Special Topic

Developing a Bench-Scale Green Diboration Reaction toward Industrial Application

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Dedicated to Prof. Maria Elena Fernandez and Prof. Carles Bo, our scientific parents

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Abstract We report a new methodology for the organocatalytic diboration reaction using inexpensive, sustainable, nontoxic, commercially available halogen salts. This is an educative manuscript for the transformation of laboratory scale reactions into a sustainable approach of appeal to industry.

Key words green chemistry, organocatalysis, boron chemistry, ate complexes

Organoboron compounds offer a versatile synthetic platform for efficient access to a wide range of functionalities and are commonly applied in the synthesis of new active pharmaceutical ingredients.¹ Currently, many research groups have been focussing on the development of transition-metal-free methodologies for the introduction of boron functionality into organic moieties.² In general, these methodologies use a Lewis base that coordinates to a diboron reagent generating an sp² nucleophilic boron species which can react with organic functionalities.³ These methodologies are a step forward in terms of sustainability in comparison with the traditional transition-metal catalysis and they can be classified as stoichiometric, using organolithiums,^{2m,u} thioethers^{2m} and fluoride salts,^{2k} or catalytic, using alkoxides,^{2d-h,2n,s,t} carbenes^{2a-c} and amines.^{2v}

Among these transition-metal-free methods, use of the salts has a great potential due to their availability, low price and low toxicity. However, current methodologies for the activation of the diboron reagent are limited to the use of stoichiometric fluoride salts.^{2k} Fluoride salts could be difficult to handle due to their highly hygroscopic nature and have some limitations in terms of protecting group compatibility, such as with silyl ethers. In our laboratory, we have



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recently developed an organocatalytic method which uses amines to activate the diboron reagent.^{2v} Amines are a softer Lewis base than alkoxides or carbenes and, therefore, are unable to engage with the most-used diboron reagent bis(pinacolato)diboron (B_2pin_2); however, amines can engage with the more Lewis acidic bis(catecholato)diboron (B_2cat_2). Thus, amines activate the B_2cat_2 reagent, generating an sp²–sp³ adduct which smoothly reacts with olefins providing high yields in the diboration reaction. This method offers the advantage of broad substrate scope while overcoming some functional and protecting group limitations of previously established methodologies.^{2v}

Building upon our previous experience,^{2v} we envisaged that use of the more Lewis acidic diboron reagent, B₂cat₂, can allow the development of a catalytic methodology with less expensive, milder and more readily available halogen salts than fluoride. Halogen salts, especially guaternary salts, have been used as phase-transfer catalysts for decades, providing a powerful and sustainable strategy for organic synthesis, which can substitute others methods involving toxic and expensive transition-metal catalysts.⁴ Our reaction of choice was the diboration reaction due to its inherently high atom economy. Recently, organocatalytic methodologies have been demonstrated as being advantageous over transition-metal approaches, offering a broader substrate scope, a higher degree of selectivity and greater protecting and functional group tolerance. However, current enantioselective organocatalytic strategies provide either low enantioselectivities or a narrow substrate scope.^{2f,o} Therefore, there is a need to develop a new organocatalytic enantioselective version of the reaction. In this context, the successful use of a variety of halogen salts as a catalyst will generate a more sustainable activation of the diboron reagents and will be amenable to potential new borylation asymmetric methodologies using chiral cations.

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Herein, we present the development of a green diboration reaction using simple halogen salts and have explored for the first time the use of quaternary ammonium salts with a different counteranion in the diboration reaction. We decided to study the catalytic potential of chloride, bromide and iodide salts due to their superior stability, availability and lower price compared with their fluoride analogues. Our initial reaction conditions involved the use of anhydrous THF and a low catalyst loading (10 mol%) under inert atmosphere (Table 1). With styrene (1a) as a model substrate, and after stirring the reaction mixture overnight at reflux, we were pleased to observe the selective formation of the desired diborated product **2a-Bcat**. Although all the tested salts provided catalytic activity, the iodide salt, TBAI. showed the highest activity with a 76% NMR vield after 14 hours (Table 1, entries 1 and 2 vs 3). It is worth noting that the iodide salt is the least expensive ammonium salt of the series, making the process economically more viable.⁵ After several other iodide salts were tested (see the Supporting Information), it was established that use of the phosphonium salt. MePPh₂I, resulted in an increased reactivity with NMR yields up to 81% (Table 1, entry 4). As previously observed, when soft Lewis bases like amines are used, the alkylic diboronic esters, B₂pin₂ and bis(neopentyl glycolato)diboron (B2neop2), remained unreactive under the same reaction conditions.

 Table 1
 Preliminary Results for the Halogen Salt Catalysed Diboration

 Reaction^a
 Preliminary Results for the Halogen Salt Catalysed Diboration



^a Reaction conditions: styrene (0.5 mmol), halogenated salt (0.05 mmol), B₂cat₂ (0.525 mmol), THF (2 mL), 70 °C, 14 h. The reactions were carried out in duplicate and the reported NMR yields are the average of them. 1,3,5-Trimethoxybenzene was used as internal standard.

With the optimised reaction conditions in hand, we explored the substrate scope of the reaction (Scheme 1). While disubstituted vinylarenes **1e** and **1f** provided only moderate yields, we were glad to observe that terminal vinylarenes **1a–d** delivered yields up to 80%. It is important to highlight that the reactivity of terminal vinylarenes is not affected by the electronic or the steric properties of the ring. Furthermore, we were pleased to observe that nonactivated alkenes successfully engaged under the present re-

action conditions. Olefins **1g** and **1h** reacted in a similar manner independently of being terminal or internal, and cyclic or acyclic. Diboration of this type of substrate provided synthetically useful yields up to 86% (**2h**, Scheme 1).



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At this point, we realised the potential of the use of inexpensive and sustainable salts in the diboration reaction. Encouraged by these results, we aimed to develop what could be one of the greenest borylation methodologies reported so far. Since boron compounds are widely used in fine industry, with 40% of the new drug candidates being synthesised using Suzuki–Miyaura cross-coupling,⁶ we decided to further optimise the reaction conditions using the toolkit recently reported by Clark and co-workers.⁷ Such a toolkit allows the evaluation of synthetic methods of interest to the pharmaceutical industry toward their optimisation into a more green and sustainable process.

With our encouraging preliminary results, we next focussed on tailoring the reactions to improve the sustainability that can be beneficial for the fine chemical industry.

To this end, each factor of the reaction was optimised by following the Clark toolkit using the First Pass (for benchtop reactions); these findings are summarised within the next paragraphs, where each reaction factor is described.

Catalyst: We initially relied on the widely used quaternary salt catalysts for the activation of the diboron reagent, B_2cat_2 , but the high molecular weight results in a lower atom economy and mass intensity of the reaction. To address this limitation, we used inorganic salts containing smaller cations, such as lithium, sodium, magnesium or potassium. These salts have a lower molecular weight than the organic ammonium or phosphonium salts, thus increasing

the sustainability of the overall process. In order to ensure that the salt was the real catalyst, only *trace metal basis* quality salts were used in this study.

Amongst the inorganic salts screened using our standard reaction conditions (Table 2, entries 1 and 2), Lil provided an interesting 65% NMR yield of the diborated product; the other salts showed a poor performance due to their very low solubility in anhydrous THF.

Solvent: The solvent is a key factor in developing a sustainable methodology because it constitutes a large percentage of the mass intensity. It is recognised that, during pharmaceutical process development, solvent selection is key in determining the sustainability of future commercial production methods. Recent benchmarking has demonstrated that solvents contribute ~50% of materials used in the manufacture of bulk active pharmaceutical ingredients.⁸ Safety, health and environmental aspects need to be taken into account when a solvent is considered for a reaction.⁹ THF is not preferred because of high water solubility, a low flash point and the potential generation of peroxides. Taking into account the low solubility of inorganic salts in organic solvents, we considered using water which will easily solubilise such salts. Water is the solvent in which chemical reactions are performed in nature, and it is inexpensive, safe and environmentally benign.¹⁰ Milli-Q quality, degassed water was used in this study.

In order to identify greener reaction conditions/approach, we tested the catalysis by a number of inorganic salts in water, and compared them with the use of organic salts. The inorganic salts performed better than the organic salts (Table 2, entries 3 and 4 vs 5–7). However, the NMR yields only reached a moderate level, up to 60% using NaI in water, which is far from the 81% yield obtained in anhydrous THF (Table 1, entry 4).

Water is not a common solvent for borylation reactions because it is a noninnocent solvent which can interact with the empty p orbital of the boron atom. However, there are some examples of borylations in aqueous systems using $B_2(OH)_4$ or using the more stable B_2pin_2 .¹¹

In our case, the higher Lewis acidity of B_2cat_2 makes it prone to decomposition under aqueous conditions. The coordinating nature of water could promote the dissociation of the catechol ligand (partially or totally). The nature of the catechol is key to enhance the Lewis acidity of the diboronic ester and, without it, the anion is unable to activate the empty *p* orbital of the diboron reagent. Also, we observed that the B_2cat_2 remained mostly insoluble during the reaction, which will definitely decrease the reaction rate.

In order to increase the solubility of the B_2cat_2 and minimise the potential decomposition, we exploited the use of a mixture (1:1 ratio) of different organic solvents in water (Table 2, entries 8–11). Our choice would be an inexpensive, readily available solvent insoluble in water. In this way, the

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Table 2 Optimisation Results^a

	salt (10 mol B ₂ cat ₂ (1.05 solvent, 70 °	%) equiv) <u>C, 14 h</u>	Bcat Bcat Bcat
Entry	Solvent	Salt (10 mol%)	NMR yield (%)
1	anhyd THF	Lil	65
2	anhyd THF	Nal	0
3	H ₂ O	MePPh ₃ I	50
4	H ₂ O	TBAI	40
5	H ₂ O	Lil	50
6	H ₂ O	Nal	60
7	H ₂ O	KI	52
8	toluene/H ₂ O ^b	Nal	85
9	hexane/H ₂ O ^b	Nal	84
10	CH_2CI_2/H_2O^b	Nal	50
11	$EtOAc/H_2O^b$	Nal	54
12	toluene/H ₂ O ^b	NaCl	44

^a Reaction conditions: styrene (0.5 mmol), salt (0.05 mmol), B₂cat₂ (0.525 mmol), solvent (2 mL), 70 °C, 14 h. The reactions were carried out in duplicate and the reported NMR yields are the average of the two. 1,3,5-Trimethoxybenzene was used as internal standard. ^b 1:1 mixture.

generated waste in the reaction is reduced and the biphasic character of the resulting reaction mixture potentially allows recycling of the catalyst or a setup for a flow approach. A flow approach is recommended in the toolkit as a greener option than a batch setup. Specifically, the use of microreactors allows precise control over the interfacial area providing an increase in yield and productivity in phase-transfer-catalysed reactions.¹² However, the generation of a flow method or the recycling of the catalyst for this reaction falls outside the scope of this study.

In our context, toluene, hexane, dichloromethane and ethyl acetate fit in the solvent scope. Apolar, hydrocarbontype solvents, toluene and hexane, provided high yields, up to 85% (Table 2, entries 8 and 9). In contrast, polar solvents provided only moderate results, up to 54% yield (Table 2, entries 10 and 11). Based on these results, toluene, which is more environmentally friendly than hexane, was our choice as the optimal solvent. Under the optimal reaction conditions, we achieved a synthetically useful 85% yield with 10 mol% NaI in toluene/water as a solvent mixture (Table 2, entry 8). This system provides a higher yield than the previous reaction conditions involving a phosphonium salt in THF (Table 1 and Scheme 1), with a greener setup. Interestingly, NaCl provides a notable 44% yield (Table 2, entry 12), giving room for future optimisation using these household goods. Due to their environmental and safety benignness, different

alcohols were tested either as a unique solvent or a combination with other solvents; however, none of these reactions provided the desired product.

Yield, Atom Economy and Reaction Mass Efficiency: ¹H NMR yields were determined using an internal standard, after the reactions were quenched. The borylated catechol product is sensitive to silica gel; therefore, it cannot be isolated using column chromatography without being derivatised. Common derivatisation methods are oxidation, transesterification, homologation or cross-coupling.¹ These derivatisations can be performed in a tandem fashion. Oxidation and transesterification are straightforward and quantitative, and the isolated yields of the corresponding alcohol and the pinacol derivatives are comparable with the obtained NMR vields (Table 1, entry 4 vs Scheme 1, 2a and 2a-Bpin). However, standard procedure transformations of boronic esters are not sustainable and need further work to improve these methodologies. Although we are currently working in this area, this part of the study falls outside the scope of the current manuscript.

As stated previously, one of the reasons to study the diboration reaction is its intrinsic complete atom economy: all the atoms of both reagents combine to form the desired product.¹³ In order to progress further, we decided to calculate the reaction mass efficiency (RME). This metric is obtained when the mass of the isolated product is compared against the total mass of the reactants and is widely used to compare mass efficiency between methods.¹⁴ As boronic esters are common intermediates in organic synthesis and they can be used without the necessity of isolation,^{20,15} we calculated the RME directly from the obtained NMR yield (Equation 1).



As small-scale reactions usually obtain a low RME value due to the high impact of the solvent weight relative to the reagent weights, we decided to scale up our diboration reaction. In a 5-mmol scale reaction, we were able to reduce the solvent amount by more than half (4.5 mL of each solvent) and also the excess B_2cat_2 to 1.01 equivalents (Scheme 2). Although the yield of the reaction decreased notably (from 85% to 61%), we were successful in increasing the RME value up to 10% (Equation 2). We believe that the RME number could be increased upon further optimisation on such a higher scale. However, this optimisation falls outside the current study.



Price and Availability: Nal has a molecular weight 2.69 times smaller than that of MePPh₃I, and both salts are commercially available in large quantities from different resellers. Considering a 100 g bottle, one mole of MePPh₃I is 6.5 times more expensive than Nal.¹⁶ This number becomes even more favourable for NaI when bigger quantities are compared.

Also, the use of toluene/water instead of anhydrous THF reduces the overall cost as there is no need to dry the organic solvent.

Energy: We performed our reactions at 70 °C, which are considered mild reaction conditions by the industry.¹⁷ However, 70 °C is the boiling point temperature when THF was used as a solvent. From the industrial point of view, boiling point temperature reactions require six times more energy than using 5 °C below the boiling point. The toluene/water reaction conditions (Table 2, entry 8) are far from boiling point temperatures, making the process much more energetically efficient.

Workup: Evaluation of the reaction outcome by NMR yield is sustainable as simple evaporation of the solvent at mild temperature is involved. After such a simple process, the desired product is pure enough to continue with the corresponding derivatisations. Therefore, if this diboration reaction is performed at the industrial level, the subsequent reaction can continue in a tandem fashion.

Substrate Scope: At this point, with the newly optimised green reaction conditions in hand, we explored the substrate scope of the reaction. Vinylarenes **1a–c**, **3a–g** provided synthetically useful yields, independently of the electronic and steric properties and substitution on the ring, with isolated yields up to 95% (Scheme 3). The method can engage with nonactivated alkenes **1g**, **3h** and **3i** to obtain the corresponding diols **2g**, **4h** and **4i** in synthetically useful isolated yields, up to 89%. In contrast with previous meth-

odologies, the presence of a protic solvent does not promote the formation of hydroborate byproducts. In addition, the reactivity is not affected by the geometry of internal alkenes. The reaction is completely diastereospecific, with only a single diastereoisomer observed by ¹H NMR spectroscopy. Unfortunately, trisubstituted olefins provided only low to moderate yields. Thus, they were not included in the present sustainable study.



After this broad general scope, we next explored the functional and protecting group compatibility of our methodology (Scheme 3). To our delight, we observed that our sustainable method tolerated alcohol protecting groups like acetyl, 4j, or benzyl, 4k, with isolated yields up to 75%. Interestingly, the carbamate group, **4I**, which can be further functionalised using established lithiation-borylation methodology, resulted in a synthetically useful yield of 69%.¹⁸ On the other hand, ketones, which provided only moderate yields with our amine methodology,^{2v} engaged perfectly under the optimised reaction conditions (e.g., giving 4m). Cyano- and halo-substituted alkenes, which provide a handle to access other groups such as amines or cross-coupling products, delivered good isolated yields, up to 83% (4n, 4o). Unfortunately, not all functional and protective groups are compatible with this methodology. AlcoDownloaded by: University of Liverpool. Copyrighted material.

hol-containing substrates remain unreactive under our optimised reaction conditions. Silicon protecting groups can be used, but the deprotected alcohol product is obtained after derivatisation of the catechol diboronic ester.

Mechanistic Studies: We have performed NMR studies along with theoretical calculations to elucidate the role of the anion in the reaction and to propose a plausible mechanism for the herein developed diboration method.^{2v,19}

However, due to solubility issues, no interaction signals between the B_2cat_2 and the iodide could be found in the ¹¹B NMR spectra when stoichiometric experiments were performed in either THF, water or toluene/water (see the Supporting Information for further details).

DFT Calculations: We selected iodide as the catalyst along with styrene, as a combination of both provided high yields of the diborated product under the optimised reaction conditions.

We envisioned a mechanism for this organocatalytic diboration reaction (Figure 1) in which iodide anion activates the diboron reagent, B_2cat_2 , in line with the previously reported mechanistic proposal by Fernández, Bo and coworkers.^{2e}

Similarly to their study, we identified two transition states (TS1 and TS2) that lead to the formation of the desired diborated product. TS1 in which the nucleophilic sp² moiety of the *in situ* formed B₂cat₂·I⁻ adduct interacts with the unsubstituted carbon of the styrene (most electrophilic carbon) is the most energetically demanding and thus rate determining for the reaction. Electronic factors play a key role in facilitating this demanding nucleophilic attack, as suggested by the difference in energy of approximately 6.5 kcal·mol⁻¹ higher for propylene (see the Supporting Information). This phenomenon is in agreement with our experimental results, since vinylarenes provided slightly better yields than the nonactivated olefins. It is noteworthy to mention that, in contrast to previous organocatalytic reports, although electronic factors stabilise TS1, the competitive hydroboration reaction is not promoted under our developed current reaction conditions.^{2e} Overall, the reaction is exothermic before the iodide catalyst is regenerated.

Importantly, we were able to locate a transition state including Na cation, along with computation of its corresponding B₂cat₂ adduct. Formation of the neutral Na[B₂cat₂I] adduct is energetically favoured, as is the generation of its anionic analogue B₂cat₂·I⁻ [$\Delta E = -15.6$ ($\Delta G = -8.7$) and $\Delta E = -19.8$ ($\Delta G = -9.5$) kcal·mol⁻¹, respectively; see gasphase calculations in the Supporting Information]. In addition, we found that the energy barrier for its nucleophilic addition to ethylene is slightly lower than for B₂cat₂·I⁻, by about 3.0 kcal·mol⁻¹.

In conclusion, we have reported a new methodology for the diboration reaction using inexpensive, sustainable, nontoxic, commercially available halogen salts. We have optimised and designed this methodology to suit all the requirements of the pharmaceutical industry. Our mechanis-



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theory,^{20,21} relative to B₂cat₂-I⁻ adduct plus styrene. tic studies have elucidated the role of the halide anion and we have proposed a plausible catalytic cycle. In conjunction, this work not achy accurate a plausible catalytic cycle in conjunction, this work not achy accurate a plausible catalytic cycle. In conjunc-

we have proposed a plausible catalytic cycle. In conjunction, this work not only provides a greener and more sustainable diboration approach, but also opens the door to further studies aimed at the design and execution of an enantioselective version of the herein reported halogen salt catalysed diboration using chiral cations.

Styrene and substrates containing stabiliser were filtered through silica gel before used. All other fine chemicals were used directly without purification, unless mentioned. Anhydrous solvents were purchased from Acros and used directly or dried by standard methods. Non-anhydrous solvents were degassed by bubbling argon for 30 min. All air- and water-sensitive reactions were carried out in flame-dried glassware under argon atmosphere using standard Schlenk manifold techniques. ¹H and ¹³C NMR spectra were acquired at various field strengths as indicated and were referenced to CHCl₃ (7.27 and 77.0 ppm for ¹H and ¹³C NMR, respectively) or TMS (0.00 ppm for ¹H and ¹³C NMR). ¹H NMR coupling constants are reported in hertz and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift, multiplicity (standard abbreviations) and integration. ¹¹B NMR spectra were recorded with complete proton decoupling using BF₃·OEt₂ (0.0 ppm) as an external standard. Aluminum-backed plates precoated (0.25 mm) with Merck silica gel 60 F254 were used for analytical TLC. Compounds were visualised by exposure to UV light or by dipping the plates in KMnO₄ stain followed by heating. Flash column chromatography was performed using Fluorochem silica gel 60 (40-63 µm).

Catalytic Diboration/Oxidation; General Procedure

An oven-dried Schlenk tube equipped with a stir bar was charged with bis(catecholato)diboron (125 mg, 0.525 mmol) and NaI (7.5 mg, 0.05 mmol) under an inert atmosphere. Degassed toluene (1 mL) and

degassed Milli-Q water (1 mL) were added and the mixture was stirred for 5 min. After this time, an alkene (0.5 mmol) was added under argon. Then, the mixture was warmed to 70 °C and stirred for 14 h. After this time, the Schlenk tube was cooled to r.t. and the volatiles were removed. THF (2 mL) was added and the mixture was cooled to 0 °C, and 3 M NaOH (2 mL) and 30% H_2O_2 (1 mL) were added dropwise to the solution which was stirred for 4 h at r.t. The reaction was then quenched with saturated aqueous $Na_2S_2O_3$ (2 mL). The mixture was extracted with EtOAc (3 × 25 mL). The organic layers were then dried over anhydrous MgSO₄ and filtered, and the solvent was removed by rotary evaporation. The crude material was purified by silica gel chromatography.

1-Phenylethane-1,2-diol

Following the general procedure with styrene (0.5-mmol scale), 1-phenylethane-1,2-diol (57 mg, 83%) was obtained as a white solid; $R_f = 0.19$ (EtOAc/*n*-hexane, 1:1).

¹H NMR (400 MHz, CDCl₃): δ = 7.38 (m, 5 H), 4.86 (dd, *J* = 8.2, 3.5 Hz, 1 H), 3.79 (dd, *J* = 11.3, 3.6 Hz, 1 H), 3.69 (dd, *J* = 11.2, 8.2 Hz, 1 H), 1.90 (br, 2 H).

 ^{13}C NMR (100 MHz, CDCl_3): δ = 140.56, 128.66, 128.15, 126.15, 74.78, 68.19.

Data are in accordance with the literature. (see Supporting Information).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590912.

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