

Catalysis

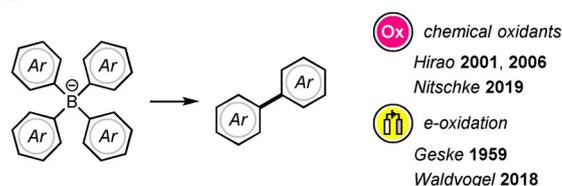
Photocatalyzed Transition-Metal-Free Oxidative Cross-Coupling Reactions of Tetraorganoborates**

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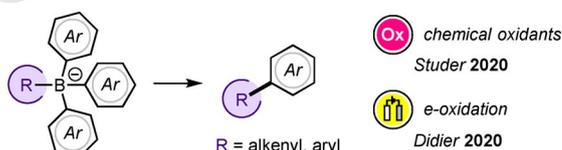
Abstract: Readily accessible tetraorganoborate salts undergo selective coupling reactions under blue light irradiation in the presence of catalytic amounts of transition-metal-free acridinium photocatalysts to furnish unsymmetrical biaryls, heterobiaryls and arylated olefins. This represents an interesting 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 1970s. 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] Moreover, 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 biaryls under electrochemical oxidation was extended to fluorinated substrates by Waldvogel in 2018.^[12] However, the intramolecular coupling of borate salts

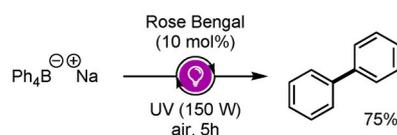
A Oxidative homocoupling reactions of tetra-organoborates



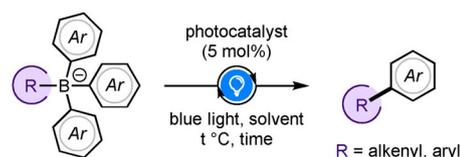
B Oxidative heterocoupling reactions of tetra-organoborates



C Only example of photocatalyzed homocoupling - Doty 1971



D This work - Photocatalyzed heterocoupling reactions



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

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 heteroarylated olefins^[14] from readily accessible tetraorganoborate salts (TOBs). The group of Studer similarly reported an elegant chemical oxidation of mixed tetraorganoborates towards hetero-biaryls 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

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offers a tunable control over oxidation and/or reduction steps for the generation of desired reactive intermediates.^[17]

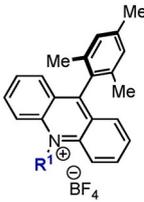
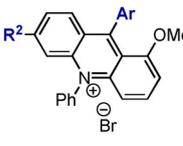
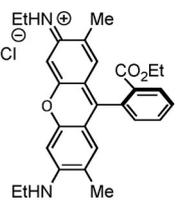
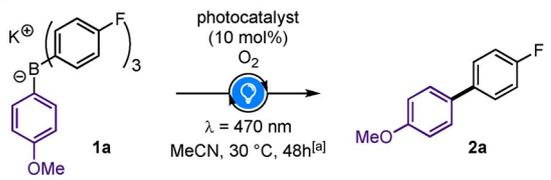
However, only few examples have been reported on the formation of C–C bonds between two aryl moieties through photoredox catalysis. The groups of Sanford, Duan and König employed either transition-metal photocatalysts ([Ru]^[18] or [Zn]-PDI^[19] complexes), or organophotocatalysts (Eosin Y or PDI)^[20] to reduce diazo-compounds and electron-poor aryl bromides under photoirradiation towards intermolecular aryl–aryl bond formation. The only example of photochemical borate rearrangement was described by Doty in 1971. Rose Bengal was employed under UV-light irradiation for the formation of bi-phenyl (Scheme 1C) from NaBPh₄ through oxygen-relayed electron transfer.^[21] The authors proposed that singlet oxygen is generated in situ, serving as the oxidizing species in the transformation.

The creation of C–C bonds under photochemical conditions is therefore largely restricted to specific substrates. Herein, we challenge the general transition-metal free photocatalyzed formation of biaryls and arylated olefins, providing innovative perspectives in the domain of photocatalysis.

Conditions were first optimized using mixed tetraarylborate salt **1a**. Rhodamine 6G and acridinium-based photocatalysts (**Acr**)^[22] were tested in the presence of Cl₃CBr or oxygen as oxidant, respectively (Table 1). While rhodamine 6G only gave the desired product **2a** in 45% conversion within 48 h under green light irradiation ($\lambda = 530$ nm), **Acr-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 (**Acr-2** to **Acr-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 48 h under blue light irradiation ($\lambda = 470$ nm). Using a more powerful setup (13 W cell⁻¹)^[23] allowed to decrease reaction times to 16 h, which also caused an increase in temperature to 50 °C. Importantly, no traces of intermolecular coupling products were detected in all cases.

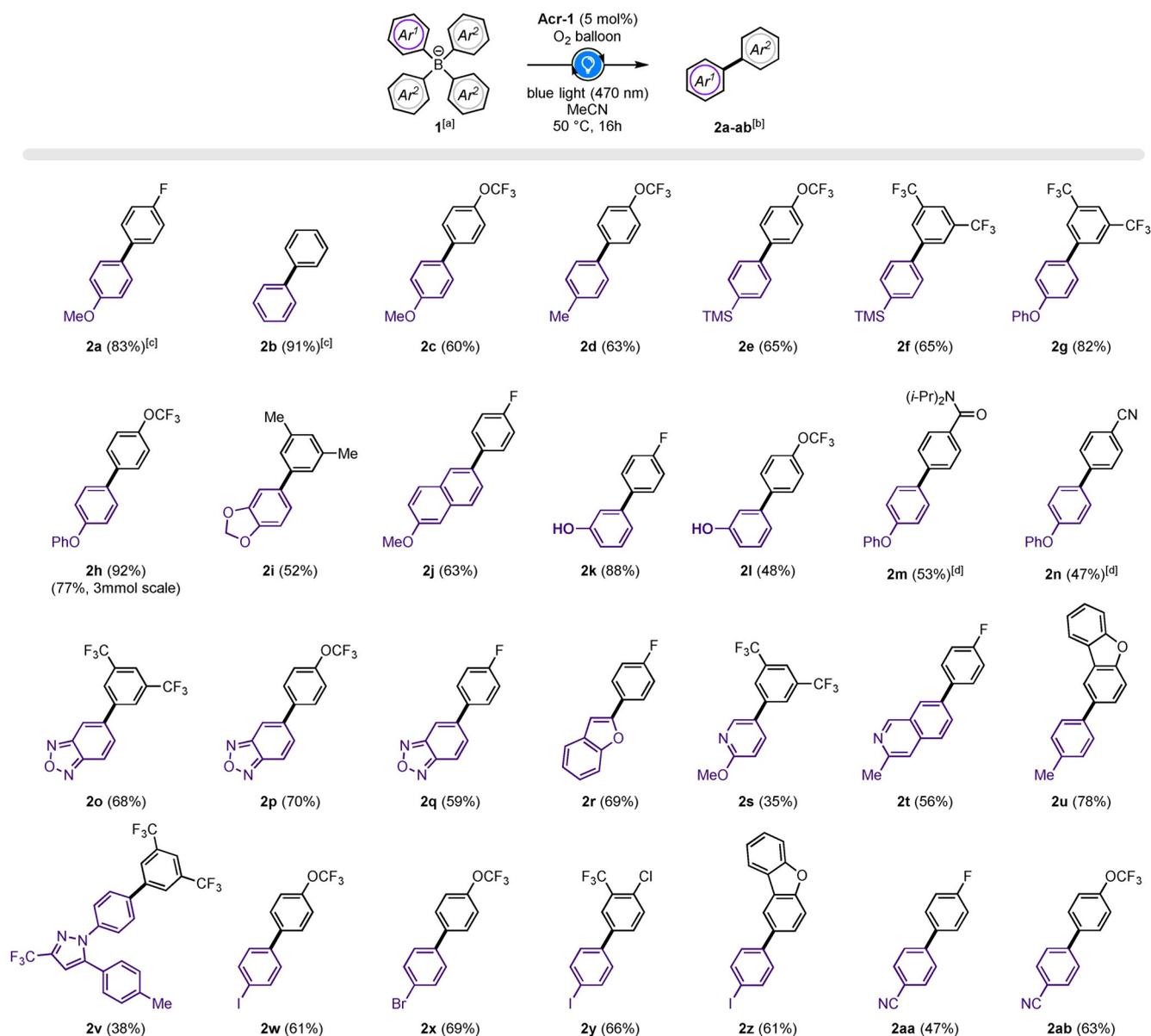
We previously demonstrated that the first oxidation of a TOB salt preferentially occurs on the most electron rich unsaturated moiety.^[13,14] As a logical consequence, structures **1** were designed to possess one electron-rich aryl group (Ar¹), surrounded by electron-poorer groups (Ar²). With optimized conditions and setup in hands, we started evaluating the scope of the aryl–aryl photocoupling (Scheme 2). It is worth noting that 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 **Acr-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 Ar¹ by introducing methyl, trimethylsilyl and ether moieties led to structures **2c–j** in good to excellent

Table 1. Optimization of the photocoupling reaction.

A Photocatalysts employed for optimizations		
		
Acr-1 (R ¹ = Me)	Ar = 2,6-(Me) ₂ -C ₆ H ₃	
Acr-2 (R ¹ = Ph)	Acr-3 (R ² = H)	
	Acr-4 (R ² = NMe ₂)	
	Ar = 1-naphthyl	
	Acr-5 (R ² = NMe ₂)	
B Model photo-coupling reaction		
		
Photocatalyst	Deviation from conditions	Conversion ^[b] (isolated yield)
Rhodamine 6G	Cl ₃ CBr instead of O ₂ , $\lambda = 530$ nm	45%
Acr-1	without O ₂	57% (50%)
Acr-1	none	85% (77%)
Acr-1	EtOH instead of MeCN, 8 days	69%
Acr-2	none	82%
Acr-3	none	83%
Acr-4	none	85% (78%)
Acr-1	5 mol% catalyst loading	85% (78%)
Acr-1	5 mol% cat., 50 °C, 16 h ^[c]	91% (83%)

[a] Control experiments show no conversion of starting material in the absence of photocatalyst or light (see Supporting Information). [b] Conversions determined by GC using *n*-undecane as internal standard. [c] Switching to a more powerful LED setup induces a temperature increase to 50 °C (self-heating), allowing to decrease the reaction time to 16 h, see Supporting Information.

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 heteroaryls such as benzoxadiazole and benzofurans were successfully coupled, yielding compounds **2o–r** (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 Ar² 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



Scheme 2. Scope of the photocoupling of TOBs. [a] Borate salts were generated in situ from the corresponding organotrifluoroborates and organomagnesium species. [b] Yields are given over two steps, see Supporting Information. [c] Photocoupling was conducted on pure, isolated salts. [d] Prepared from organo-zinc reagents.

they open the possibility for further functionalization. While classical cross-coupling methods usually give complex mixtures of products through uncontrolled oxidative additions,^[24] 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 photocatalyzed conditions, furnishing halogenated biaryls **2w–2z** 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%).

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

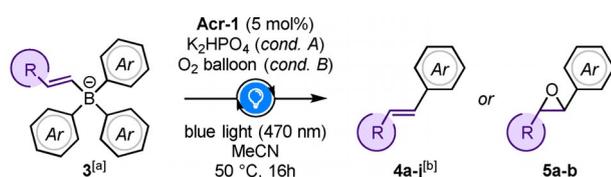
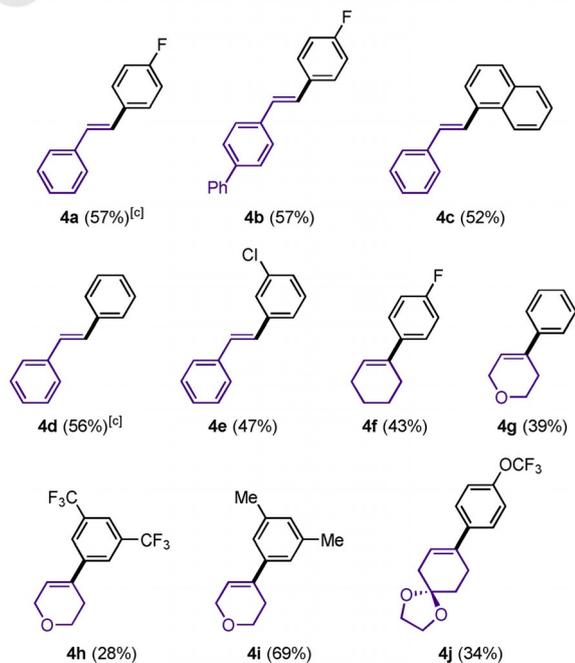
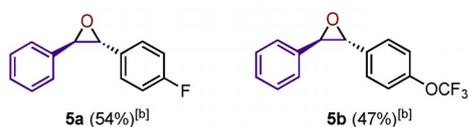
provide an interesting alternative for the formation of styryl derivatives. Model substrate **3a** was employed for optimizations, assuming that the oxidation of the alkenyl substituent would be preferred over the remaining aryl groups.^[14] Performing the reaction with 5 mol% of **Acr-1** without oxidant afforded **4a** in 35% yield and similar conditions to the ones used for biaryl formation only pushed the conversion to 65% (Table 2).

However, the main product was found to be the overoxidized epoxide **5a** (see Scheme 3). Diphenyldisulfide did not improve the conversion of **3a**, and dipotassium 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

Table 2. Optimization of the photo-olefination reaction.

Oxidant	Conversion ^[a] (isolated yield)	Oxidant	Conversion ^[a] (isolated yield)
O ₂	65% (< 10%) ^[b]	PhSSPh	57% (40%)
none	45% (35%)	K ₂ HPO ₄	73% (57%)

[a] Conversions determined by GC. [b] The epoxide **5a** (from **4a**) was isolated, see Scheme 3.

**A** Photocatalyzed olefination of aryls (cond. A)**B** Photocatalyzed olefination/epoxidation (cond. B)

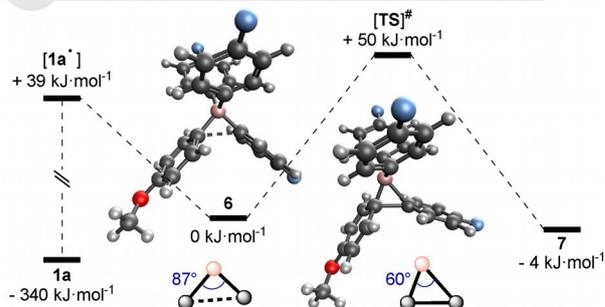
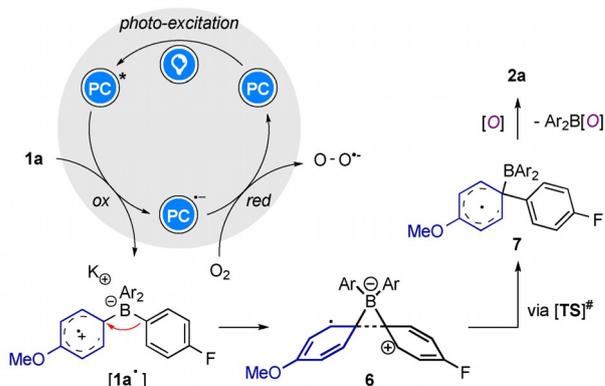
Scheme 3. Photo-olefination of alkenylborates. [a] Borate salts were generated in situ from the corresponding organotrifluoroborates. [b] Yields are given over two steps, see Supporting Information. [c] Photocoupling was conducted on pure, isolated salts.

to the stereoselective 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 K₂HPO₄, *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][‡]. Oxygen further intervenes to regenerate the photocatalyst from its reduced form, producing [O₂]^{•−}.^[25] As witnessed in the reaction of alkenyl derivatives, we know that oxygen interacts with the intermediates to produce the corresponding epoxides. Consequently, we suggest 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

A Theoretical studies of the rearrangement**B** Proposed catalytic cycle and mechanism**Scheme 4.** Theoretical studies and proposed mechanism.

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** at a barrier height of 50 kJ mol⁻¹ as depicted in Scheme 4. This completes the picture of the reaction mechanism: the oxidation of the anion is followed by a relaxation during which the reacting six-membered rings rotate to face each other, therefore coming closer together. The C-B-C angle of 108° in the anion changes to 87° in **6**. This structure has C₅ symmetry when rotationally averaging over the atomic positions of the methoxy group. During the reaction, the B-C bond is cleaved while the C-C bond is formed. The C₅ symmetry is maintained while the bond breaks and lowered only afterwards. The C-B-C angle in the transition state is 60° and shrinks further while the tetrahedral coordination at the carbon atom in the oxidized ring is restored.

In summary, we have demonstrated the feasibility of a chemoselective coupling of tetraorganoborates using organo-photocatalysis. This conceptual approach has allowed us to access a wide range of biaryl, heterobiaryl and olefin products under blue light irradiation, in a simple and practical setup. A deeper analysis of the mechanism through experimental and theoretical studies led us to propose an unusual reaction path that goes through a cyclic intermediate, essential to the formation of the C-C bond. Heterocoupling reactions were achieved and we are currently working on alternative borate salts with increased sustainability and atom economy. There is no doubt that these advances within the field of photocatalysis will enable the discovery of new reactions in the near future.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling · heterocoupling · organoborates · oxidation · photocatalysis

- [1] a) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418–3430; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470.

- [2] a) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144a; b) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.
- [3] E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348.
- [4] a) N. Miyaoura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 866–867; b) N. Miyaoura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
- [5] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.
- [6] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447–2464; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; *Angew. Chem.* **2009**, *121*, 9976–10011; d) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; *Angew. Chem.* **2012**, *124*, 10382–10401; e) R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172–1175; f) Y. Yang, J. Lan, J. You, *Chem. Rev.* **2017**, *117*, 8787–8863; g) Y.-F. Zhang, Z.-J. Shi, *Acc. Chem. Res.* **2019**, *52*, 161–169; h) J. L. Röckl, D. Pollok, R. Franke, S. R. Waldvogel, *Acc. Chem. Res.* **2020**, *53*, 45–61.
- [7] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664; b) O. Baudoin, *Angew. Chem. Int. Ed.* **2007**, *46*, 1373–1375; *Angew. Chem.* **2007**, *119*, 1395–1397; c) G. J. P. Perry, I. Larrosa, *Eur. J. Org. Chem.* **2017**, 3517–3527.
- [8] H. Mizuno, H. Sakurai, T. Amaya, T. Hirao, *Chem. Commun.* **2006**, 5042.5044.
- [9] P. Abley, J. Halpern, *J. Chem. Soc. D* **1971**, 1238–1239.
- [10] Z. Lu, R. Lavendomme, O. Burghaus, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2019**, *58*, 9073–9077; *Angew. Chem.* **2019**, *131*, 9171–9175.
- [11] a) D. H. Geske, *J. Phys. Chem.* **1959**, *63*, 1062; b) D. H. Geske, *J. Phys. Chem.* **1962**, *66*, 17431744.
- [12] S. B. Beil, S. Möhle, P. Enders, S. R. Waldvogel, *Chem. Commun.* **2018**, *54*, 6128–6131.
- [13] A. Music, A. N. Baumann, P. Spieß, A. Plantefol, T. C. Jagau, D. Didier, *J. Am. Chem. Soc.* **2020**, *142*, 4341–4348.
- [14] A. N. Baumann, A. Music, J. Dechent, N. Müller, T. C. Jagau, D. Didier, *Chem. Eur. J.* **2020**, *26*, 8382–8387.
- [15] C. Gerleve, A. Studer, *Angew. Chem. Int. Ed.* **2020**, *59*, 15468–15473; *Angew. Chem.* **2020**, *132*, 15596–15601.
- [16] L. Marzo, S. K. Pagire, O. Reiser, B. König, *Angew. Chem. Int. Ed.* **2018**, *57*, 10034–10072; *Angew. Chem.* **2018**, *130*, 10188–10228.
- [17] a) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.
- [18] D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569.
- [19] L. Zeng, T. Liu, C. He, D. Shi, F. Zhang, C. Duan, *J. Am. Chem. Soc.* **2016**, *138*, 3958–3961.
- [20] a) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961; b) I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, *Science* **2014**, *346*, 725–728; c) A. U. Meyer, T. Slanina, C.-J. Yao, B. König, *ACS Catal.* **2016**, *6*, 369–375.
- [21] J. C. Doty, P. J. Grisdale, T. R. Evans, J. L. R. Williams, *J. Organomet. Chem.* **1971**, *32*, C35–C37.
- [22] B. Zilate, C. Fischer, C. Sparr, *Chem. Commun.* **2020**, *56*, 1767–1775.
- [23] See the Supporting Information.
- [24] R. Rossi, F. Bellina, M. Lessi, *Adv. Synth. Catal.* **2012**, *354*, 1181–1255.
- [25] a) B. Zomer, L. Collé, A. Jedyńska, G. Pasterkamp, I. Kooter, H. Bloemen, *Anal. Bioanal. Chem.* **2011**, *401*, 2945–2954; b) K. Ohkubo, K. Mizushima, R. Iwata, K. Souma, N. Suzuki, S. Fukuzumi, *Chem. Commun.* **2010**, *46*, 601–603; c) K. Ohkubo, K. Suga, S. Fukuzumi, *Chem. Commun.* **2006**, 2018–2020.
- [26] Y. Shao, et al., *Mol. Phys.* **2015**, *113*, 184–215.
- [27] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

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