Abstract: Organoboron compounds are versatile synthetic building blocks. We herein report a new strategy, a photochemical gold-catalyzed chemo-selective Hiyama arylation of B,Si bifunctional reagents with diazonium salts, which is orthogonal to common strategies and therefore a unique tool for synthesis of valuable biarylboronates. With this new methodology a wide array of diversely functionalized spand sp^3-hybridized biarylboronates were obtained. Notably, the synergism of gold catalysis with copper catalysis or palladium catalysis, allows for one-pot iterative C–X (heteroatom) and C–C couplings for the rapid assembly of several simple fragments to relatively complex molecules. Mechanistic studies indicated that photosensitizer-free conditions were superior to gold/Ru(bpy)_3Cl_2 dual catalysis.

Biaryl units represent a fundamental and important scaffold for the generation of molecular complexity. They are indispensable structural linkers for a great number of pharmacophores, natural products, agrochemicals, and molecular machines. So far, their synthesis mainly relies on classical Pd-catalyzed cross-coupling between two aromatic subunits, one electrophilic (Ar^1-X) and one nucleophilic (Ar^2-M) building block.[2] Recently, directed C–H arylation[3] and oxidative cross-dehydrogenative coupling of two arenes[4] become an alternative, despite of the selectivity issue these methods are associated with. Still, an entirely different synthetic disconnection involving preformed boron-containing biaryl units, which are applied as a versatile class of building blocks for diversification, would be desirable. Although post-borylation of biaryl bromides (Suzuki coupling products) can afford biarylboronates by additional steps, still this new synthetic strategy allows a convergent route for a functionalization at a relatively late stage, which could be enormously beneficial in lead identification in pharmaceutical/medicinal chemistry.[5] Due to the inherent poor compatibility of palladium catalysts with boronic acid derivatives,[6] the synthesis of biarylboronates by catalytic coupling represents an important aim in the field of catalytic C–C coupling; however, practical strategies are still rare. For example, by exploiting the different reactivities of two types of boronic acid derivatives, Burke[7,8] and Suginome[9,10] splendidly introduced Pd-catalyzed boron-masking Suzuki–Miyaura couplings (Scheme 1a). Although powerful, these methods require additional steps for the synthesis of the substrates and need special conditions such as additional bases to prevent the masked organoborons from hydrolysis. Moreover, bifunctional R_2B-Ar^1-Ar^2-X (X = I, Br, OTf etc.) products, which

Scheme 1. Strategies for the synthesis of biarylboronates.

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would represent the most interesting building blocks for modular synthesis, are accessible by long synthetic routes only. A comparison of the key intermediate Ar-PdCl2X and the isoelectronic Ar-AuCl2X species indicates that the latter potentially is more reactive. We envisioned that due to this feature an aryl activation/πσps substitution[11] of an Ar-SiR3 moiety should be preponderant over the direct transmetalation with arylboronic acid derivatives[12] (Scheme 1b). This would enable a simple site-selective arylation of aryl compounds bearing both silyl and boronic ester derivatives giving rise to privileged biarylboronate building blocks in an orthogonal manner to common methodologies. In palladium catalyst substrates carrying both, boron and silicon substituents undergo a transmetalation of the boronic ester[13,14] thus needing at least two more steps for the conversion of the resulting arylsilane products into arylboronates.

Generally, gold redox catalysis requires the use of sacrificial external oxidants to complete the AuIII/AuI catalytic cycle.[15–20] In this context, by using [16]F− as oxidants, seminal works from Lloyd-Jones’ and Russell’s,[11,21–23] Nevada’s[12,24] and Youg’s[25] groups have demonstrated that both Ar-SiR3 and Ar-B(OR)2 (R = H or alkyl) were vital coupling partners for gold-catalyzed oxidative biaryl syntheses with electronically or directing group-controlled specific CAr−H bonds. Alternatively, gold-catalyzed oxidative cross-couplings between electron-rich and electron-poor arynes have been recently achieved by Larrosa’s group.[26] Despite the significant progress, redox-neutral gold-catalyzed site-selective arylation of bimetallic R2Si-Ar-B(OR)2 reagents are a fundamentally new challenge. Recently, Góris and Toste, among others, have contributed an facile route to reactive Ar-AuIII intermediates in the presence of Ru-based photosensitizer, not needing external strong oxidants.[27–30] In 2016, we developed the first photosensitizer-free, photochemical generation of Ar-AuIII species from diazonium salts and gold(I)-complexes, including catalytic transformations.[31,32] Herein we report a visible-light-induced gold-catalyzed redox-neutral arylation of mechanistically discriminative B,Si bimetallic coupling reagents (B-Ar-Si) with diazonium salts (Scheme 1c); mechanistic studies demonstrate that photosensitizer-free conditions are superior to gold/Ru(bpy)3Cl2 dual catalysis.

The commercially available B,Si-bimetallic reagent 1a and 4-bromobenzenediazonium salt 2a were selected for the test reaction to optimize the conditions (Table 1, other reagents in Tables S1–S3 in the Supporting Information). When Ph3PdAuCl2 was used as the catalyst under the irradiation of blue LEDs, the desired bifunctionalyzed halobiarylboronate product 3a was exclusively formed in acetonitrile and pivalonitrile (entries 1 and 2). Other solvents (MeOH, DCE, DMF, acetone, dioxane) gave no product (entry 3). The important role of nitrile-based solvents might be rationalized by the effect of ligand stabilization avoiding a rapid reductive elimination from the generated Ar-AuIII-PPh3 intermediate to form [Ar-PPh3]+ salts.[33] The use of cationic Ph3PdAuNTf2 can improve the yield to 78% (entry 4). Other transition-metal catalysts examined (Fe, Cu, Ni, Ir) failed to initiate this transformation and Pd(Ph3P)2 led to 14% yield along with the undesired byproduct 4a at room temperature (see Supporting Information). Further studies indicated that the use of Pd-based catalysts leads to the normal Suzuki coupling products for -Bpin and -Bnep bimetallic substrates. Shortening the reaction time from 10 h to 6 h even increased the yield from 78% to 82%. A lower yield was obtained when the catalyst loading was decreased to 5 mol%. Control experiments demonstrated that both light and gold catalyst were essential for the reaction to proceed.

Under the optimized reaction conditions a wide array of arenediazonium salts were investigated (Scheme 2). With 1.2–2.0 equivalents of arenediazonium salt, both the less reactive -Bnep and the reactive -Bpin/-Bnep containing B,Si-bimetallic reagents successfully furnished the desired biarylboronates 3a–v in 40–86% yields. Especially, the excellent compatibility with activated -Bpin and -Bnep makes this new technique very attractive for subsequent “classical” Pd-catalyzed C–C couplings.[2] For Bnep type bimetallic reagents, the reactions are clean and the desired products 3a–v can conveniently be obtained by recrystallization without chromatography. Diazonium salts bearing electron-rich, as well as electron-poor functional groups in the o-, m-, and p-positions mostly reacted well. A series of synthetically valuable functional groups (-CF3, -F, -COOMe, -COMe, -NO2, -CN, -SO2Me, etc.) were compatible. In addition, the successful coupling to bifunctionalyzed halobiarylboronate motifs (-I, -Cl, -Br; 3a, 3c, 3g, 3j, 3k, 3p, 3t) allows post-modifications by Pd-catalyzed C–C cross coupling. With 4methoxybenzenediazonium salts containing strong electron-donating groups the reactions were sluggish. The identity of the product 3b was unambiguously confirmed by an X-ray single crystal structure analysis.[41]

The synthesis of structurally diverse Ar-CF3 units for agrochemicals and pharmaceuticals has gained great momentum in the past ten years.[42] Valuable trifluoromethylated arylboronates were now obtained by using 4-CF3-substituted aryl diazonium salts, several representative B,Si-bimetallic reagents were used (Scheme 3). Besides TMS, other trialkyl-
Scheme 2. Scope with respect to the boronic acid derivative and the diazonium salt. [a] 200 μmol scale; yield after recrystallization or chromatography. [b] 1000 μmol scale.

Scheme 3. Scope with regard to B,Si-bimetallic reagents. [a] 200 μmol scale; yield after chromatography. [b] Successive oxidation of aryloboronates with 5 equiv NaOH and 5 equiv H₂O₂ at 0°C. [c] 2 equiv diazonium salts were used.
silyl-substituted arylboronates 1d,e could also undergo the site-selective arylation. Both electron-withdrawing and electron-donating groups at the aryl core of the B,Si-bimetallic reagents were efficient (1b–j, 1l–n), and -CHO and -Br as versatile groups for post modification also were tolerated (3y and 3z). With an alkynyl moiety (1k), only a low yield of desired coupling product was obtained due to a competing 1,2-difunctionalization of the alkynyl.[37] The concis synthesis of congested biallylboronates (1l–n) is also possible. The heteroaryl-containing B,Si-bimetallic reagent 1p affords polynuclear aromatic 1,2-diazotization of the alkyne.

Both -I and -OTf are very important moieties for transition metal-catalyzed C–C couplings. Therefore, it is still a great challenge to keep these relatively weak chemical bonds intact in any cross-coupling scenario. By exploiting our new method, bifunctionalized haloarylilane 5a and pseudo-haloarylilane 5b both furnished the desired products 6a and 6b in satisfactory yields (Scheme 4), which further complements existing Pd-catalysis.

To illustrate the synthetic possibilities, one-pot iterative C–C and C–X coupling strategies are presented in Scheme 5. Through the synergism of gold catalysis with another catalysis system, it was possible to synthesize interesting molecules in a one-pot iterative fashion. For example, the gold-catalyzed site-selective arylation of B,Si-bimetallic reagent 1f and subsequent oxidation with H₂O₂ afforded trifluoromethylated biphenol 7 in 76% yield. Similarly, arylation and subsequent amination was achieved in moderate yield (8). The combination of gold catalysis and palladium catalysis demonstrates the versatility for the rapid construction of complex target molecules for medicinal chemistry or molecular materials (9–11) from easily available substrates.

Several control experiments were conducted (Scheme 6). We found that both light and gold-catalyst were crucial for a successful conversion. Without light, even by heating to 60°C, no product was formed. To our surprise, the addition of Ru(bpy)₃Cl₂ as photosensitizer significantly decreased the yield from 97% to 37%; this is caused by a rapid and unselective decomposition of the arenediazonium salts (Scheme 6a). The screening with different light sources revealed that UVA or a fluorescent lamp (FL) instead of blue LEDs slightly lowers the yield (Scheme 6b). However, if UVC light (λ = 254 nm) was used, only 12% yield were obtained. This may indicate that the direct photolysis of diazonium salts with UV light to give aryl radical is less likely. It was also found that the diazonium salt’s counter anion was important, OTf⁻ and Cl⁻ anions instead of BF₄⁻ stopped the reaction (Scheme 6c).

The kinetic profiles were examined as well and the initial reaction rates are presented in Figure 1. The initial reaction rate for the arylation of 1a and 2b is first-order dependent on [1a] and [Ph₃PAuNTf₂]. In contrast, the reaction rate is independent on the arenediazonium salts [2b]; a zero order rate was observed. The first order dependence on gold catalyst suggests that the really reactive catalytic species should be mononuclear gold complex. Moreover, these kinetic results indicate that the turnover limiting step of


Scheme 5. Iterative modular synthetic methodology. The final isolated yields are shown and the average yield for each step is given in brackets.

Scheme 6. Mechanistic experiments.
gold-catalyzed Hiyama arylation may be the aryl ipso substitution step.

While Lee and co-workers recently presented the transmetalation of Ph₃PAuNTf₂ with boronic acids,[33] no such activation was observed for arylsilane by mixing 1 equiv of 1a and 1 equiv of Ph₃PAuNTf₂ for 6 hours. This indicates a completely different reactivity pattern of arylsilanes and arylboronic acids. Monitoring the reaction in Equation (2) by ³¹P NMR suggested the generation of [Ph₃P⁺-Ar]X, which should arise from the reductive elimination from the organogold(III) intermediate.[40] Stoichiometric treatment of Ph₃PauAr and 1a in the presence of the external oxidant Selectfluor was carried out at room temperature for 2 h without irradiation (Scheme 7). Selectfluor enables the facile oxidation of 11 to Au⁺⁺ 12. Pleasingly, the desired products 3b and 14 can be formed in 75% and 19% yields. The better efficiency for the electron-withdrawing aryl group can be rationalized by the higher reactivity towards an arylsilane ipso substitution of intermediate 12. This would also explain the low yield for strongly electron-donating arenediazonium salts in this transformation. At present, it seems that the highly electrophilic organogold(III)-mediated π-activation and subsequent ipso substitution aryl fragment of 1a to generate 13 is highly likely.

A possible mechanism is shown in Scheme 8. Under the irradiation of blue LEDs, gold-activated arenediazonium salts are able to undergo oxidative addition to gold(II)[37–39]. The resulting highly electrophilic 15 coordinates to 1a to initiate the aryl ipso substitution assisted by the BF₄⁻ anion.[11,44] Finally, reductive elimination from 18 gave the desired boron-containing product. Alternatively, reductive elimination from intermediate 15 give rise to byproduct Ar²-PPh₃X, which could be detected by HRMS-ESI analysis. In addition, the reaction needs continuous irradiation, and no conversion was observed without light. Thus, the arenediazonium salts-triggered radical chain propagation pathway is less likely.[45–47]

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In conclusion, a gold-catalyzed selective Hiyama arylation of B,Si-bimetallic reagents was presented. The resulting biarylboronates are versatile building blocks for the robust assembly of several small molecules via one-pot iterative orthogonal C–C and C–X couplings. This new protocol complements the common Pd-catalyzed C–C coupling strategies from the view of chemoselectivity and functional group compatibility. We anticipate that this redox-neutral arylation technology will streamline pharmaceutical lead discovery, agrochemical and organic material synthesis.

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Conflict of interest

The authors declare no conflict of interest.

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[41] CCDC 1535250 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.