

Cite this: *Chem. Sci.*, 2021, 12, 10514

All publication charges for this article have been paid for by the Royal Society of Chemistry

## Exploring benzylic *gem*-C(sp<sup>3</sup>)-boron-silicon and boron-tin centers as a synthetic platform†

Wei W. Chen,<sup>ab</sup> Nahiane Pipaon Fernández,<sup>a</sup> Marta Díaz Baranda,<sup>ab</sup> Anton Cunillera,<sup>b</sup> Laura G. Rodríguez,<sup>ab</sup> Alexandr Shafir<sup>\*b</sup> and Ana B. Cuenca<sup>†a</sup>

A stepwise build-up of multi-substituted C<sub>sp<sup>3</sup></sub> carbon centers is an attractive, conceptually simple, but often synthetically challenging type of disconnection. To this end, this report describes how *gem*- $\alpha,\alpha$ -dimetalloid-substituted benzylic reagents bearing boron/silicon or boron/tin substituent sets are an excellent stepping stone towards diverse substitution patterns. These *gem*-dimetalloids were readily accessed, either by known carbenoid insertion into C–B bonds or by the newly developed scalable deprotonation/metallation approach. Highly chemoselective transformations of either the C–Si (or C–Sn) or the C–B bonds in the newly formed *gem*-C<sub>sp<sup>3</sup></sub> centers have been achieved through a set of approaches, with a particular focus on exploiting the synthetically versatile polarity reversal in organometalloids by  $\lambda^3$ -aryliodanes. Of particular note is the metal-free arylation of the C–Si (or C–Sn) bonds in such *gem*-dimetalloids *via* the iodane-guided C–H coupling approach. DFT calculations show that this transfer of the ( $\alpha$ -Bpin)benzyl group proceeds *via* unusual [5,5]-sigmatropic rearrangement and is driven by the high-energy iodine(III) center. As a complementary tool, the *gem*-dimetalloid C–B bond is shown to undergo a potent and chemoselective Suzuki–Miyaura arylation with diverse Ar–Cl, thanks to the development of the reactive *gem*- $\alpha,\alpha$ -silyl/BF<sub>3</sub>K building blocks.

Received 27th March 2021

Accepted 28th June 2021

DOI: 10.1039/d1sc01741a

rsc.li/chemical-science

### Background and motivation

In the context of diversity-oriented synthesis, reagents bearing geminally disposed bis-metalloid units represent an attractive class of building blocks. Expected to act as bis-nucleophilic components in a variety of reactivity patterns, such molecules may set the stage for densely 1,1-disubstituted carbon centers through sequential reactions with two electrophilic partners, including *via* catalytic cross-coupling. A potentially rewarding aim is the use of the C<sub>sp<sup>3</sup></sub>-*gem*-dimetalloid group as a platform for straightforward access to multi-substituted methanes.<sup>1</sup> This basic unit received a renewed spotlight as part of medicinal chemistry's "escape from the flatland" endeavor,<sup>2</sup> and has been the subject of important recent methodological breakthroughs.<sup>3</sup> In terms of the substitution pattern, compounds featuring a carbon center anchoring a *gem*-boron/boron pair have been particularly popular, whereby a variety of methods have been developed to form such C<sub>sp<sup>3</sup></sub>-*gem*-diboronates and to selectively transform one or both of their C–B sites.<sup>4</sup>

Along these lines, the prospect of selective introduction of two different substituents has also prompted interest in derivatives bearing mutually distinct metalloids, either as chemically differentiated boryl fragments<sup>5</sup> or as a hetero-metalloid pair. Inherent reactivity differences between the two carbon-metalloid bonds can then be leveraged to gain chemo-control in modular C–C and/or C–heteroatom bond-forming sequences, with 1,1-silyl-boranes constituting an obvious paradigm for such a hetero-*gem*-dimetalloid platform.<sup>6</sup> As part of our interest in this area, some of us recently showed that 1,1-SiMe<sub>3</sub>/B(OR)<sub>2</sub> disubstituted alkenes could be obtained by a novel boron-Wittig-type olefination using the 1,1,1-B,B,Si-trimetalloid methane species,<sup>7</sup> and that the newly formed olefinic C<sub>sp<sup>2</sup></sub>-*gem*-Si,B group could be engaged in stereoselective access to tetra-substituted olefins. Encouraged by these earlier advances, we set our sight on the *gem*-B/Si-benzylic scaffold of type **1** (Scheme 1). Creative recent approaches to **1** include a Suzuki–Miyaura mono-arylation of the aforementioned 1,1-bis-(Bpin)-trialkylsilyl methane **2**,<sup>8</sup> including its enantioselective desymmetrization variant,<sup>8b</sup> or a homologation of an Ar–B bond using the diazo-reagent Me<sub>3</sub>SiCHN<sub>2</sub>, **3** (Scheme 1A and B).<sup>9</sup> However, these advances in the preparation of **1** contrast with the scarcity of methods that employ such *gem*-dimetalloids in the modular build-up of poly-substituted C<sub>sp<sup>3</sup></sub> centers. For example, while the C–Bpin bond in such species was recently shown to undergo a Pd-catalyzed coupling with iodoarenes (Scheme 1C),<sup>9b</sup> the

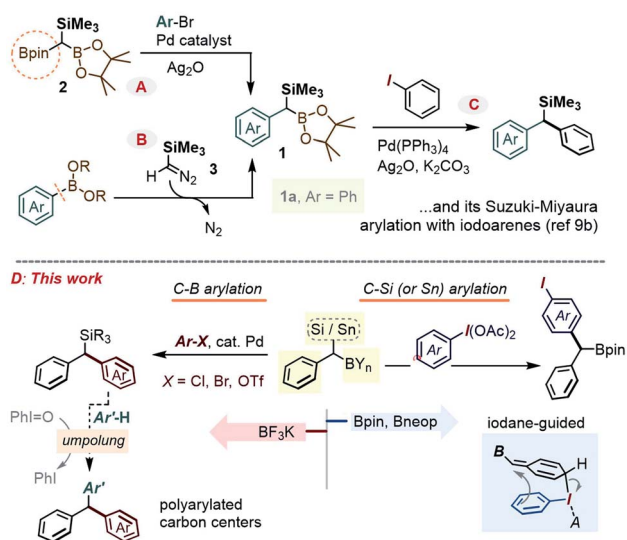
<sup>a</sup>Department of Organic and Pharmaceutical Chemistry, Institut Químic de Sarrià, URL, Via Augusta 390, Barcelona 08017, Spain. E-mail: anabelen.cuenca@iqs.url.edu

<sup>b</sup>Department of Biological Chemistry, Institute of Advanced Chemistry of Catalonia, IQAC-CSIC, c/ Jordi Girona 20, Barcelona 08034, Spain. E-mail: alexandr.shafir@iqac.csic.es

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc01741a



Precedents in the synthesis of the gem-B/Si scaffold **1** (refs. 8, 9a,b)...



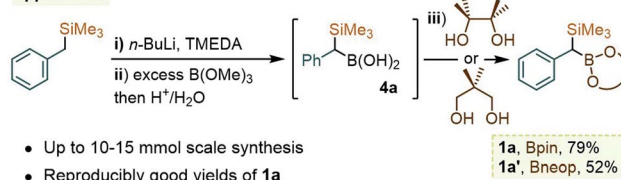
**Scheme 1** (A and B) Recent approaches to the gem-Si/B compound class **1**, and (C) an example of Pd-catalyzed arylation of **1** with Ar-I; (D) the outline of the gem-dimetalloid diversification strategy described herein.

chemistry at the C-Si bond has been largely limited to the more established desilylative  $\text{S}_{\text{N}}2$  alkylations.<sup>9b</sup> In this report, we describe a series of approaches to expand the arsenal of chemoselective transformations of the gem-B/Si-benzylic scaffold **1**. In particular, our prior experience in polarity reversal and rearrangement reactions of organosilanes induced by hypervalent iodine compounds has now been leveraged to achieve a metal-free selective C-Si and C-Sn arylation, along with a series of umpolung reactions (Scheme 1D). Among interesting gem-dimetalloid targets, we also show that the trifluoroborate analogue of **1** can be prepared, allowing for the Suzuki-Miyaura arylation (see Scheme 1D left) using bromo- and chloro-arenes.

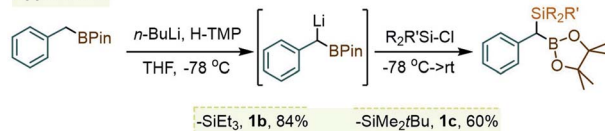
## Results and discussion

As was readily appreciated from the outset, the successful usage of the gem-Si/B molecular platform such as **1** would be contingent upon more ready access to this compound class. Our initial approach to **1a** involved the insertion of the carbenoid-type fragment “SiMe<sub>3</sub>(H)C:” of the diazo species Me<sub>3</sub>SiCHN<sub>2</sub>, **3**, into the B-C bond of arylboroxines, as reported recently by Ley and co-workers.<sup>9a</sup> Following this route (as in Scheme 1B), the phenyl derivative **1a** was obtained in good yields by heating phenylboroxine, (PhBO)<sub>3</sub>, with **3** in toluene. Despite the success of this approach on small scales (1–2 mmol), we continued our search for a complementary method to access gram quantities of the reagent. After some trials, it was found that **1a** could be conveniently prepared from commercial benzyl(trimethyl)silane by deprotonation at the benzylic position, followed by quenching the resulting benzyllithium species with an electrophilic B(OR)<sub>3</sub> reagent (Scheme 2, approach A). In our hands, treating the  $\alpha$ -B(OH)<sub>2</sub> intermediate **4a** with pinacol provided **1a**

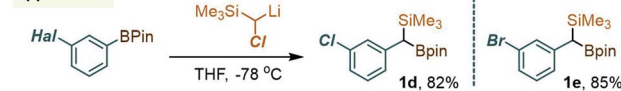
### Approach A



### Approach B



### Approach C

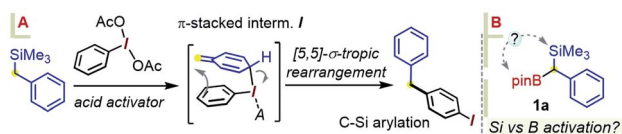


**Scheme 2** Complementary deprotonation/quench approaches to the benzylic gem-Si/B core **1a**. Approach A: (i) in hexane using 1.0 equiv. of *n*-BuLi at rt; (ii) with 3 equiv. of B(OMe)<sub>3</sub>, –78 °C to rt. Approach B: Li-TMP generated at –40 °C prior to addition of BnBpin at –78 °C. Approach C: lithiation of Me<sub>3</sub>SiCH<sub>2</sub>Cl with *sec*-BuLi/TMEDA followed by addition of Ar-Bpin.

in reproducibly good yields on scales of up to 10–15 mmol. Similarly, capping the C<sub>sp</sub><sup>3</sup>-B unit with dimethylpropane-1,3-diol could be used to obtain the Bneop derivative **1a'** in 52%; the diminished yield in the latter case is likely due to the instability of the Bneop derivatives under column chromatography on SiO<sub>2</sub>. A second approach was also developed starting with a commercial benzylboronate core *via* deprotonation using a hindered lithium 2,2,6,6-tetramethylpiperidide base (Li-TMP), followed by the addition of a chlorosilane.<sup>10</sup> This route was convenient for producing derivatives with silyl groups other than SiMe<sub>3</sub>, such as the gem-SiEt<sub>3</sub> species **1b** (84%, Scheme 2, approach B) or the Si(*t*Bu)Me<sub>2</sub> analogue **1c** (60%). Finally, when a suitable B- or Si-benzylic precursor was not readily available, a Matteson-type homologation<sup>9c</sup> of several Ar-Bpin species with an *in situ* generated Me<sub>3</sub>Si(Cl)CH-Li reagent was found to proceed smoothly. Following this route, the *meta*-halo gem derivatives **1d** and **1e** were obtained in 82% and 85% yields, respectively (Scheme 2, approach C).

With gram quantities of the model gem-hetero-dimetalloid **1a** now accessible, we turned our attention to a selective transformation of its C-Si moiety. Although a Hiyama-type metal-catalyzed C-Si arylation coupling would be a valuable tool in this system, the applications of this reaction even to simple benzylsilanes are scarce, and generally require an activated silicon group.<sup>11</sup> As an alternative, we sought to engage **1a** in metal-free C-Si arylation with  $\lambda^3$ -ArI(OAc)<sub>2</sub> species. This possibility was based on our recent experience in the iodane-guided C-H benzylation of iodoarene cores, a process reported independently by the Hyatt and our laboratories.<sup>12</sup> As depicted in Scheme 3A for a benzylsilane model, this unusual manifold would begin with the benzyl group transfer to the iodine(III) center. While related to the iodane-guided *ortho*-C-H coupling processes,<sup>13,14</sup> the benzyl group in such case gave rise

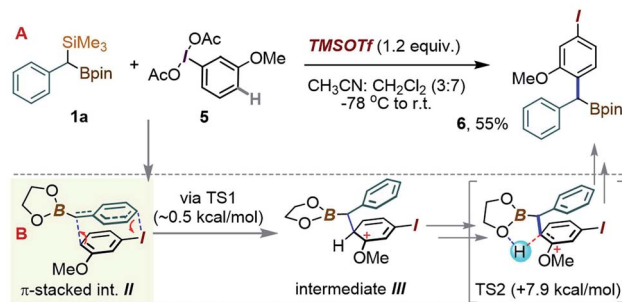




Scheme 3 (A) A precedent in the iodane-guided C–Si arylation of benzylsilanes with  $\lambda^3$ -iodanes (Hyatt *et al.* and Shafir *et al.*), 2018–19. (B) Potential selectivity dilemma in the analogous arylation of **1a**.

to a cationic head-to-tail  $\pi$ -stacked intermediate **I**, which evolves *via* the C–C bond formation at the ArI *para*-C–H position.<sup>12b</sup> We note that the Hyatt lab also showed the possibility of similarly engaging benzylic trifluoroborate nucleophiles.<sup>12a</sup>

Considering an application of such a manifold to **1a**, an interesting question arises as to which of the substrate's two metalloid groups, *i.e.* Si or B, would be retained in the product (Scheme 3B). Thus, the reactivity of **1a** with the iodoanisole-based  $\lambda^3$ -ArI(OAc)<sub>2</sub> reagent **5** was probed at  $-78$  °C. While no reaction took place between **1a** and **5** in a CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> mixture without an acid additive, enhancing the reactivity of the  $\lambda^3$ -iodane with an acidic activator, either BF<sub>3</sub>·Et<sub>2</sub>O or TMSOTf,<sup>15</sup> led to the new benzylated species **6** in 55% yield, with the new C–C created *para* to the iodine (Scheme 4). The product retains the Bpin group, suggesting a more reactive nature of the C–Si bond during the putative transmetalation step, a feature that contrasts with C–B-specific Pd-catalyzed coupling reactions (as in Scheme 1C). A DFT analysis was used to understand how the process could play out for a *gem*-B/Si-dimetalloid substrate. Calculations on the  $\pi$ -glycolate analogue of **1a** ( $\pi$ -Bgly, Scheme 4B) point to a cationic  $\pi$ -stacked intermediate **II** with a head-to-tail alignment of the two aromatic fragments. This species is analogous to the adduct **I**, previously identified in a *para*-CH-benylation (Scheme 3), and similarly evolves *via* a low-lying ( $\sim 0.5$  kcal mol<sup>-1</sup>) transition state to form a new carbon-carbon bond *para* to iodine (Scheme 4B). The rearrangement is expected to initially provide the ring protonated intermediate **III**. Although the final aromatization may then take place through proton transfer to an external base, the presence of the boronate group in **III** may also enable an interesting low-barrier internal proton transfer from the acidic



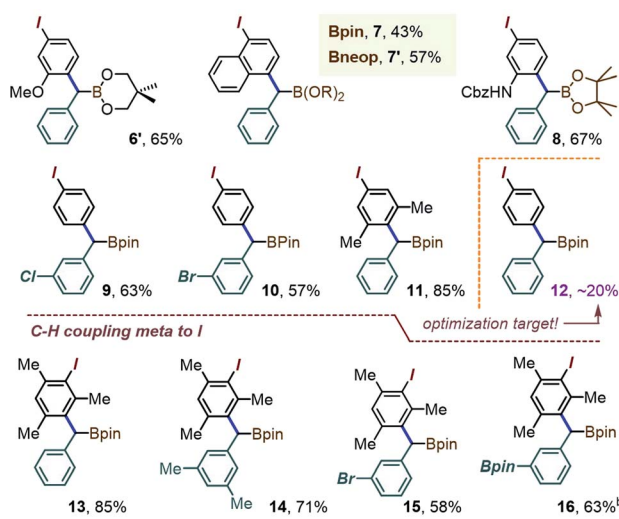
Scheme 4 (A) *Para*-selective C–H ( $\alpha$ -borylbenzylation) of the iodoanisole core. (B) DFT proposal for the C–C bond forming step.

C–H site to one of the boronate O atoms (see TS2 in Scheme 4B).

A brief scope survey showed that the coupling efficiency may benefit from the presumably less encumbered Bneop substituent, as seen in the formation of the Bneop analogue **6'** in 65% yield starting from **1a'** (Table 1). A similar moderate improvement was also seen for the C–H benzylation at the 4-position of  $\lambda^3$ -1-(diacetoxyiodo)-naphthalene, with a 43% yield obtained for the  $\alpha$ -Bpin derivative **7** and a 57% yield (NMR) for the Bneop analogue **7'**. The reaction was also successful in providing the *para*-( $\alpha$ -boryl)benzylated derivative of the protected 3-iodoaniline (prod. **8**, 67%), the *meta*-halo derivatives **9** and **10** (63% and 57%), and the iodoxyline coupling product **11** (85%). The success of these reaction may partly be due to the presence of electron-releasing substituents in most of the iodoarene cores.<sup>16</sup> Indeed, the use of the non-activated simple PhI(OAc)<sub>2</sub> initially led to the target arylated species **12** in yields of  $\sim 20\%$ . Finally, as we previously observed for  $\lambda^3$ -iodoanes blocked at the *para* position,<sup>12b</sup> exposing **1a** to the  $\lambda^3$ -iodane derived from iodomesitylene led to an efficient formation of the *meta*-CH-benzylated species **13**.<sup>17</sup> The scope of this *meta*-substitution was then extended to the *m*-xylyl derivative **14** and the bromo-target **15**. The method was also tolerant of a *gem*-Si/B reagent bearing a second BPin substituent on the aromatic ring (Table 1, prod. **16**).

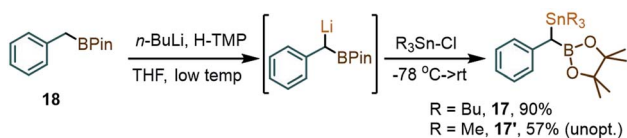
In view of the initially low yields in the coupling between **1a** and PhI(OAc)<sub>2</sub>, due to the formation of benzaldehyde and other benzylic oxidation side products, we considered replacing the SiMe<sub>3</sub> fragment with a potentially more reactive SnBu<sub>3</sub> group. With that in mind, two new *gem*-Sn/B-dimetalloids **17** and **17'** were synthesized from the benzylboronate **18** *via* benzylic deprotonation followed by quenching with R<sub>3</sub>SnCl (Scheme 5).

Table 1 Chemoselective C–Si bond transformation in **1a** and **1a'** *via* iodane-guided *para* C–H coupling<sup>a</sup>

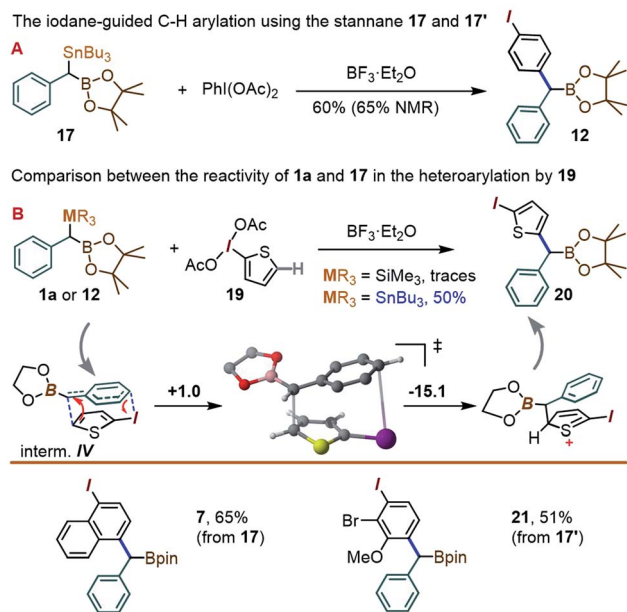


<sup>a</sup> Conditions analogous to those in Scheme 4A; ESI. <sup>b</sup> Using a *gem*-Si/B precursor obtained by Suzuki–Miyaura borylation of the Ar–Cl **1d**.



Scheme 5 Formation of the *gem*-stannyl-boryl precursors **17** and **17'**.

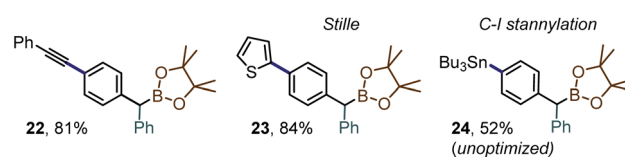
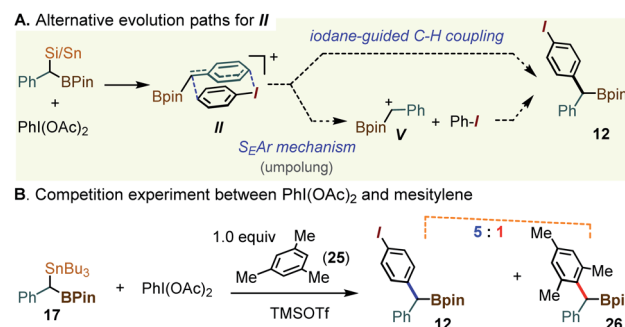
To our delight, a reaction between **17** and the  $\lambda^3$ -iodane  $\text{PhI}(\text{OAc})_2$  led to the *para*-benzylated target **12** in 60% yield (65% by NMR), *i.e.* is  $\sim 3$  times higher than for the silyl analogue **1a** (Scheme 6A). This improvement may be tentatively explained by the enhanced ability of organo-stannanes to undergo transmetallation in iodane-guided C–H coupling reactions, a feature illustrated in the 1990's by the Ochiai group,<sup>13</sup> and recently leveraged by Peng and co-workers in *ortho*-directed C–H cyanoalkylation.<sup>18</sup> Similarly, while barely a trace amount of coupling took place between **1a** and the 2-iodothiophene-derived  $\lambda^3$ -iodane **19**, switching to **17** led to the thienyl product **20** in 50% yield (Scheme 6B). We note that although the 2-iodothiophene core does not possess a *para* position *per se* with respect to **I**, the substrate's C(5)–H unit does correspond to a C–C coupling site predicted for a putative [5,5]-sigmatropic rearrangement path (see ESI†). Indeed, a DFT optimization of the expected  $\pi$ -stacked intermediate **IV** (analogous to **III** in Scheme 4) converges to a conformation with the benzylic  $\text{CH}(\text{BPin})$  group placed directly above the thiophene C(5)–H site (Scheme 6 bottom). Finally, the use of the  $\text{Bu}_3\text{Sn}$  species **17** allowed for the synthesis of the naphthyl-derived **7** to be improved from the 43% reported in Table 1 using **1a** to 65%. The use of **17'** also allowed for the C–H coupling of an *o*-Br, *m*-OMe iodane precursor to give **21** in 51% yield.

Scheme 6 The C–H coupling reaction of the new *gem*-Sn–B benzylic derivatives **17** and **17'**. The free energies in the mechanistic scheme are in  $\text{kcal mol}^{-1}$ .

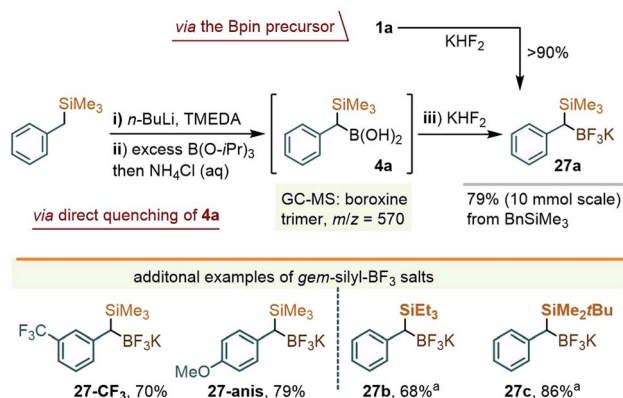
Along with the transfer of an intact boryl substituent, an important feature of the iodane-guided arylation reactions is the retention of the synthetically versatile iodine handle. A variety of downstream diversification routes could thus be assayed, including Pd-catalyzed cross-coupling reactions, *e.g.* Sonogashira alkynylation, Stille coupling or stannylation reactions (Scheme 7, prods. **22–24**).

While the pronounced *para*-C–H selectivity in the arylation of **1a** and **17** is consistent with the iodane-guided rearrangement mechanism outlined in Scheme 4, the outcome could in principle be rationalized through a particularly selective Friedel–Crafts type benzylation mechanism. Indeed, organosilanes can undergo the umpolung of the C–Si unit in the presence of simple  $\lambda^3$ -iodane oxidants. In the case of the *gem*-dimetalloids **1** or **17**, such a process might involve the benzyl iodonium intermediate such as **II**, which would evolve by a dissociation into the parent iodoarene and the  $\alpha$ -boryl benzyl cation **V**. In such a sequence, the product would arise through an electrophilic attack at the *ArI* *para* position (see Scheme 8A). To test for the presence of free carbocationic species **V**, **17** was allowed to react with  $\text{PhI}(\text{OAc})_2$  in the presence of 1 equiv. of mesitylene, **25**. A concerted iodane-guided path would still favor the iodobenzene-derived **12**, while any free **V** would be expected to cause the functionalization of mesitylene. Here, the highly nucleophilic mesitylene was chosen so as to stack the odds in favor of such a hypothetical Friedel–Crafts process. Although the mesitylene-derived diarylmethane **26** was observed, this compound was present as a minor component, in a 1 : 5 ratio with **12** (Scheme 8B, also see the ESI for Fig. S2†). This result indicates that while the electrophilic aromatic substitution is possible, such a route does not represent the major path in the formation of **12**.

While these studies were underway, a parallel effort was directed towards securing a complementary method for the

Scheme 7 Examples of downstream C–I diversification of **12**.Scheme 8 Mechanistic assessment of the umpolung manifold in the oxidative coupling of **17** promoted by  $\lambda^3$ -iodanes.

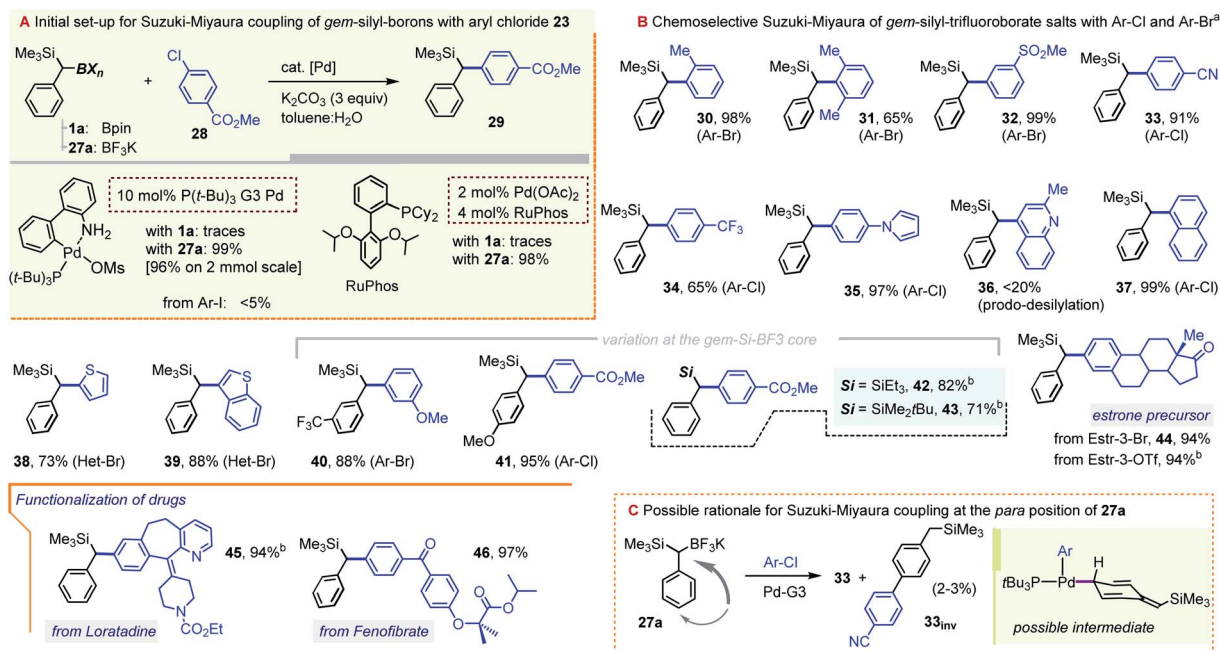
arylation of the C–B bond in *gem*-Si/B precursors, which we thought to be possible through a metal-catalyzed coupling approach. In fact, at the time when our early efforts were getting underway (late 2018), there existed no literature reports on the coupling of  $\alpha$ -silylated benzylboranes such as **1a**. More recently, however, Wang and co-workers described the arylation of **1** with iodoarenes using a Pd-catalyzed Ag-promoted coupling.<sup>9b,19</sup> In our case, the study centered on solving a more difficult coupling of *gem*-silylborylated cores with bromo- and chloro-arenes, which we hoped could be achieved using a series of newer Pd catalysts. Initial attempts to engage the Bpin precursor **1a** in the coupling with chloroarenes under a variety of catalytic conditions led to unsatisfactory results. Reasoning that a more reactive boryl substituent might prove beneficial, we sought to access the trifluoroborate derivative of **1a**. Borrowing a page from the Molander group's synthesis of the methylene reagent Me<sub>3</sub>Si–CH<sub>2</sub>BF<sub>3</sub>K,<sup>20</sup> a treatment of **1a** with KHF<sub>2</sub> in an Et<sub>2</sub>O/H<sub>2</sub>O mixture led to the precipitation of a white solid identified as the *gem*-silyl potassium trifluoroborate **27a** (Scheme 9, top path). The NMR spectra of this species presented the benzylic <sup>1</sup>H CH signal at 1.26 ppm (broadened quartet, *J*<sub>H–F</sub> = 7.1 Hz), and showed a displacement of the <sup>11</sup>B-NMR resonance from ~33 ppm for the –Bpin group in **1a** to ~1 ppm for **27a**. Noteworthy, no fluoro-desilylation of **27a** was observed at this stage. It was subsequently found that the lithiation/borylation approach, used earlier for the synthesis of **1a** (*i.e.* as in Scheme 2), may be redirected toward **27a** by intercepting the crude intermediate **4a** (identified by GC-MS as two diastereomeric boroxine trimers, *m/z* = 570, see the ESI<sup>†</sup>), with KHF<sub>2</sub> (Scheme 9). This method circumvents the need for the isolation of **1a** and allows for the ready synthesis of **27a** on a gram scale. A small family of additional trifluoroborate salts were also prepared, including **27-CF<sub>3</sub>** and **27-anis**, as well the species **27b** and **27c**, the latter with variations at the silyl group (Scheme 9), either from the corresponding –Bpin precursor or *via* deprotonation/silylation sequences. All were isolated as white or off-white powders.



Scheme 9 A telescope synthesis of **27a** from benzyl(trimethyl)silane. (i) In hexane using 1.0 equiv. of *n*-BuLi at rt; (ii) with 3 equiv. of B(O-*i*Pr)<sub>3</sub>, –78 °C to rt, and overnight; (iii) in Et<sub>2</sub>O/H<sub>2</sub>O 4 : 1. <sup>a</sup>Prepared from the corresponding –Bpin precursors.

As we hoped for, a switch from a Bpin to a BF<sub>3</sub>K *gem*-dime-talloid proved highly beneficial for the Suzuki–Miyaura coupling with chloroarenes. While in our hands **1a** failed to undergo a C–B arylation with the *p*-Cl-methylbenzoate **28**, the use of **27a** led to very promising yields of the target diaryl-methane **29** using a number of modern catalytic systems. In particular, virtually quantitative conversions were achieved by using the RuPhos/Pd(OAc)<sub>2</sub> combination,<sup>21</sup> or by applying the 3<sup>rd</sup> generation *t*Bu<sub>3</sub>P–Pd palladacycle precatalyst (*t*Bu<sub>3</sub>P–Pd G3), the latter as used by Biscoe and co-workers for the aliphatic secondary trifluoroborate species (Scheme 10, gray inset).<sup>22</sup> The system was also suitable for bromoarenes, but gave unsatisfactory results with iodoarenes. This coupling efficiency is remarkable, given that the challenging Ar–Cl electrophile is joined with the bulky  $\alpha$ -SiMe<sub>3</sub>-substituted C(sp<sup>3</sup>) nucleophile without the loss of the potentially sensitive  $\alpha$ -silyl substituent. While the two catalyst systems showed similar performances, the scope of the arylation of **27a** (Scheme 10) is mainly illustrated using the Pd-G3 metallacycle. Hence, steric hindrance at the Ar–X partner was found to be well tolerated, with nearly quantitative yields obtained with the *ortho*-bromotoluene (prod. **30**, 98%), and a somewhat diminished yield for *o,o*-dimethyl bromoarene (**31**, 65%). Efficient coupling was also observed for a series of substituted haloarenes to give diarylmethanes **32–35** in generally excellent yields. As a limitation, the coupling of the strongly  $\pi$ -deficient chloroquinoline was inefficient due to rampant product desilylation (prod. **36**, <20%, observed by GC-MS). Nevertheless, the C–C coupling was also well-suited for naphthalene and thiophene-based haloarenes (see prods. **37–39**), with a somewhat lower yield in the isolation of **38** possibly due to mechanical losses during purification. The method is also suited for structure variations on the *gem*-Si–BF<sub>3</sub>K component, including the successful formation of trifluorotolyl and anisyl derivatives **40** and **41**. Additionally, the method allowed for the ready formation of SiEt<sub>3</sub> and *t*BuMe<sub>2</sub>Si analogues **42** and **43**, albeit with a somewhat lower yield for the latter. Our initial venture into bio-active core functionalization involved the coupling of the estrone moiety, which was possible starting with the corresponding 3-Br derivative. Interestingly, the RuPhos-based catalyst (but not the Pd-G3 system) also allowed for the direct coupling of the more readily available 3-OTf form of the precursor (prod. **44**, 94%). The method was also applied to the C–Cl moiety of the antihistaminic drug Loratadine, a polycyclic *N*-containing bioactive chloroarene, providing the  $\alpha$ -silyl-benzylated core **45** in an excellent 94% yield. Likewise, the reaction proved almost quantitative for the PPAR $\alpha$  activator Fenofibrate as the Ar–Cl partner. Incidentally, the latter hyper-lipidemic prodrug was recently considered for repurposing as a SARS-CoV-2 infection inhibitor.<sup>23</sup> Only mono-arylation was observed in all cases, confirming the expected resistance of the C<sub>sp<sup>3</sup></sub>–SiMe<sub>3</sub> group towards conventional cross-coupling. Interestingly, although the two pre-catalysts were largely interchangeable, reactions conducted with the *t*Bu<sub>3</sub>P–Pd G3 system frequently showed a minor GC-MS peak with the same *m/z* value as the target product (typically in a ~25–30 : 1 area ratio). For the –CN derivative **33**, this minor isomer, **33<sub>inv</sub>**, was isolated and shown by NMR to correspond to the arylation at the *para* C–H



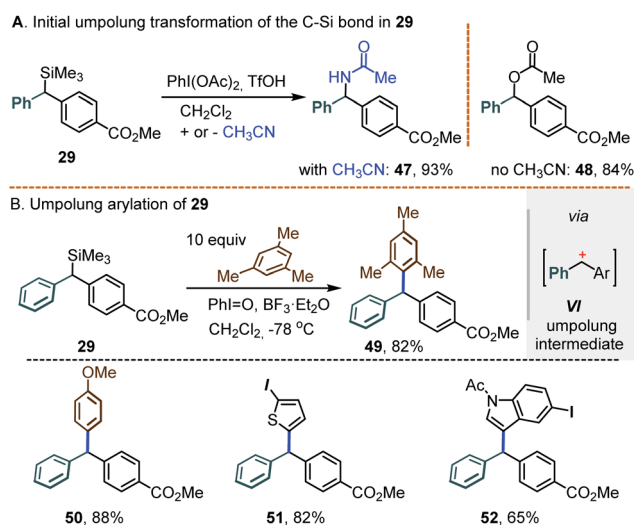


**Scheme 10** Pd-catalyzed Suzuki-Miyaura coupling between benzyl-*gem*-silyl-trifluoroborates and chloro- or bromo-arenes. <sup>a</sup>Most examples were carried out using the *t*Bu<sub>3</sub>P–Pd G3 catalyst system: aryl halide (1 equiv.), *gem*-Si-BF<sub>3</sub>K precursor (2.0 equiv.), 2–10 mol% of Pd-G3 catalyst, and K<sub>2</sub>CO<sub>3</sub> (3.0 equiv.), in a toluene : H<sub>2</sub>O mixture; see the ESI† for details in each case. <sup>b</sup>Employing a system composed of Pd(OAc)<sub>2</sub> (2–3%) and RuPhos (4–6%) and using the *gem*-Si-BF<sub>3</sub>K precursor (1.1–1.3 equiv.) and K<sub>2</sub>CO<sub>3</sub> (3.0 equiv.).

position of the benzylic precursor (Scheme 10C). We note that while related Pd-catalyzed *para*-selective coupling in benzylic systems is known, it typically relies on the use of benzylic electrophiles (*e.g.* benzyl chlorides), and not nucleophiles, as is the case in our system.<sup>24</sup> While a number of mechanistic manifolds can be envisioned leading to such side-products, one possibility is illustrated in the beige inset in Scheme 10C. Assuming a canonical oxidative addition/transmetalation path, species **33<sub>inv</sub>** could arise from the isomerization of the Pd(II)-benzyl fragment to one of its *para*-palladated forms prior to reductive elimination. The bulky  $\alpha$ -SiMe<sub>3</sub> group appears to influence the process, as no such product was observed in the control coupling using the simple benzyltrifluoroborate precursor (see the ESI†). In a few cases, *e.g.* for the Loratadine-derived **46**, the *para*-coupled species were formed in yields of up to 10%. Gratifyingly, this side reaction is fully suppressed by switching to the RuPhos-based catalyst system (*i.e.* the system used to obtain the 94% yield of **46** as shown).

As a final note, we envision that the retention of the C–Si bond under Pd catalysis opens the door for the introduction of a 3<sup>rd</sup> substituent at the central carbon. While this task was not extensively pursued, some preliminary results shown below attest to its viability. Specifically, our experience with hypervalent iodine chemistry<sup>14a,b</sup> led us to seek the introduction of a 3<sup>rd</sup> substituent *via* an umpolung transformation. It was found that exposing the silylated diarylmethane **29** to PhI(OAc)<sub>2</sub> and BF<sub>3</sub>·Et<sub>2</sub>O in the standard CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN medium led to the acetamide **47** as the main product (93%); in the absence of acetonitrile, the *O*-acetate **48** was obtained instead (84%, Scheme 11A). Seeking to suppress this C–O/N bond formation,

further tests were conducted in CH<sub>2</sub>Cl<sub>2</sub> using iodosobenzene, PhI=O, as an “acetate-free”  $\lambda^3$ -iodane oxidant. Under such conditions, a reaction between **29** and mesitylene (10 equiv.) afforded the differentially substituted triarylmethane **49** in an 82% yield, presumably *via* the intermediacy of the corresponding doubly benzylic carbocation **VI** (Scheme 11B). In a similar manner, a family of  $\pi$ -excessive arenes were also engaged, including anisole, 2-iodothiophene and *N*-tosyl-5-iodoindole (see triarylmethanes **50–52**, Scheme 11B, bottom).



**Scheme 11** Iodane-promoted umpolung transformations of the *gem*-diaryl- $\alpha$ -silyl substrate **29**.



## Conclusions

In summary, this work expands the synthetic landscape of versatile benzylic *gem*-boron–silicon and *gem*-boron–tin molecules, going from the generation of these species to their C–M reactivity applications. A new approach has been developed, which complements prior routes and by which gram quantities of benzylic *gem*-boron–silicon and *gem*-boron–tin reagents are obtained *via* the straightforward electrophilic  $\alpha$ -borylation of the benzylsilane core. The products were isolated either as *B*pin or novel *gem*-silylated trifluoroborate salt derivatives. The C–Si or C–Sn sites in these species undergo metal-free oxidative arylation employing  $\lambda^3$ -bis(acetoxy)iiodoarenes. The “iodane-guided” mechanism leads to selective coupling at the Ar–I *para* C–H site, with the molecule thus retaining both the C–I and the C–B functional groups. In addition, a protocol was identified for the Pd-catalyzed C–B arylation of hindered *gem*-SiMe<sub>3</sub>–BF<sub>3</sub>K substrates with chloro- and bromo-arenes. We envisage that these advances provide a strong foothold for further method development directed towards the modular iterative construction of multi-substituted carbon centers, a task of great importance in modern synthetic chemistry.

## Data availability

Details of the experimental procedures, spectroscopic data and the results of the DFT calculations are available in the ESI file.

## Author contributions

W. W. C., N. P. F., M. D. B., A. C. and L. G. R. contributed to the experimental work; A. B. C. and A. S. contributed to ideation and writing of the paper.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was funded by MINECO (CTQ2017-86936-P), MICINN (PID2020-113661GB-I00) and AGAUR (2017 SGR 01051 and 2017 SGR 00294), as well as financial support from URL (2019-URL\_Proj-034), IQS-Obra Social La Caixa (2017-URL-Intermac-010) and an entry-level grant from CSIC. IQS is also acknowledged for a doctoral scholarship to W. W. C., and CSIC for the JAE Intro scholarship for L. R. G.

## Notes and references

- For a specific review on C<sub>sp</sub>I. Marek and J. F. Normant, *Chem. Rev.*, 1996, **96**, 3241–3267-*gem*-dimetallated species, see:
- (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (b) D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458; (c) T. T. Talele, *J. Med. Chem.*, 2020, **63**, 13291–13315.
- For the selected recent reviews on advances in triarylmethane synthesis, see: (a) M. Nambo and C. M. Crudden, *ACS Catal.*, 2015, **5**, 4734–4742; (b) X. Liu, X. Wu, L. Zhang, X. Lin and D. Huang, *Synthesis*, 2020, **52**, 2311–2329.
- For reviews on the chemistry of *gem*-diborylalkanes, see: (a) R. Nallagonda, K. Padala and A. Masarwa, *Org. Biomol. Chem.*, 2018, **16**, 1050–1064; (b) N. Miralles, R. J. Maza and E. Fernández, *Adv. Synth. Catal.*, 2018, **360**, 1306–1327; (c) C. Wu and J. Wang, *Tetrahedron Lett.*, 2018, **59**, 2128–2140. For Pd-catalyzed mono-arylation of *gem*-diboryl species, including enantioselective variants, see (d) H.-Y. Sun, K. Kubota and D. Hall, *Chem.–Eur. J.*, 2015, **21**, 19186–19194; (e) C. Sun, B. Potter and J. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 6534–6537; (f) S. H. Cho and J. F. Hartwig, *Chem. Sci.*, 2014, **5**, 694–698; (g) K. Endo, T. Ohkubo, M. Hirokami and T. Shibata, *J. Am. Chem. Soc.*, 2010, **132**, 11033–11035. For additional selective functionalization of C<sub>sp</sub><sup>3</sup>-*gem*-diboryls, see: (h) C. E. Iacono, T. C. Stephens, T. S. Rajan and G. Pattison, *J. Am. Chem. Soc.*, 2018, **140**, 2036–2040; (i) S. A. Murray, J. C. Green, S. B. Tailor and S. J. Meek, *Angew. Chem., Int. Ed.*, 2016, **55**, 9065–9069.
- (a) K. N. Babu, F. Massarwe, R. R. Reddy, N. Eghbarieh, M. Jakob and A. Masarwa, *Molecules*, 2020, **25**, 959–989; (b) A. B. Cuenca, J. Cid, D. García-López, J. J. Carbó and E. Fernández, *Org. Biomol. Chem.*, 2015, **13**, 9659–9664.
- W. Sun, Y. Hu, C. Xia and C. Liu, *New J. Chem.*, 2021, DOI: 10.1039/d0nj01344g.
- (a) E. La Cascia, A. B. Cuenca and E. Fernández, *Chem.–Eur. J.*, 2016, **22**, 18737–18741. For a recent tutorial review on boron–Wittig olefination with *gem*-bis(boryl)alkanes, see: (b) A. B. Cuenca and E. Fernández, *Chem. Soc. Rev.*, 2021, **50**, 72–86.
- (a) K. Endo, F. Kurosawa and Y. Ukaji, *Chem. Lett.*, 2013, **42**, 1363–1365; (b) J. Kim and S. H. Cho, *ACS Catal.*, 2019, **9**, 230–235.
- (a) C. Bomio, M. A. Kabeshov, A. R. Lit, S. H. Lau, J. Ehlert, C. Battilocchio and S. V. Ley, *Chem. Sci.*, 2017, **8**, 6071–6075; (b) C. Wu, Z. Bao, X. Xua and J. Wang, *Org. Biomol. Chem.*, 2019, **17**, 5714–5724. For the original Matteson C–boron homologation: (c) D. J. S. Tsai and D. S. Matteson, *Organometallics*, 1983, **2**, 236–241. For an interesting *gem*-silylborylation approach, see (d) L. Wang, T. Zhang, W. Sun, Z. He, C. Xia, Y. Lan and C. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 5257–5264.
- While this manuscript was in preparation, the formation of analogous  $\alpha$ -boryl carbanions was reported by Lee and Chirik (in a different methodological context) *via* the mono-deborylation of *gem*-bis-boryl precursors: B. Lee and P. J. Chirik, *J. Am. Chem. Soc.*, 2020, **142**, 2429–2437.
- For a notable example of a Hiyama-type benzylation, see: K. Itami, M. Mineno, T. Kamei and J. I. Yoshida, *Org. Lett.*, 2002, **4**, 3635–3638.
- (a) C. Mowdawalla, F. Ahmed, T. Li, K. Pham, L. Dave, G. Kim and I. F. D. Hyatt, *Beilstein J. Org. Chem.*, 2018, **14**, 1039–1045; (b) Y. Wu, S. Bouvet, S. Izquierdo and A. Shafir, *Angew. Chem., Int. Ed.*, 2019, **58**, 2617–2621.



- 13 For one of the earliest forays into iodane-guided C–H coupling, see M. Ochiai, T. Ito, Y. Takaoka and Y. Masaki, *J. Am. Chem. Soc.*, 1991, **113**, 1319–1323.
- 14 (a) For a recent overview on iodane-guided C–H coupling, including a discussion on the unproductive Umpolung phenomenon, see W. W. Chen, A. B. Cuenca and A. Shafir, *Angew. Chem., Int. Ed.*, 2020, **59**, 16294–16309. For related review articles, see: (b) A. Bauer and N. Maulide, *Chem. Sci.*, 2021, **12**, 853–864; (c) I. F. D. Hyatt, L. Dave, N. David, K. Kaur, M. Medard and C. Mowdawalla, *Org. Biomol. Chem.*, 2019, **17**, 7822–7848.
- 15 For the activation of  $\text{ArI}(\text{OAc})_2$  reagents by acids such as HOTf and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , see: S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós and A. Shafir, *J. Am. Chem. Soc.*, 2016, **138**, 12747–12750.
- 16 For earlier examples of improved performance of electron-rich  $\lambda^3$ -iodanes in related processes, see: (a) M. Ochiai, M. Kida and T. Okuyama, *Tetrahedron Lett.*, 1998, **39**, 6207–6210; (b) H. R. Khatri and J. Zhu, *Chem.–Eur. J.*, 2012, **18**, 12232–12236.
- 17 The *meta* selectivity arises from the blocked aromatization for the initial cationic intermediate which forms immediately after the rearrangement step (species similar to **III**). In such a case, the benzyl group in **III** may undergo a [1,2] shift to the ring *meta* position prior to final aromatization.
- 18 J. Tian, F. Luo, C. Zhang, X. Huang, Y. Zhang, L. Zhang, L. Kong, X. Hu, Z. X. Wang and B. Peng, *Angew. Chem., Int. Ed.*, 2018, **57**, 9078–9082.
- 19 For the closely related precedent on the use of  $\text{Ag}_2\text{O}$ , see: (a) D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024–5025. For the origin of the acceleration of certain Suzuki–Miyaura coupling by  $\text{Ag}_2\text{O}$ , see: (b) J. Uenishi, J. M. Beau, R. W. Armstrong and Y. Kishi, *J. Am. Chem. Soc.*, 1987, **109**, 4756–4758.
- 20 G. A. Molander, C. S. Yun, M. Ribagorda and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 5534–5539.
- 21 S. D. Dreher, S.-E. Lim, D. L. Sandrock and G. A. Molander, *J. Org. Chem.*, 2009, **74**, 3626–3631.
- 22 (a) L. Li, S. Zhao, A. Joshi-Pangu, M. Diane and M. R. Biscoe, *J. Am. Chem. Soc.*, 2014, **136**, 14027–14030; (b) N. C. Bruno, M. T. Tudge and S. L. Buchwald, *Chem. Sci.*, 2013, **4**, 916–920.
- 23 S. P. Davies, C. J. Mycroft-West, I. Pagani, H. J. Hill, Y.-H. Chen, R. Karlsson, I. Bagdonaite, S. E. Guimond, Z. Stamataki, M. Andrade De Lima, J. E. Turnbull, Z. Yang, E. Vicenzi, M. A. Skidmore, F. Khanim and A. Richardson, *bioRxiv*, 2021, DOI: 10.1101/2021.01.10.426114.
- 24 For a recent example of a related *para* C–H coupling in a benzylic system, see: (a) F. de Azambuja, M.-H. Yang, T. Feoktistova, M. Selvaraju, A. C. Brueckner, M. A. Grove, S. Koley, P. H.-Y. Cheong and R. A. Altman, *Nat. Chem.*, 2020, **12**, 489–496. For a review on the reactivity of Pd-benzyl intermediates, see: (b) S. Zhang, Y. Yamamoto and M. Bao, *Adv. Synth. Catal.*, 2021, **363**, 587–601.

