Photocatalyzed Transition-Metal-Free Oxidative Cross-Coupling Reactions of Tetraorganoborates

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Abstract: Readily accessible tetraorganoborate salts undergo selective coupling reactions under blue light irradiation in the presence of catalytic amounts of transition-metal-free acidinium and rhodamine photocatalysts to furnish unsymmetrical biaryls, heterobiaryls and arylated olefins. This represents an interesting conceptual approach to forge C-C bonds between aryl, heteroaryl and alkenyl groups under smooth photochemical conditions. Computational studies were conducted to investigate the mechanism of the transformation.

Biaryl derivatives constitute an essential class of compounds for the development of pharmaceuticals and organic materials.[1] The use of transition metal catalysis to forge C-C bonds between two aryls has become inevitable, following the pivotal groundwork laid by Corriu-Kumada-Tamao,[2] Negishi,[3] Suzuki-Miyaura[4] and Stille[5] in the 1970’s. Although these traditional methods dominate the world of cross-coupling reactions, modern synthetic planning also includes direct C-H functionalization[6] and decarboxylative strategies.[7] Besides, efforts have been made towards transition-metal-free alternatives using borates as templates for intramolecular biaryl formation. Few methods depict homocoupling reactions using chemical oxidants such as VO(OEt)Cl2,[8] iridium[9] and zinc complexes[10] (Scheme 1A). Pioneered by Geske in 1959,[11] the formation of symmetrical biaryl under electrochemical oxidation was extended to fluorinated substrates by Waldvogel in 2018.[12] However, the intramolecular coupling of borate salts was restrained to homocoupling products until very recently (Scheme 1B). Building on methodologies developed in our group to access functionalized organoboron derivatives, we recently demonstrated an efficient and chemoselective electrochemical synthesis of unsymmetrical biaryls[13] and (hetero)-arylated olefins[14] from readily accessible tetraorganoborate salts (TOBs). The group of Studer similarly reported an elegant chemical oxidation of unsymmetrical tetraorganoborates towards heterobiaryls using Bobbitt’s salt.[15]

The renaissance of photochemistry in past decades stems mainly from the advantageous features it presents and the reactivity it promotes in comparison with classical chemical processes.[16] Photoredox catalysis is a rapidly expanding field as it offers a tunable control over oxidation and/or reduction steps for the generation of desired reactive intermediates.[17] Only few examples have been reported on the formation of C-C bonds between two aryl moieties through photoredox catalysis. The groups of Sanford, Duan and König employed either transition-metal photocatalysts ([Ru]18) or [Zn]-PD19 complexes), or organophotocatalysts (Eosin Y or PDI)20 to reduce diazo-compounds and electron-poor aryl bromides under photoradiation towards intramolecular aryl-aryl bond formation.

Scheme 1. Previous and present contributions to coupling reactions of TOBs.

The only example of photochemical borate rearrangement was described by Doiy in 1971. Rose Bengal was employed under UV-light irradiation for the formation of biphenyl (Scheme 1C) from NaBPh4 through oxygen-relayed electron transfer.[21] The authors...
presented a conceptual hetero-coupling approach towards functionalized biaryls and arylated olefins by harvesting the potential of visible light photocatalysis to promote the oxidation step needed to trigger the key C-C bond formation.

Table 1. Optimization of the photo-coupling reaction.

| Photocatalysts employed for optimizations | Conversion (Isolated yield) |
|------------------------------------------|----------------------------|
| Rhodamine 6G                             | 45%                        |
| Acrr-1                                   | 57% (50%)                  |
| Acrr-1 (R^1 = Me)                        | 85% (77%)                  |
| Acrr-1 (R^1 = Ph)                        | 82%                        |
| Acrr-3 (R^1 = EtO)                       | 83%                        |
| Acrr-4 (EtO)                             | 85% (78%)                  |
| Acrr-5 (R^1 = Me)                        | 85% (83%)                  |

Conditions were first optimized using unsymmetrical tetraarylborate salt 1a. Rhodamine 6G and acridinium-based photocatalysts (Acrr)[26] were tested in the presence of Cl2CBF or oxygen as oxidant, respectively (Table 1). While rhodamine 6G only gave the desired product 2a in 45% conversion within 48h under green light irradiation (\( \lambda = 530 \text{ nm} \)), Acrr-1 allowed for its formation in 57% without oxidant (50% isolated yield). In the presence of oxygen, the conversion went up to 85% and modifying the substitution pattern of the photocatalyst (Acrr-2 to Acrr-4) gave similar results (82 to 85% conversion). Switching the solvent to ethanol proved less efficient (69% conversion within 8 days). However, decreasing the catalyst loading to 5 mol% did not alter the rate of coupling reaction, furnishing 2a in 78% yield after 48h under blue light irradiation (\( \lambda = 470 \text{ nm} \)). Using a more powerful setup (13 W/cell)[23] allowed to decrease reaction times to 16h, which also caused an increase in temperature to 50 °C. Importantly, no traces of intermolecular coupling products were detected in all cases.

We previously demonstrated that the first oxidation of a TOB salt preferentially occurs on the most electron rich unsaturated moiety,[13,14] As a logical consequence, structures 1 were designed to possess one electron-richer aryl group (Ar'), surrounded by electron-poorer groups (Ar^2). With optimized conditions and setup in hands, we started evaluating the scope of the aryl-aryl photocoupling (Scheme 2). Worthy of note, tetraarylborate salts were accessed ex-situ by reaction of an aryltrifluoroborate species with the appropriate Grignard (or zinc) reagent and were engaged further without purification. The yields in Scheme 2 are therefore given for the two-step sequence. In the presence of Acrr-1 under blue light irradiation, we were able to push the conversion to its maximum for the formation of biphenyl 2b (91%), showing great improvement in comparison with the conditions previously described by the group of Doty (75% under UV irradiation). Varying the substitution pattern of Ar^1 by introducing methyl, trimethylsilyl and ether moieties led to structures 2c-d in good to excellent yields (up to 92%). Scaling up the reaction to 3 mmol also gave 2h in a reasonable yield (77%). Interestingly, these conditions allowed for an efficient coupling of unprotected phenol derivatives 2k-l in up to 83% isolated yield, verifying the functional group tolerance of the method. Amides and nitriles also proved tolerable (2m-n), although lower yields were obtained (47 to 53%). This can be attributed to the lower reactivity of organozinc reagents (necessary for the tolerance of amides and nitriles) towards starting trifluoroborates in the initial formation of TOB salts. Electron-rich heteroaryl such as benzoxadiazole and benzofurans were successfully coupled, yielding compounds 2o-t (up to 70%). The transformation of electron-poor pyridyl and quinolyl TOB derivatives proved more difficult to achieve and compounds 2s-t were only isolated in up to 56% yields. However, the presence of dibenzofurans as Ar^2 groups led to 78% of coupling product (2u). Functionalization of the pharmacologically relevant celecoxib structure gave 2v in 38% yield. The photocoupling reaction of sensitive halogenated and pseudo-halogenated scaffolds was examined next, as they open the possibility for further functionalization. While classical cross-coupling methods usually give complex mixtures of products through uncontrolled oxidative additions, we have previously demonstrated that an electrochemical process can be employed to gain control over the formation of desired functionalized compounds.[13] Remarkably, iodinated and brominated substrates were tolerated under our photocatalytic conditions, furnishing halogenated biaryls 2w-z in up to 69% yield. Nitrile-substituted trifluoroborate substrates were also used in this two-step sequence, leading to structures 2aa-ab in moderate yields (47 to 63%).
Scheme 2. Scope of the photo-coupling of TOBs. \[a\] Borate salts were generated in-situ from the corresponding organotrifluoroborates and organomagnesium species. \[b\] Yields are given over two steps, see SI. \[c\] Photocoupling was conducted on pure, isolated salts. \[d\] Prepared from organozinc reagents.

Having supported the proof of concept for photocoupling reactions with a broad scope of biaryl products, we set out to examine olefinations under similar conditions, as those would provide an interesting alternative for the formation of styryl derivatives. Model substrate 3a was employed for optimizations, assuming that the oxidation of the alkenyl substituent would be preferred over the remaining aryl groups.\[14\] Performing the reaction with 5 mol% of Acr-1 without oxidant afforded 4a in 35% yield and similar conditions to the ones used for biaryl formation only pushed the conversion to 65% (Table 2).

Table 2. Optimization of the photo-olefination reaction.

| oxidant  | Conversion (\[a\]) (Isolated yield) | oxidant  | Conversion (\[b\]) (Isolated yield) |
|----------|-----------------------------------|----------|-----------------------------------|
| O₂       | 65% (\(<10\)%\[b\])             | PhSSPh   | 57% (40%)                         |
| none     | 45% (35%)                         | KgHPO₄    | 73% (57%)                         |
Conversions determined by GC. The epoxide 5a (from 4a) was isolated, see Scheme 3. However, the main product was found to be the overoxidized epoxide 5a (see Scheme 3). Diphényldisulfide did not improve the conversion of 3a, and di-potassium phosphate furnished 4a in 57% isolated yield (73% conversion of 3a). These last conditions (cond. A, Scheme 3A) were therefore used in the exploration of the reaction scope. β-styryl moieties were evaluated first, providing (E)-bisarylated olefins 4a-e with up to 57% yield. Interestingly, engaging (E)-alkenyl substrates led to the stereospecific formation of products (E)-4 under thermodynamic control. Cyclic olefins 4f-j were synthesized next, although conversions were generally lower than for acyclic ones, with the exception of 4i (69% isolated yield). When oxygen was used instead of K$_2$HPO$_4$, trans-epoxides 5a and 5b were formed in up to 54% yield.

More than adding synthetic interest to the method, these findings indicate that the oxidant plays an essential role in the transformation and its associated catalytic cycle. In contrast to the work from Doty, our different set of conditions leads us to believe that oxygen plays a role in the re-oxidation of the catalyst, rather than in the oxidation of the substrate itself.

We therefore propose a reaction mechanism in which the oxygen is implicated as the oxidant that enables the catalyst regeneration (Scheme 4). Blue light irradiation (470 nm) allows for the acridinium to reach its active, excited state to abstract an electron from substrate 1a. The resulting oxidized species [1a$^+$] undergoes a pseudo 1,2-metallate rearrangement,$^{[13,14]}$ giving the cyclic intermediate 6, which further opens towards 7 through [TS]$^r$. Oxygen further intervenes to regenerate the photocatalyst from its reduced form, producing [O$_2$]$^-$. As witnessed in the reaction of alkenyl derivatives, we know that oxygen interacts with the intermediates to produce the corresponding epoxides. In consequence, we advance that an active oxygen species reacts with [7] to promote an elimination reaction towards the formation of 2a.

To assess a plausible reaction path, we performed a series of density functional theory calculations on 1a using the software Q-Chem$^{[26]}$ with the B3LYP functional$^{[27]}$ and the 6-31G* basis set. Here we determined equilibrium structures and computed the Gibbs free energies for the initial anion 1a and radical [1a$^+$] as well as for the radicals 6 and 7. We found a transition state between 6 and 7.
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