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Synthetic Methods

Triply Selective & Sequential Diversification at C_{sp}^3: Expansion of Alkyl Germane Reactivity for C–C & C–Heteroatom Bond Formation

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Abstract: We report the triply selective and sequential diversification of a single C_{sp}^3 carbon carrying Cl, Bpin and $GeEt_3$ for the modular and programmable construction of sp^3-rich molecules. Various functionalizations of C_{sp}^3–Cl and C_{sp}^3–BPin (e.g. alkylation, arylation, homologation, amination, hydroxylation) were tolerated by the C_{sp}^3–$GeEt_3$ group. Moreover, the methodological repertoire of alkyl germane functionalization was significantly expanded beyond the hitherto known Giese addition and arylation to alkynylation, alkenylation, cyanation, halogenation, azidation, C–S bond formation as well as the first demonstration of stereo-selective functionalization of a C_{sp}^3-[Ge] bond.

The phrase *"the escape from flatland"* is a reflection of the dominance of sp^2-rich architectures in drug-related research and the considerable current interest to expand to untapped sp^3-rich structural space for the identification of the next innovative drugs or bioactive molecules.[1] In light of the large potential "drug-like" chemical space (with an estimated 10^{60} potential candidates),[2] there is an ever increasing demand for synthetic methods that allow the rapid construction of C_{sp}^3 molecules to effectively navigate in this chemical landscape,[3] and also allow for optimizations of structure/activity relationships through straightforward access to diverse structural analogues (Figure 1a). Modular synthetic approaches are especially powerful to realize this goal. In this context, the employment of defined building blocks that bear multiple reactive handles would in principle allow to straightforwardly assemble molecular complexity through sequential or iterative functionalization.[4,5] While

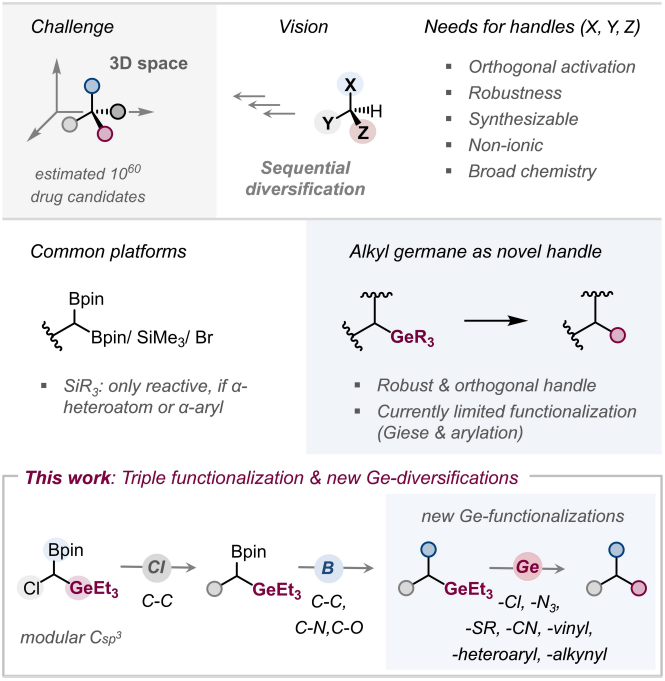

Figure 1. Modular functionalization in 3D space.

modular capabilities have advanced in recent years, especially leveraging alkylboron-handles[6] (in competition with halides or low-reactivity silanes[7]), the extent of modularity overall depends on the number of available handles and the ability to differentiate their reactivity. To maximize generality and diversity, the handles are ideally functionalized through discrete and orthogonal processes, while displaying robustness (bench-stability) and operational simplicity (e.g. being non-ionic to ease purification of intermediates or allow for automation). Such orthogonal activation modes are especially needed when the handles are positioned at the same sp^3-carbon, where selectivity control is most challenging and the intermediates formed at the central carbon must be tolerated by the alternative handles.

With the aim to enhance modularity in sp^3-space, we recently set out to explore a fundamentally novel diversification handle, which would be robust, neutral, non-toxic and compatible with the rich chemistry of organoboron and alkyl halide compounds. We explored alkyl germanes in this context,[8,9] especially R–$GeEt_3$.[10] While we were able to

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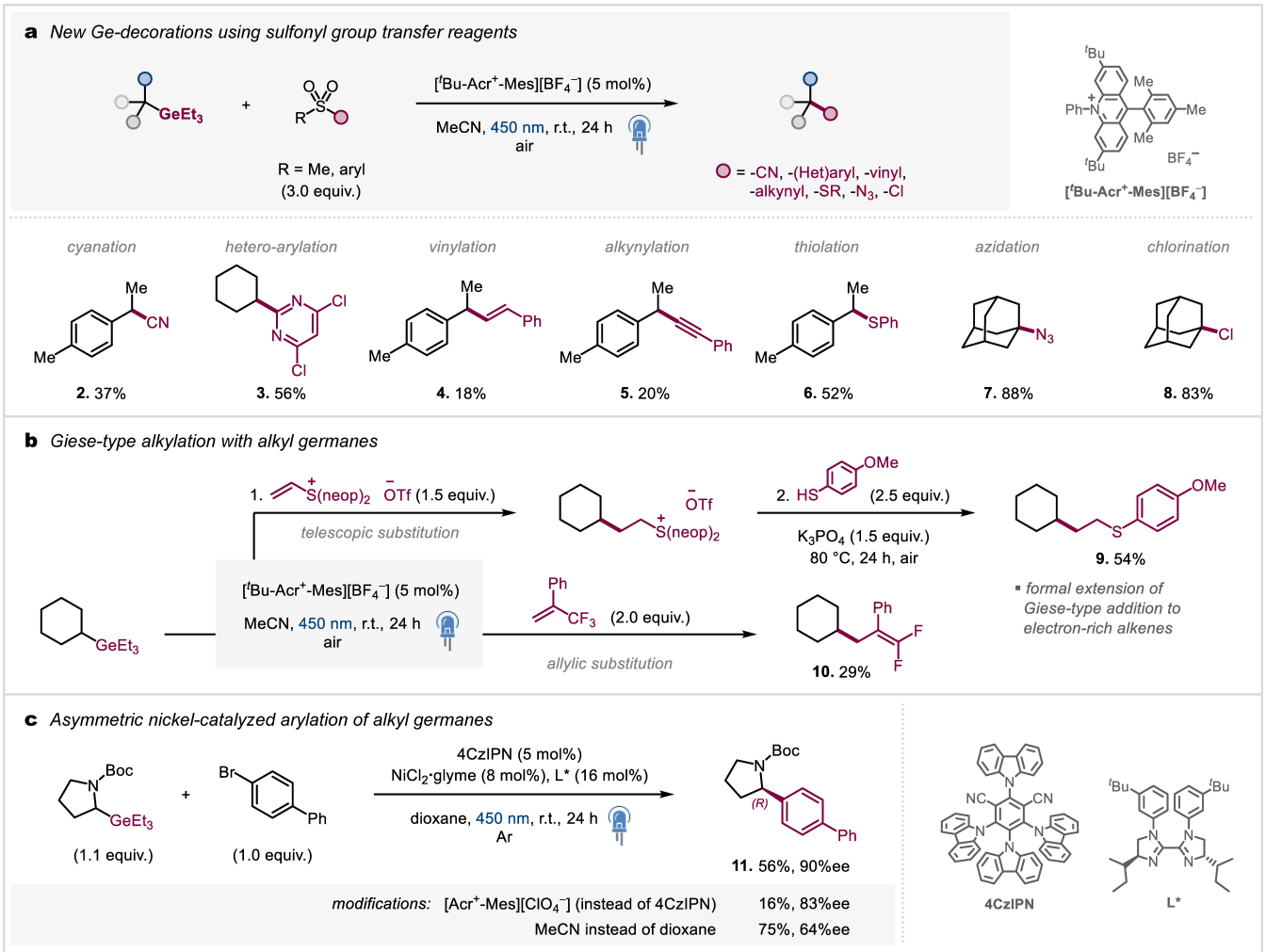
show the robustness of R–$GeEt_3$ towards various chemical transformations and the ability to chemoselectively functionalize either Bpin in the presence of GeR_3 or vice versa in preliminary investigations,[10] the triply selective and complete functionalization of a modular sp^3 building block as shown in Figure 1 has so far not been realized. Moreover, the methodological repertoire to functionalize alkyl germanes is currently limited to Giese additions with electron-deficient olefins or Ni-mediated arylations as shown by Xiao's and our group.[10,11]

This work reports the first successful realization of the full diversification of all three handles (halogen, BPin, [Ge]) at the same C_{sp3} and expands the functionalizations of alkyl germanes beyond Giese and arylation reactions to cyanation, alkynylation, alkenylation, halogenation, azidation, C–S bond formation as well as the first demonstration of stereo-selective decorations of C_{sp^3}-[Ge] bonds.

We started our investigations with the motivation to expand the set of possible functionalizations of alkyl germanes beyond the previously demonstrated Giese addition or Ni-mediated arylation. Alkyl germanes can efficiently be cleaved at room temperature to the corresponding alkyl radical under oxidative conditions, employing an organic acridinium photocatalyst along with blue light in polar solvent.[10,11] We hence set out to explore whether alternative functionalizations of the generated radical would be compatible with the conditions used to activate the alkyl germane. We identified that the use of sulfonyl group transfer reagents proved to be effective,[12] enabling the corresponding cyanation (**2**), heteroarylation (**3**), vinylation (**4**) and alkynylation (**5**) (Scheme 1a). Carbon-heteroatom bond formation was similarly effective, which allowed for the first formal conversion of alkyl germanes to the corresponding sulfide (**6**), azide (**7**) or chloride (**8**), which



a. Reaction conditions: *using sulfonyl group transfer reagent*: alkyl germane (1.0 equiv.), [^{t}Bu-Acr$^+$-Mes][BF_4^-] (5 mol%), electrophile (3.0 equiv.), MeCN or DCE (0.05 – 0.1 M), 450 nm (blue LED), r.t., 24 h; *telescopic Giese alkylation*: alkyl germane (1.0 equiv.), dineopentyl(vinyl)sulfonium triflate (1.5 equiv.), [^{t}Bu-Acr$^+$-Mes][BF_4^-] (5 mol%), MeCN (0.1 M), 450 nm (blue LED), r.t., 48 h, then thiol (2.5 equiv.), K_3PO_4 (1.5 equiv.), 80 °C, 24 h; *Giese-type addition*: alkyl germane (1.0 equiv.), [^{t}Bu-Acr$^+$-Mes][BF_4^-] (5 mol%), alkene (2.0 equiv.), MeCN/MeOH (1:1, 0.1 M), 450 nm (blue LED), r.t., 24 h; *asymmetric Ni-cat. arylation*: alkyl germane (1.1 equiv.), aryl bromide (1.0 equiv.), 4CzIPN (5 mol%), $NiCl_2$•glyme (8 mol%), L* (16 mol%), dioxane (0.1 M), 450 nm (blue LED), r.t., 24 h.

Scheme 1. Functionalizations of alkyl germanes.[a]

overall expands the diversification repertoire for alkyl germanes from Giese and arylation to seven novel decorations.

To potentially widen the diversity of C_{sp}^3 - C_{sp}^3 bond formation from the currently known[10,11] Giese additions with electron-deficient Michael acceptors to formally electron-rich products, we examined the compatibility of Silvi's elegant telescopic substitution method, which leverages vinyl sulfonium salts as Giese acceptors (using 4CzIPN as a photocatalyst to generate organic radicals from carboxylic acids) that can subsequently readily be decorated with nucleophiles.[13] This Giese/substitution sequence proved indeed compatible also with alkyl germanes with an acridinium-based photocatalyst to give the formally alkyl sulfide–extended product **9** in 54 %. Moreover, terminal difluoroalkene (**10**) could be formed from α-CF_3 styrene (Scheme 1b).

These functionalizations of alkyl germanes do not discriminate stereochemistry and generate solely racemic products.[14] The generation of sp^3-rich compounds implies that molecules with stereo control would hence be highly enabling. Indeed, the ideal realization of a modular platform would not only allow for various diversification opportunities but also enable access to desired stereoisomers. Inspired by prior demonstrations of stereoconvergent functionalization of photoredox-generated alkyl radicals with a chiral Ni-catalyst,[15] we explored the compatibility of this concept with conditions of alkyl germane activation. Our initial efforts employed an acridinium photocatalyst along with chiral bis(imidazoline) ligand (**L***, 16 mol %) and Ni (8 mol %).[16] While low enantioselectivity was seen with MeCN as solvent (70 % *ee*), the chiral product **11** was generated in 83 % *ee* in dioxane, albeit in relatively low yield (16 %). However, utilizing the less oxidizing organic photocatalyst 4CzIPN in dioxane delivered **11** in good yield (56 %) and 90 % *ee*, which presents a proof-of-principle that stereocontrol is feasible also.

With these novel functionalizations established, we next set out to explore their scope in the full functionalization of the modular C_{sp}^3 platform **1** (Scheme 2).[17] The sequence commenced with the functionalization of the C-halogen site of **1** with various alkylations and arylation. Nucleophilic substitution with readily accessible Grignard reagents provided consistently high yields and incorporated protected alcohols (**12**), aldehydes (**13**), linear and branched alkyl chains (**14**–**16**) as well as aryl substitution (**17**) (Scheme 2a).

Subsequently, the C–Bpin site was derivatized (Scheme 2b). A variety of widely utilized synthetic transformations such as oxidation[18] (**18**–**20**), homologation[18] (**21**, **22**), amidation[19] (**23**–**25**), and arylation[20] (**26**, **27**) were compatible with the germane substituent on the same carbon, often providing quantitative yields. The $GeEt_3$ remained completely untouched despite the employed basic, nucleophilic and oxidizing reaction conditions, highlighting its robustness and orthogonal reactivity space.

Finally, the sequence was completed with photoredox-based C–$GeEt_3$ functionalization (Scheme 2c). We performed several alkylations via Giese-type additions with electron-deficient olefins (**28**–**31**) - after either previous oxidation or amidation of the Bpin moiety. The polarity inversion approach[13] with a vinyl sulfonium salt as acceptor, followed by substitution with 4-methoxybenzenethiol also proved compatible with intermediate **24** to give **32** in 46 % yield, and consequently showcases the possibility to generate formally electron-rich and deficient alkylated variants.

Similarly, arylation under Ni/photoredox catalysis[11] was compatible with the previously homologated, arylated, oxidized, or amidated building blocks (**33**–**37**). Notably, using the previously oxidized platform (i.e. obtained after oxidation of Bpin moiety to alcohol) allowed for selective adjustment of the oxidation state: Using the germane in excess leads to the expected α-arylated hydroxy product (**35**), while using the germane as the limiting species selectively furnished the α-arylated ketone (**36**) instead. We speculate that this divergent reactivity is related to the catalyst availability to perform follow-up oxidation of the alcohol.[21,22]

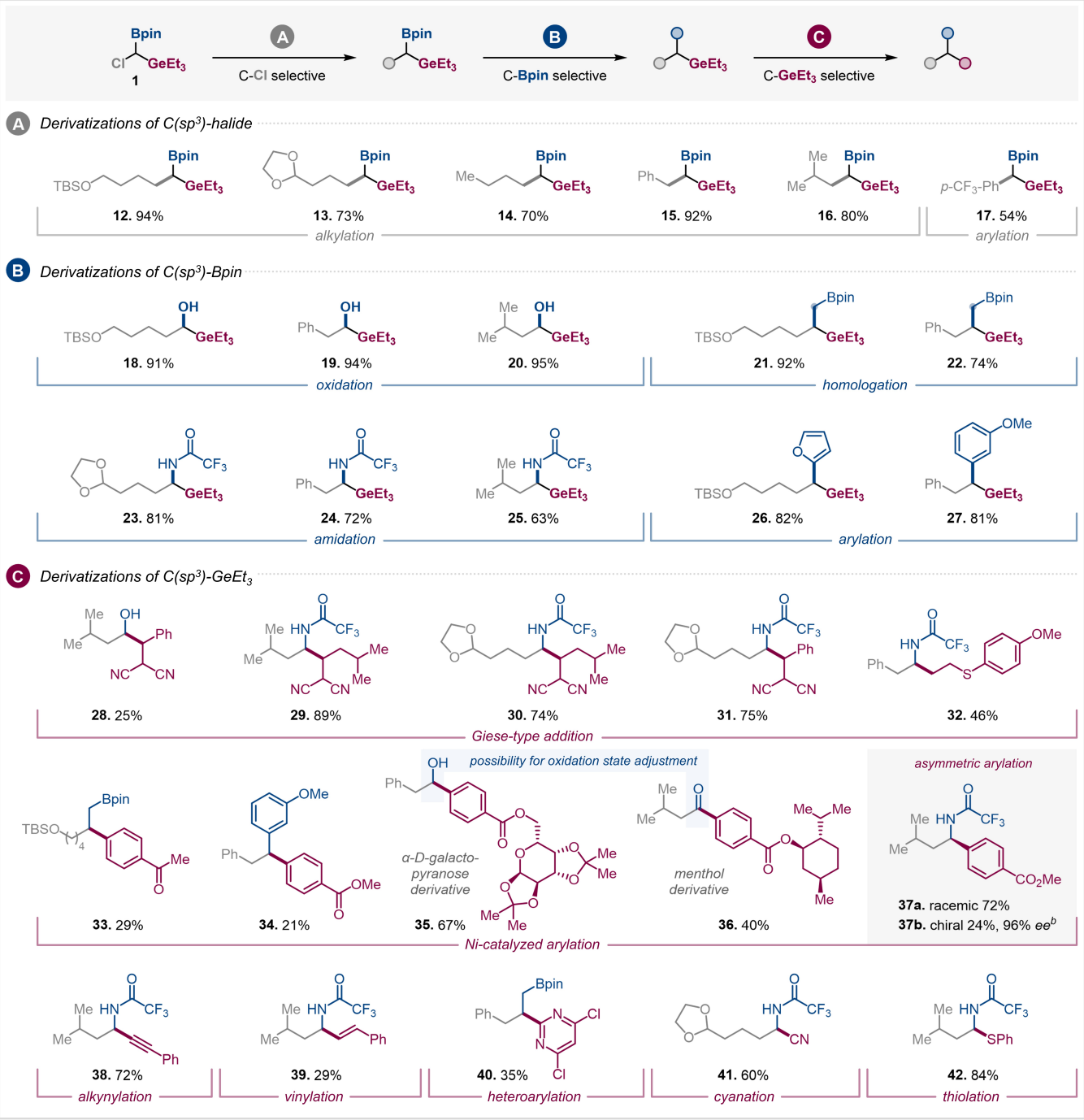
Notably, also the asymmetric arylation was possible to yield **37b**, with high enantioselectivity (96 % *ee*).

Leveraging sulfonyl group transfer reagents for alternative radical decorations also proved compatible with the higher substituted alkyl germanes. Using our optimized reaction conditions (Scheme 1a) allowed for efficient alkynylation (**38**), vinylation (**39**), heteroarylation (**40**) and cyanation (**41**). Moreover, we could also use this strategy to introduce heteroatoms, as showcased in thiolation to yield **42**.

To showcase the utility of the modular sp^3-building block **1** for the synthesis of functional molecule of pharmaceutical potential, we further functionalized the alkylated and amidated germane **29** (Scheme 3a). Oxidative cleavage of malononitrile[23] furnished methyl ester **43** and hydrolysis of the ester provided non-natural β-amino acid (**44**). In contrast, treating **29** with strong base and prolonged heating resulted in lactam formation (**45**) and subsequent hydrolysis yielded the corresponding γ-amino acid and derivative of pregabalin (**46**), which is employed to treat various neurological disorders (such as epilepsy, restless leg syndrome, opioid withdrawal, generalized anxiety disorder).[24]

In light of the omnipresent utilization of redox-active esters as radical precursors and their recently demonstrated potential in organic synthesis,[25] we next set out to also explore the compatibility and potential orthogonality of the alkyl germane with redox active esters.

As proof-of-concept, building block **47** was synthesized which contains two different photoredox active motifs, the alkyl germane and the *N*-hydroxy phthalimide ester (Scheme 3b). The redox-active ester stayed intact under oxidative conditions using acridinium-based photocatalyst, allowing for the selective functionalization of C–Ge with sulfonyl group transfer reagents. This facilitated cyanation (**48**), thiolation (**49**) and introduction of a C-halide bond through chlorination (**50**). Vice versa applying reductive photoredox conditions activated the redox-active ester selectively in the presence of the germane. Utilizing $[Ru(bpy)_3Cl_2]$ as photocatalyst allowed alkynylation of the phthalimide ester to form **51**, also using a sulfonyl group transfer reagent.[26]

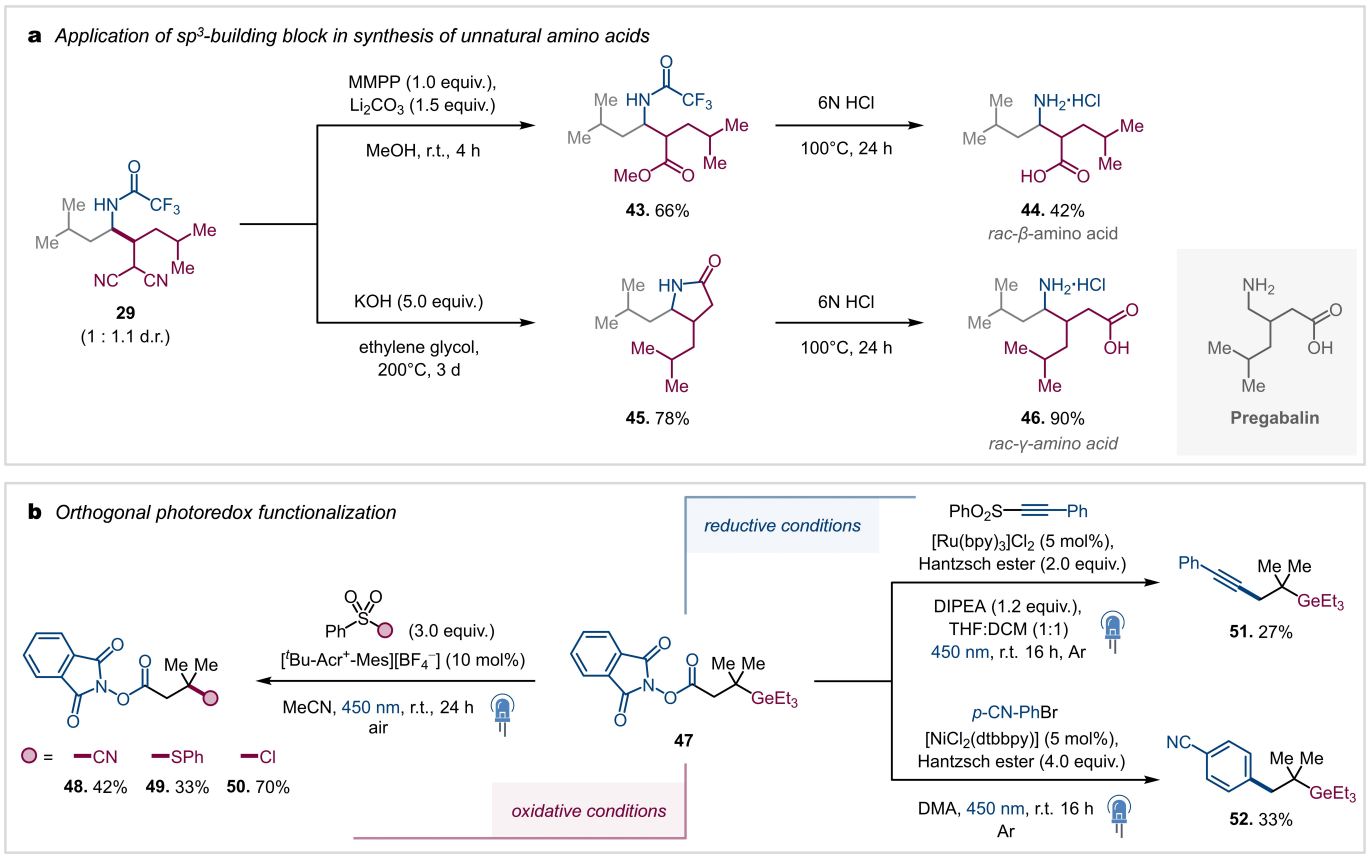


a. Reaction conditions: (i) **1** (1.0 equiv.), RMgX (1.2 – 2.4 equiv.), THF, 0 °C – r.t., 2 – 12 h; (ii) *oxidation*: alkyl-Bpin (1.0 equiv.), aq. NaOH (3 M, 3 equiv.), H_2O_2 (30 wt%, in H_2O, 9 equiv.), THF, 0 °C – r.t., 12 h; *homologation*: alkyl-Bpin (1.0 equiv.), ^{n}BuLi (1.6 M, 1.1 – 3.0 equiv.), CH_2ICl (1.1 equiv.), THF, -78 °C, 1 h, then r.t., 1 h; *amidation*: alkyl-Bpin (1.0 equiv.), NH_2-DABCO (1.3 equiv.), KO^{t}Bu (4.0 equiv.), THF, 100 °C, 2 h, then TFAA (2.0 equiv.), r.t., then 100 °C, 1 h; *arylation*: Ar-Br or HetAr-H (1.2 equiv.), ^{n}BuLi (1.2 equiv.), THF, -78 °C, 1 h, then alkyl-Bpin (1.0 equiv.), -78 °C, 1 h, then NBS (1.2 equiv.) in THF or MeOH, -78 °C, 1 h ; (iii) *Giese-type addition*: alkyl germane (1.0 equiv.), [^{t}Bu-Acr$^+$-Mes][BF_4^-] (5 – 10 mol%), alkene (2.0 equiv.), MeCN/MeOH (1:1, 0.1 M), 450 nm (blue LED), r.t., 24 h; *Ni-cat. arylation*: alkyl germane (1.0 equiv.), aryl halide (1.2 – 2.0 equiv.), Ni(phen)Cl_2 (5 – 10 mol%), [^{t}Bu-Acr$^+$-Mes][BF_4^-] (5 – 10 mol%), MeCN (0.1 M), 450 nm (blue LED), r.t., 24 h;. *using sulfonyl group transfer reagent*: alkyl germane (1.0 equiv.), [^{t}Bu-Acr$^+$-Mes][BF_4^-] (5 – 10 mol%), electrophile (1.5 – 3.0 equiv.), MeCN or DCE (0.05 – 0.1 M), 450 nm (blue LED), r.t., 24 h. *b.* Alkyl germane (1.0 equiv.), aryl bromide (1.5 equiv.), [^{t}Bu-Acr$^+$-Mes][BF_4^-] (10 mol%), $NiCl_2$•dme (5 mol%), L* (10 mol%), dioxane (0.1 M), 450 nm (blue LED), r.t., 48 h.

Scheme 2. Scope of triple functionalization of modular platform **1**.[a]

Selective arylation to yield **52** was also possible under Ni-catalyzed dual photoredox conditions.[27]

In conclusion, we showed the broad utility and robustness of alkyl germanes as an orthogonal coupling handle in



Scheme 3. Applications of modular synthesis platform, derivatization and orthogonality in photocatalysis.

the modular synthesis of sp^3-rich molecules. The C_{sp^3}–$GeEt_3$ group tolerated the sequential functionalization at the same carbon center of Cl, followed by BPin in various C–C and C-heteroatom bond formations. The triply selective sequence was completed with the functionalization of the [Ge]-group in the presence of rich functionality. Beyond the hitherto known Giese and arylation C–C bond formations of alkyl germanes, we significantly expanded the diversification repertoire to cyanation, alkynylation, alkenylation, halogenation, azidation, C–S bond formation as well as the first demonstration of stereoselective decorations of C_{sp^3}-[Ge]. Moreover, the orthogonal reactivity of C_{sp^3}-[Ge] to redox active esters under photocatalysis conditions was also shown, allowing for modular decorations of either the redox-active ester or the [Ge]-group.

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Conflict of Interest

The authors declare no conflict of interests.

Data Availability Statement

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

Keywords: site-selectivity · alkyl germane · modularity · catalysis · radical chemistry · photochemistry

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