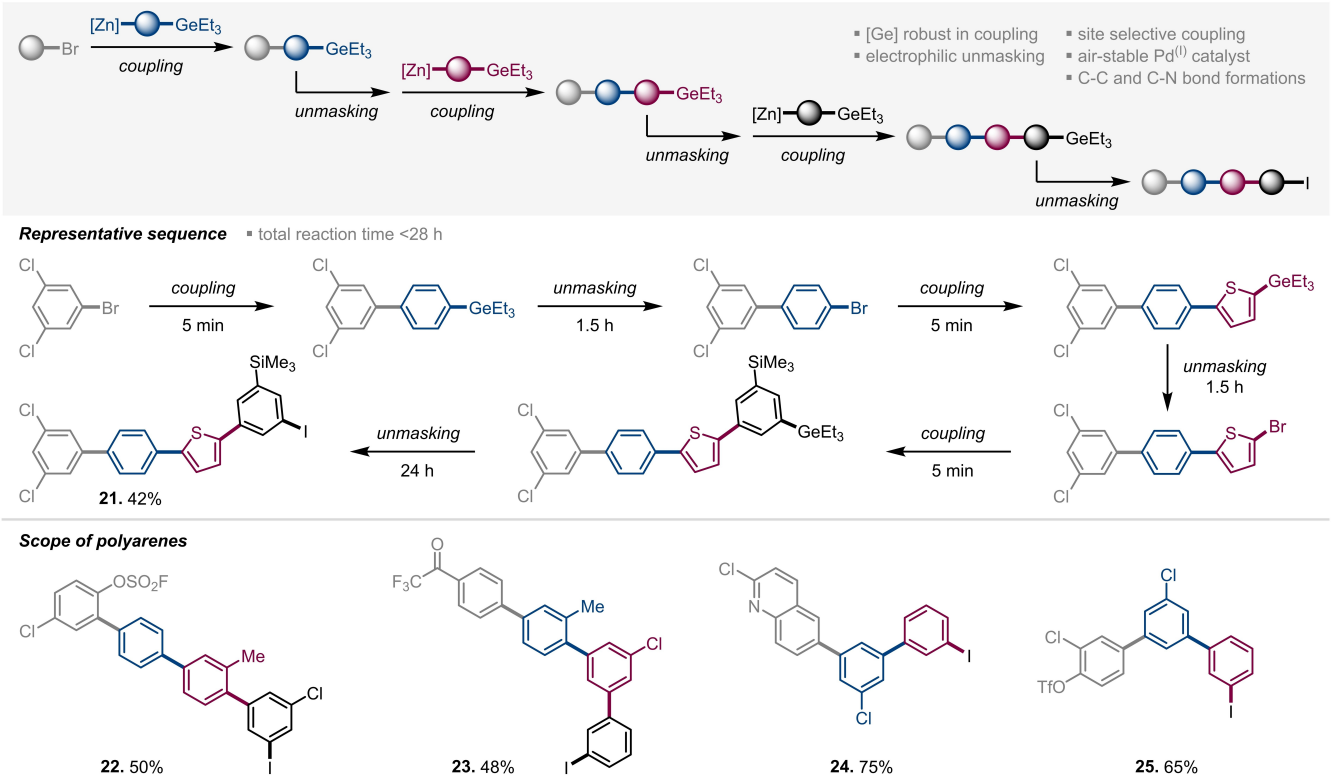
The described approach thus far requires a Br/$GeEt_3$ bifunctional arene and primarily diversifies at a single arene unit. For the build-up of larger molecules as well as additional synthetic diversity it would also be advantageous to start from a simple aryl halide or poly(pseudo)-halogenated arene and then couple with a distinct building block that introduces the $GeEt_3$-functionality in an iterative manner. This way, the C–$GeEt_3$ does not need to be present in the initial molecule. For this to be viable, the coupling reagent [Ge]–Ar–[Zn] needs to be reasonably stable. As a proof of concept, we prepared [Ge]–Ar–ZnX by first forming the corresponding Grignard reagent from [Ge]–Ar–Br, followed by transmetalation with $ZnCl_2$. The $GeEt_3$-functionality proved to be fully robust. Our subsequent tests of this [Ge]–Ar–[Zn] reagent in site-selective couplings highlighted that the $GeEt_3$-functionality also did not impede the exquisite site-selectivity previously observed in Pd^I-based couplings; **18** was rapidly coupled selectively at the C–Br site in less than 5 min at room temperature using the germylated aryl organozinc (Scheme 3).

A solvent switch to the more polar NMP[8f] and addition of *n*BuZnCl·LiCl enabled an sp^2–sp^3 cross-coupling with the aryl triflate generating doubly cross-coupled product **19** in an excellent yield of 91 %. Pleasingly, iodination of the germyl arene as the final step was facile and high yielding to provide **20**.

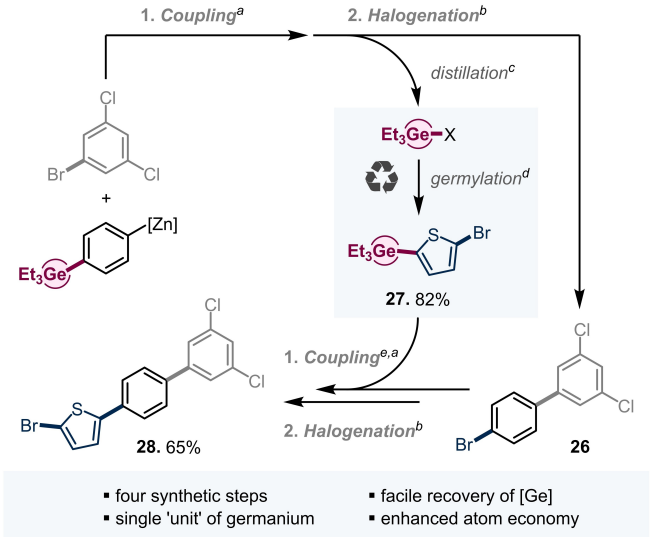
These examples highlight that modular and site-selective diversification in sp^2 and sp^3 space is readily possible in the presence of the $GeEt_3$-functionality; yet the C–$GeEt_3$



Scheme 3. Compatibility of germylated organozinc in cross-coupling and unmasking by iodination. Reaction conditions: a) **1** (2.5 mol%), **18** (0.2 mmol), RZnCl (0.3 mmol), toluene (2 mL), argon, r.t., 5 min. b) **1** (2.5 mol%), ArOTf (0.2 mmol), *n*BuZnCl·LiCl (0.3 mmol), NMP (2 mL), argon, r.t., 10 min. c) **19** (0.18 mmol), DMF (1.8 mL), NIS (0.36 mmol), 60 °C, 30 h.



Scheme 4. Sequential couplings and scope of polyarenes. Reaction conditions: *C–C coupling*: **1** (2.5 mol%), ArBr (1.0 mmol), RZnCl (1.5 mmol), toluene (5 mL), argon, r.t., 5–15 min; *Bromination*: NBS (2.0 equiv), MeCN (0.2 M) or HFIP (0.2 M for electron-deficient arenes), 60 °C, 1.5 h. *Iodination*: $ArGeEt_3$, NIS (2.0 equiv), HFIP (0.2 M), 60 °C, 24 h. Isolated yields over all steps, i.e. based on initial aryl bromide, are reported.

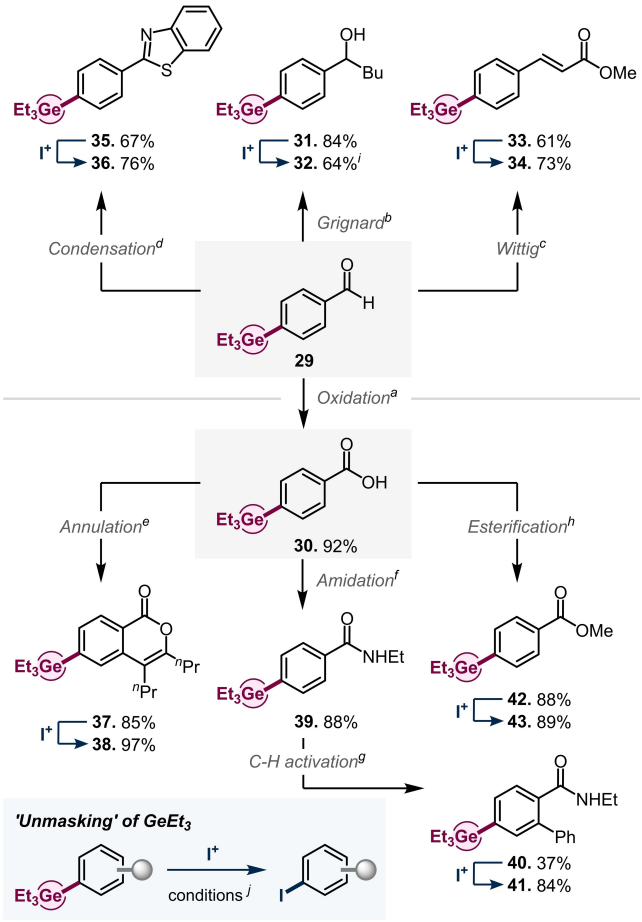


Scheme 5. Recycling of germanium masking group (at 1 mmol scale). Reaction conditions: a) **1** (2.5 mol%), ArBr (1.0 mmol), RZnCl (1.5 mmol), toluene (5 mL), argon, r.t., 5 min. b) $ArGeEt_3$, MeCN (0.2 M), NBS (3.0 equiv), NH_4Br (5.0 equiv), 60 °C, 1.5 h. c) Kugelrohr distillation (70 °C, 10 mbar). d) (5-bromothiophen-2-yl) magnesium bromide (2.0 equiv), THF (1 M), r.t., 16 h. e) ArBr (1.0 equiv), Mg (1.5 equiv), LiCl (1.1 equiv), THF (1 M), then $ZnCl_2$ (1.1 equiv), LiCl (0.5 M in THF, 1.1 equiv), r.t., 10 min.

site is highly reactive towards final iodination (or bromination). The ability to introduce a $GeEt_3$ moiety from an aryl zincate significantly enhances the number of iterations which can be achieved, and we set out to demonstrate this with several examples (see Scheme 4). To minimize potential side species especially with increasing number of iterations, we extended the unmasking step (i.e. bromination) in these instances to 1.5 hours and purified the coupling products by column chromatography after each step. Pleasingly, excellent yields of the polyarenes were observed after six steps, with an average of at least 87 % yield per step for the thiophene-containing polyarene **21**. In line with previous results,[8] aryl bromides were selectively coupled in the presence of aryl chlorides and aryl fluorosulfates, such as **22**. Also *ortho*-substituents were well tolerated (**22**, **23**). Heteroaromatic germanes such as the thiophene moiety in **21** were also successfully iodinated, allowing access to iodinated poly(hetero)arenes in an extremely efficient manner.

We next sought to explore the potential of greater atom-economy of the process by recovering germanium and recycling it for use in subsequent couplings (Scheme 5).

After coupling of 1-bromo-3,5-dichlorobenzene with Et_3Ge–Ar–[Zn], followed by bromination of the C–[Ge] site to **26**, Et_3GeX was recovered by distillation from the crude



Scheme 6. Stability of C-$GeEt_3$ in various synthetic transformations. *Reaction conditions:* a) **29** (0.3 mmol), *t*BuOH (1.8 mL), NaH_2PO_4 (5 w/w% aq., 1.2 mL), $KMnO_4$ (1 M aq., 1.8 mL), r.t., 20 min. b) **29** (0.3 mmol), THF (0.1 M), $LaCl_3{\cdot}2\,LiCl$ (30 mol%), *n*BuMgCl (0.45 mmol) r.t., 2 h. c) **29** (0.3 mmol), methyl(triphenylphosphoranylidene)acetate (0.45 mmol), THF (0.2 M), reflux, 3 h. d) **29** (0.39 mmol), 2-iodoaniline (0.3 mmol), K_2CO_3 (0.6 mmol), sulfur (0.9 mmol), $CuCl_2$ (10 mol%), 1,10-phenanthroline (10 mol%), H_2O (0.1 M), 100 °C, 48 h. e) **30** (0.34 mmol), $[RuCl_2(p\text{-cumene})]_2$ (2.5 mol%), KPF_6 (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.26 mmol), 4-octyne (0.17 mmol), *t*AmOH (0.3 M), 120 °C, 19 h. f) **30** (0.3 mmol) $SOCl_2$ (1.0 mL), reflux, 3 h, then Et_2O (0.5 M), triethylamine (0.6 mmol), ethylamine (0.45 mmol), r.t., 3 h. g) **39** (0.27 mmol), $[RuCl_2(p\text{-cumene})]_2$ (3 mol%), $AgSbF_6$ (12 mol%), Ag_2O (0.27 mmol), $PhB(OH)_2$ (0.4 mmol), THF (0.3 M), 110 °C, 20 h. h) **30** (0.28 mmol), MeOH (0.1 M), $SOCl_2$ (0.3 mL), r.t., 2 h. i) TBDPSCl (1.1 equiv), imidazole (3.0 equiv), DMF (0.3 M), 70 °C, 3.5 h, then NIS (2.0 equiv), HFIP (3.0 mL), 60 °C, 16 h, then TBAF (2.0 equiv), THF (1 mL), r.t., 4 h. j) NIS (2.0 equiv), HFIP (0.1 M), 60 °C, 16 h.

reaction mixture.[27] We subsequently recycled the recovered Et_3GeX (X = Br, Cl) in the synthesis of **27** (through reaction with (5-bromothiophen-2-yl)magnesium bromide). This could then be quantitatively converted to the required [Ge]–Ar–[Zn] reagent, which was utilized in another coupling/halogenation sequence to afford **28**. As such, a singular "unit" of $GeEt_3$ can in principle be used for multiple iteration to build polyarenes.

Lastly, to investigate the wider potential of the $GeEt_3$ functionality as a halogen masking group in synthesis, we also studied its general robustness to other chemical transformations beyond Pd^I-based couplings. To this end, a wide range of synthetic transformations were tested, including oxidation, reduction, C–H activation and reactions under basic/acidic media (Scheme 6). Pleasingly, the [Ge]-functionality showed complete robustness to all reaction conditions. The subsequent iodination was also possible, highlighting the utility of germanium as a late-stage halogen masking group.

Conclusion

In summary, we showcased [$GeEt_3$] as a suitable masking group for halogens, with application in sequential and iterative coupling sequences as well as a variety of other synthetic transformations. This work is complimentary to existing strategies, allowing "deprotection" of the germane masking group under electrophilic conditions, which contrasts established protocols based on boron masking groups, where nucleophilic, often basic media are required. Our approach using the air-stable Pd^I dimer $[Pd(\mu\text{-}I)(P\textit{t}Bu_3)]_2$ for site-selective cross-couplings significantly shortens the time required to build such polyarenes compared to already established methods. In addition, the conditions are mild with reactions at room temperature allowing arylation, alkylation and amination (previously not possible in sequential coupling approach) in a site-selective fashion with ease. In addition, facile unmasking of the [Ge] functionality at the end of the sequence provides access to diverse iodinated motifs, which to date cannot be accessed in a modular synthetic fashion.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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