Modularity in C_{sp3} Space – Alkyl Germanes as Orthogonal Molecular Handles for Chemoselective Diversification

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Supporting Information Placeholder

ABSTRACT: To meet the need for rapid, streamlined and potentially automatable molecule synthesis, modular coupling approaches are highly desired. While the diversification of aromatic molecules, *i.e.* C_{sp2} space, has greatly advanced, modular syntheses in C_{sp3} space are comparably much less developed. This report explores the potential of alternative functional handles, *i.e.* alkyl germanes, in this context, which combine features of stability, synthesizability with selective reactivity. We show the chemoselective functionalization of alkyl germanes (R-$GeEt_3$) under photoredox conditions (Giese addition) as well as the implementation in a modular building block, which allows for selective diversification of C_{sp3}-halogen vs. C_{sp3}-Bpin vs. C_{sp3}-$GeEt_3$ sites.

Modular coupling strategies are considered highly attractive owing to the ability to rapidly generate a diverse range of compounds through sequential and chemoselective manipulations.[1] While chemoselective coupling approaches have made great progress in the functionalization of aromatic systems,[2] especially through couplings with poly(pseudo)-halogenated arenes[3] or through different typical transmetalating groups,[4] modular coupling approaches in the C_{sp3} space have, by comparison, seen much less development.[5-10] This is likely due to the inherently greater challenges in doing C_{sp3}-couplings on the one hand, but also likely due to limitations in reactivity as well as stability of available alkyl functional groups for derivatizations. For multidimensional modularity to be realized, robust functional groups are needed that allow for their independent and orthogonal functionalization in the presence of each other. Alkyl halides (*i.e.* C-I vs. C-Br vs. C-Cl) are – as opposed to their aromatic counterparts – unlikely differentiated in a general manner from each other, especially if positioned on the same carbon, and alternative functional groups are needed to realize modularity. Dual selective building blocks, containing C-Bpin and C-halogen (see Figure 1) have been developed, and largely been applied in arylations as functionalizations.[6] Alkyl $SiMe_3$ on the other hand is rather robust and can be involved in C-C couplings only if positioned α to a stabilizing group, such as an aromatic ring, which impacts the overall accessible diversity (see Figure 1).[7] *Bis*-BPin building blocks[8] allow for deborylative alkylation to alkylated BPin derivatives[9] and rich alkyl BPin derivatizations (such as homologation, halogenation, hydroxylation, amination, arylation, alkenylation).[10]

We envisioned that the identification of an alternative functionality could be advantageous in this context, as it could offer an additional site for diversification. Ideally, this group should possess pronounced chemical robustness, easy accessibility and an orthogonal activation mode.

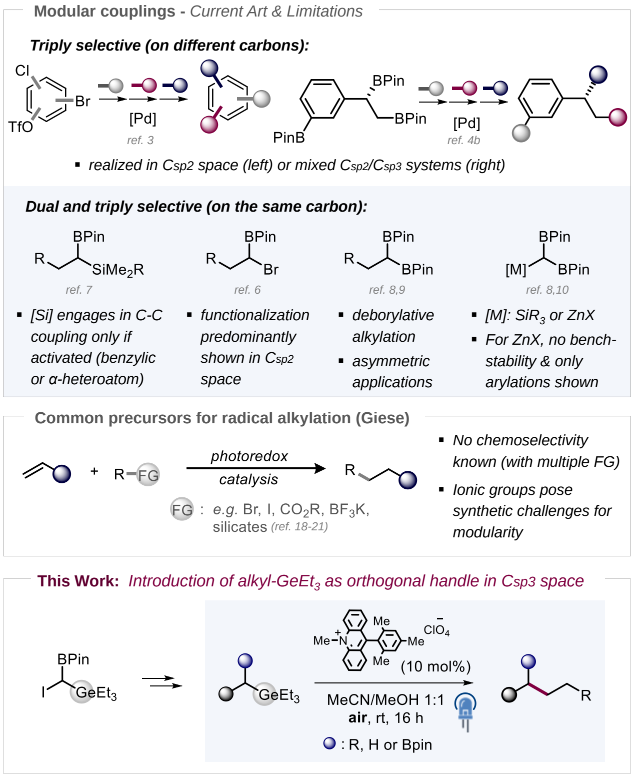


Figure 1. State of the art in modular construction of 3D molecules.

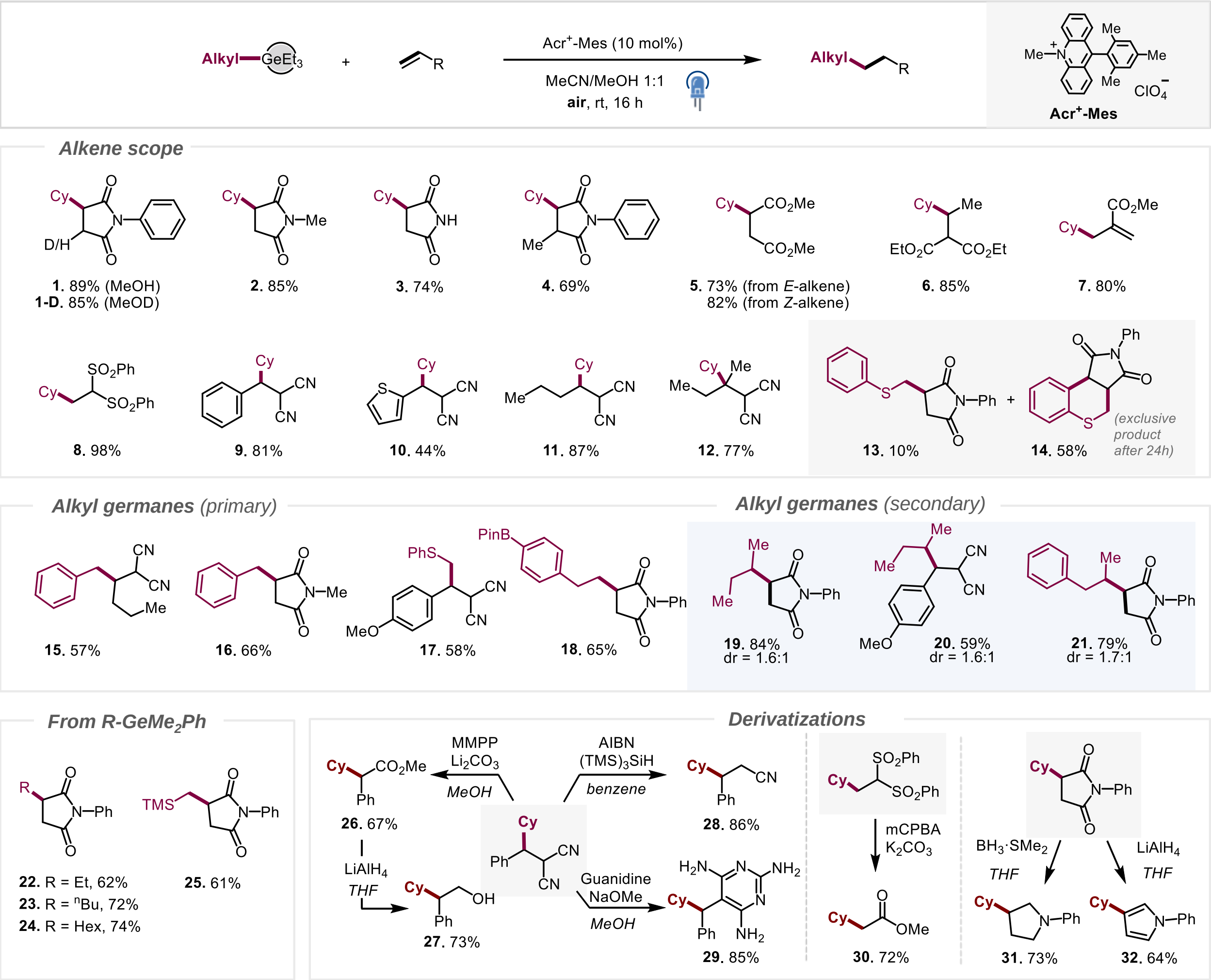
Encouraged by our recent chemoselective developments with aryl triethylgermanes,[11,12] we focused on the corresponding alkyl triethylgermanium. We could recently show straightforward synthetic access to various aliphatic triethylgermanes, and that these compounds are chemically very robust species towards acids, bases and various reaction conditions.[13,14] However, methodology to functionalize such alkyl germanium compounds is virtually non-existent: while primary alkyl germatranes were previously shown to participate in Pd-catalyzed cross couplings with aryl halides,[15] this required harsh conditions (80-120°C) and the transformation was applicable only to unsubstituted primary germatranes. Early precedence by Kobayashi demonstraded that benzyl substituted trialkyl germanes could be activated under UV-irradiation to the corresponding benzyl radicals.[16] We were therefore intrigued to study the possibility of generating a wider scope of alkyl radicals from alkyl-$GeEt_3$ (beyond benzylic) and focused on a milder photoredox-based approach.

Photoredox chemistry has been greatly enabling in the context of alkylations in recent years, relying on the activation (*via* oxidation or reduction) of a suitable group to the corresponding radical, followed by trapping, *e.g.* with an olefin (Giese reaction).[17] The Giese approach allows to alkylate silicates[18] and also organoboron derivatives,[19] especially C-BF_3K,[20] as well as alternative species, such as pyridinium salts[21] or carboxylic acid derivatives or halides.[17,22] However, in the context of implementing Giese chemistry into a modular C_{sp3} building block, challenges in the synthesis and chemical robustness exist (*e.g.* for the ionic groups) or also in reactivity (requiring generation of a stabilized radical for certain groups) or that the groups have a similar redox reactivity window. Indeed, Giese-type functionalizations with multiple potential reactive sites have not been demonstrated.[23] We therefore initially set out to study the possibility and scope of a mild photoredox-based activation of alkyl-$GeEt_3$[24] and then test the compatibility in a modularity context.

Our DFT calculations[25,26] of the model compound cyclohexyl triethylgermane ($CyGeEt_3$) suggested that its oxidation potential is in the range of benzyl-TMS (even 0.04 V lower), suggesting that unactivated alkyl germanes should in principle be oxidizable with catalysts that are effective for benzyl-TMS. We therefore set out to experimentally test the activation of $CyGeEt_3$ with the organic photocatalyst Acr^+-Mes, which was previously employed for the activation of benzylic silanes.[7d,27,28] Pleasingly, we observed efficient alkylation of *N*-phenylmaleimide to give product **1** in high yield (89%) at room temperature in MeCN/MeOH (1:1) and in the presence of air (see Scheme 1).

Other oxidizing photocatalysts, such as 2,4,6-triphenylpyrylium tetrafluoroborate, $Ir[dF(CF_3)ppy]_2(dtbpy)$ PF_6, $Ru(bpz)_3(PF_6)_2$, $Ru(bpy)_3(PF_6)_2$ and 4CzIPN displayed no conversion of starting cyclohexyl triethylgermane; it remained fully untouched, indicating potential for chemoselective photochemical activation in its presence.[29] The transformation was found to be similarly compatible with alternative acceptors (see Scheme 1, top). In this context, several maleimide derivatives, *N*-methyl (**2**), unprotected *N*-H (**3**) were successfully alkylated with cyclohexyl triethyl-germane in high yields, including the more sterically encumbered 3-methyl-*N*-phenylmaleimide (**4**).

Scheme 1. Scope of blue light enabled photocatalytic activation of alkyl-$GeEt_3$[a] & derivatizations.



[a]Reaction conditions: Alkyl-GeR_3 (1 equiv.), alkene (2 equiv.), Acr^+-Mes (10 mol%) in MeCN/MeOH (1:1, 0.1 M), subjected to air for 5 min, blue LED. (MMPP = magnesium monoperoxyphthalate hexahydrate)

The protocol proved also to be effective for other activated olefins such as dimethyl furamate and maleate (**5**), 2-methylenemalonate (**6**) and vinyl sulfones (**8**). Furthermore, a range of alkylidene malononitriles were used as trapping reagents, and afforded the corresponding coupling products in good to high yields. As such, this degermylative C-C bond formation reaction tolerates aryl (**9**), heteroaryl (**10**) and alkyl (**11**) mono-substituted alkylidene malonitriles, as well as disubstitued olefin partners (**12**).

These synthesized Giese products are powerful platforms for further derivatization, which we demonstrated with numerous downstream functionalizations, enabling access to heterocyclic motifs such as pyrroles, pyrrolidines, pyrimidines as well as valuable functionalities, such as alcohols or esters (**26**-**32**, Scheme 1).

We also demonstrated the compatibility of various other secondary alkyl triethylgermanes in this transformation beyond cyclohexyl, which proved to be equally effective (**19**-**21**). Certain primary alkyl germanes could also be selectively activated to the corresponding alkyl radicals, as long as suitable stabilizing groups favored this cleavage over potential competing Ge-Et cleavage. Benzylic (**15**, **16**), homobenzylic (**18**) or the *α*-heteroatom containing alkyl triethylgermanes (**17**) were converted in high yields. Notably, the competing ethylation (from $GeEt_3$ moiety) was not observed in any of the above cases. Interestingly, with *N*-phenylmaleimide, organogermane bearing a thioether functionality was also successfully transformed, but led to a thiochromane derivative (**14**) in 58% yield, resulting from a ring-closing process of the Giese addition product (**13**). Increase of the reaction time to 24h led to full consumption of **13** and exclusive formation of **14**.

We next considered the generation of unactivated primary radicals, such as ^{n}butyl, hexyl or ethyl radicals, which would in the R-$GeEt_3$ framework naturally lead to competing Et-radical generation from the $GeEt_3$ unit. To circumvent this, we tuned the Ge-unit towards an equally robust and non-volatile radical precursor, which is also readily accessible from commercial and non-volatile precursors. Using alkyl-$GeMe_2Ph$ instead, we were able to bias the oxidative bond cleavage towards the selective generation of simple, unactivated alkyl radicals (**22**-**25**). Notable, no methylation took place. Also, the TMS functionality was not activated at all in product **25**.

Our preliminary mechanistic data strongly support a radical mechanism. Reaction with $CyGeEt_3$ and *N*-phenylmaleimide in presence of 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO), allowed us to detect cyclohexyl-TEMPO-adduct by GC-MS analysis, whilst the expected Giese addition product (**1**) was not observed. Moreover, isotope labeling experiments highlighted the role of MeOH, which serves as a proton source for an anionic intermediate,[30] with deuterated product (**1-D**) being isolated in 85% yield in presence of MeOD. Also, MeOH, as a weakly nucleophilic solvent, promoted the degermylation of intermediate $[\text{Alk-GeEt}_3]^{\bullet+}$, and favors the formation of the alkyl radical (side-product $Et_3Ge\text{-}OMe$ has been detected by GC-MS analysis).[31] The presence of oxygen was beneficial to the system, with superior conversion of the starting alkyl germanes observed compared to reactions performed under argon (see the proposed mechanism in SI).[32]

Having established that alkyl germanes can function as robust and powerful radical precursors for C_{sp3}-C_{sp3} couplings, we next set out to address the potential for chemoselectivity and modularity in the presence of other powerful molecular handles. To this end, we initially undertook an additive screen[33] to assess the tolerance towards alternative molecular handles (such as halides, silanes or boron derivatives) in intermolecular competition experiments as well as gain insight on possibilities for further compatible decorations. Interestingly, inter-molecular competitions of Giese addition to *N*-phenyl-maleimide with Cy-$GeEt_3$ vs. the corresponding silane, iodide, bromide and boronic ester gave exclusive activation of the C-$GeEt_3$ bond, leaving C-[Si], C-Bpin, C-halogen fully untouched (Figure 2, top). To the best of our knowledge, such selectivity under photoredox conditions is unprecedented.

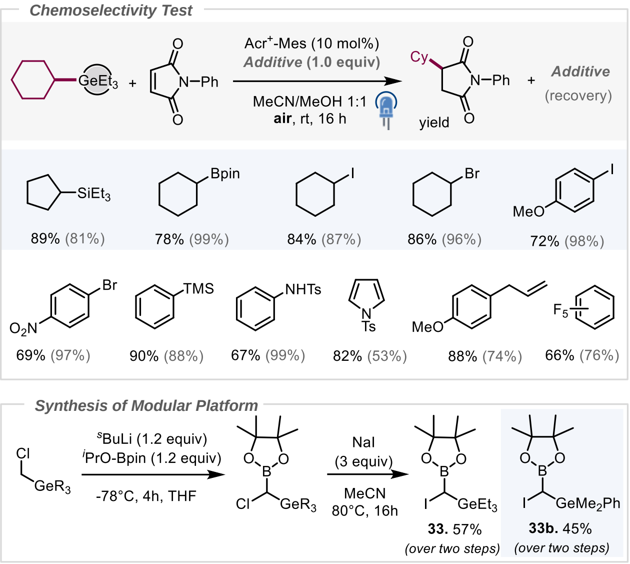


Figure 2. Chemoselectivity tests via additive screen and synthesis of modular C_{sp3}-building block.

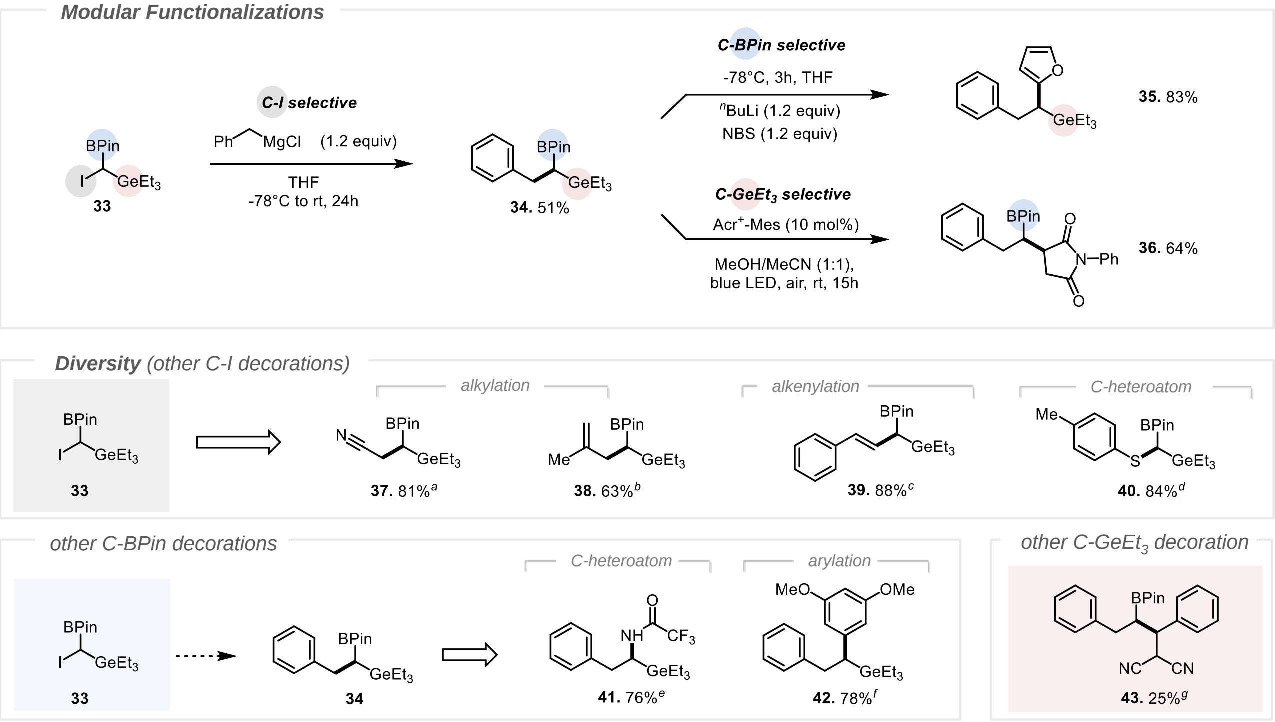
Other functionalities, such as electron-rich aniline or heterocyclic pyrrole, electron-rich alkenes or more sensitive pentafluorobenzene substrates were also not significantly affected by the employed reaction conditions and did not impede the Ge-functionalization (Figure 2).

With these insights in hand, we next investigated the feasibility of the preparation of a unified modular C_{sp3} platform and targeted the challenge of three different C_{sp3}-handles. Owing to the scope limitations of SiR_3 as well as synthetic limitations to incorporate ionic groups (such as silicates), we targeted a single methylene carbon substituted with halogen, BPin and $GeEt_3$.

A successful route towards this compound is shown in Figure 2, and consists of a straightforward functional-ization of triethylgermyl methylene chloride with BPin, followed by substitution of the less reactive C-Cl for an iodide to give **33**. Pleasingly, the synthesized modular platform **33** was highly stable and could be stored on the bench. The synthesis can also be adapted to alternative boron- or germane-derivatives. Indeed, we made $GeMe_2Ph$-platform **33b** with the same route. We next investigated the reactivity of the newly made modular platform **33**. With C-I being the most vulnerable group, we targeted to first derivatize this site (see Scheme 2), for which rich C_{sp3}-C_{sp3} (**34**, **37**, **38**), C_{sp3}-C_{sp2} (**39**) as well as C-heteroatom bond formation (**40**) was found to be possible, yielding alkyl, aryl, alkenyl and sulfide derivatives (**37**-**40**).

We next assessed the intramolecular selectivity of C-BPin vs. C-$GeEt_3$ while being positioned on the same carbon (with **34**, see Scheme 2), which constitutes an added challenge to the intermolecular competitions performed in Figure 2. To our delight, our photo-oxidative protocol also allowed for selective intramolecular [Ge]-activation in the presence of BPin, generating for example the alkylated products **36** and **43**. Conversely, owing to the exquisite robustness of the Et_3Ge functionality, we were also able to derivatize C-BPin in the presence of C-[Ge] with *e.g.* basic organometallic reagents (**35**, **42**) or under oxidative C-N bond forming conditions (**41**). Clearly, individual custom syntheses of such Et_3Ge-containing derivatives without this modular platform would not be feasible with the currently known synthetic methodology[14] to access alkyl germanes (which relies on standard organometallic reactivity, most commonly the reaction of an alkyl Grignard with Ge-electrophiles, or hydrogermylation).

Scheme 2. Demonstration of modularity in 3D space.



Reaction conditions for derivatizations: [a]MeCN (0.5 mmol, 1 equiv.) in THF (0.5 mL) at -78°C, LDA (1.1 equiv.), 30 min, then **33** (1.1 equiv.) in THF (0.5 mL), r.t., 15h. [b]**33** (0.3 mmol, 1 equiv.) in THF (0.6 mL) at -78°C, 2-methylallylmagnesium chloride (1.2 equiv.), r.t., 24h. [c]Pd Xantphos G3 (10 mol%), DIPEA (2 equiv.), styrene (1.5 equiv.), **33** (2.5 mmol, 1 equiv.) in benzene (10 mL) under blue LEDs, r.t., 24h. [d]4-methylbenzenethiol (3 equiv.) in THF (1.5 mL), LiHMDS (1M in THF, 3 equiv.), 15 min, then **33** (0.3 mmol, 1 equiv.), r.t., 15h. [e]**34** (0.3 mmol, 1 equiv.), NH_2-DABCO (1-amino-1,4-diazabicyclo[2.2.2]octane-1,4-diium iodide; 1 equiv.), KO^tBu (2.4 equiv.) in THF (3.6 mL), 80°C, 2h, then TFAA (2 equiv.), 80°C, 2h. [f]3,5-dimethoxybromobenzene (1.2 equiv.) in THF (2.5 mL) at -78°C, ^tBuLi (2.4 equiv.) 1h, then **34** (0.2 mmol, 1 equiv.) in THF (1 mL), -78°C, 1h; removal of volatiles, redissolved in MeOH (2 mL) at 78°C, NBS (1.2 equiv.) in MeOH (1 mL), r.t., 1h. [g]**34** (0.2 mmol, 1.0 equiv.), Acr^+-Mes (10 mol%) in MeCN/MeOH (1:1, 0.1 M), subjected to air for 5 min, under blue LEDs, r.t., 24h.

In conclusion, we developed a chemoselective alkylation of alkyl germanes in the presence of C-halogen, C-BPin, C-silanes and various additional functional groups, which constitutes the first chemoselective photoredox-based alkylation in C_{sp3} space. These developments allowed to develop a modular methylene derived platform, consisting of three distinct handles and enabled the triply selective diversification of C-I versus C-BPin and C-$GeEt_3$ via alkylation, arylation, alkenylation or C-heteroatom bond formation (thiolation, amination). In light of the ever increasing demands for molecular diversity and the associated need for rapid and automatable syntheses, we anticipate widespread interest in our findings towards unlocking the modular construction of molecules in C_{sp3} space.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data of compounds, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) This intermediate is obtained after reduction, by back-electron transfer from the reduced photocatalyst, of the radical intermediate following the addition of Giese.

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