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Cyrene as a Bio-Based Solvent for the Suzuki–Miyaura Cross-Coupling

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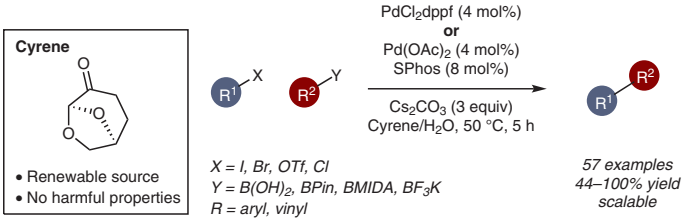

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Abstract The Suzuki–Miyaura (SM) cross-coupling is the most broadly utilized Pd-catalyzed C–C bond-forming reaction in the chemical industry. A large proportion of SM couplings employ dipolar aprotic solvents; however, current sustainability initiatives and increasingly stringent regulations advocate the use of alternatives that exhibit more desirable properties. Here we describe the scope and utility of the bio-derived solvent Cyrene™ in SM cross-couplings and evaluate its suitability as a reaction medium for this benchmark transformation from discovery to gram scale.

Key words boron, cross-coupling, green chemistry, palladium, solvents

Palladium-catalyzed bond-forming reactions are prevalent in the industrial arena and throughout academia.[1–4] Of these reactions, the Suzuki–Miyaura (SM) cross-coupling of organoboronic acids and their derivatives is the most prominent and has firmly established itself as a workhorse reaction within the medicinal chemists toolbox. This is evident in the increasing application of the biaryl motif in the development of druglike fragments.[5,6] The level of utility of this reaction is primarily due to its robustness and the ease of access to various stable boron species as well as the requisite electrophilic species (aryl halides, etc.).[7] Whilst traditionally the SM reaction is operated in polar aprotic solvents, such as 1,4-dioxane, THF, and DMF, the continuing endeavours of the pharmaceutical and agrochemical industries towards safe and sustainable practice call for the replacement of a number of these solvents with alternatives that have a lower perceived risk to both the environment and human health.[8–13]

As such, pharmaceutical companies and academic research groups have designated solvent selection a key area of research, with a selection of tools and guides produced to rank existing solvents, based on risks posed or favourable attributes offered, to aid in the identification of suitable substitutions.[14–20] In general, these guides allow synthetic chemists to evaluate their reaction methods and to adjust accordingly, providing positive steps towards alignment to current regulations, legislation, and advisory guidelines.[21,22] Despite these efforts the integration of sustainability into the discovery pipeline is challenging. The desire to ensure that a testing cascade flows smoothly, with a constant stream of compounds, often leads to the use of less desirable solvents. Solvent optimization is rarely carried out at this stage due to time constraints and, in relation to SM cross-coupling, direct solvent substitution is often difficult with many of the advised alternatives lacking the ability to maintain the generality and robustness with which we have become familiar and that has resulted in the broad application of this transformation.[23–29]

Biomass as a feedstock for solvent production is a growing area of interest within green chemistry,[30–37] with many examples addressing the sustainability movement within Pd-catalyzed cross-coupling.[38–45] Whilst successful research has been carried out with regard to the use of bio-derived solvents within the SM transformation, their application is limited by factors such as scope, the stability and commercial availability of novel catalyst systems, and reduced yields.[23–29]

Dihydrolevoglucosenone (Cyrene™, Figure 1), which can be accessed from cellulose in two steps, has been shown to possess similar physical properties to DMF and other dipolar aprotic solvents and is currently unassociated with any harmful effects.[46–50] Cyrene has recently been shown to be a useful solvent for Sonogashira cross-coupling,[45] urea synthesis,[51] graphene processing,[52] and solid-phase synthesis.[53]

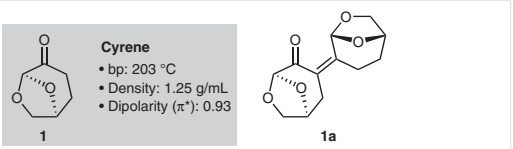
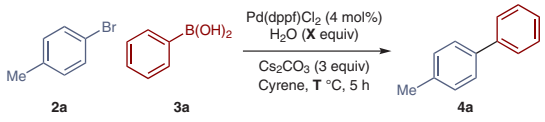


Figure 1 Cyrene (**1**) and its aldol condensation dimer product (**1a**)

Here, we describe the development of general conditions for the SM reaction using Cyrene as the organic solvent medium, whilst providing a balanced viewpoint on Cyrene's capacity to fulfil the criteria which define a successful chemical process on preparative (gram) scale.[54]

We previously reported that Cyrene exhibits sensitivity to inorganic bases under specific reaction conditions (Figure 1).[45] This sensitivity relates to enolization at the carbonyl and subsequent homo-aldol condensation. Although the resultant aldol condensation product **1a** can create issues with reaction mixture homogeneity, the use of inorganic bases such as K_3PO_4, K_2CO_3, or Cs_2CO_3 is necessary to generate the hydroxide needed for both possible catalytic pathways of the SM reaction to take place effectively.[55,56] To investigate the application of Cyrene in the SM reaction, conditions established within our laboratories[57] were employed in the benchmark coupling of 4-bromotoluene with phenylboronic acid (Table 1).

Table 1 Reaction Optimization[a]

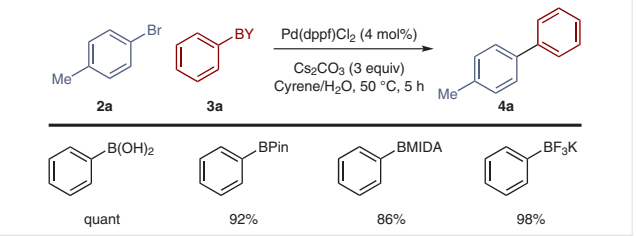


Entry	Reaction conditions	Yield (μ ± σ%)[b]
1	1 mL Cyrene, H_2O (5 equiv), 20 °C	82 ± 16
2	1 mL Cyrene, H_2O (5 equiv), 30 °C	–[c]
3	1 mL Cyrene, H_2O (1.8 mL), 20 °C	81 ± 15
4	1 mL Cyrene, H_2O (1.8 mL), 30 °C	80 ± 12
5	1 mL Cyrene, H_2O (1.8 mL), 50 °C	94 ± 5
6	1 mL DMF, H_2O (1.8 mL), 50 °C	98[d]
7	1 mL THF, H_2O (1.8 mL), 50 °C	92[d]
8	1 mL 1,4-dioxane, H_2O (1.8 mL), 50 °C	100[d]
9	H_2O, 50 °C	31[d]

[a]4-Bromotoluene (1 equiv, 0.25 mmol), phenylboronic acid (1 equiv, 0.25 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol%).
[b]Isolated yield given as an average over four reactions and standard deviation.
[c]Reaction mixture solidified, product was not isolated.
[d] n = 1.

An initial evaluation of inorganic bases (see ESI) identified Cs_2CO_3 (Table 1, entry 1) as the most promising delivering 82% isolated yield. However, replicate reactions failed to deliver consistency. This may be attributed to the variable formation of solid dimer **1a**, resulting in a reaction mixture which was inconsistent with regards to its homogeneity and mobility. However, the addition of water as a co-solvent (Table 1, entry 3; see ESI for full evaluation of H_2O loading) increased fluidity of the reaction mixture, which enabled consistent stirring and prevented solidification when the reaction temperature was increased as observed in Table 1, entry 2. Moving to co-solvent levels of H_2O failed to improve consistency of the isolated yield at 30 °C (Table 1, entries 3 and 4). However, when combined with a further temperature increase (50 °C, Table 1, entry 5) a 94% yield was achieved with considerably reduced variability. The performance of Cyrene was also evaluated vs. conventional solvents (DMF, THF, 1,4-dioxane) under equivalent reaction conditions (Table 1, entries 6–9). Comparable yields were recorded (>90%), whilst the absence of an organic co-solvent, i.e., in neat H_2O, impacted on the isolated yield due to reduced solubility of reaction components (Table 1, entry 9).

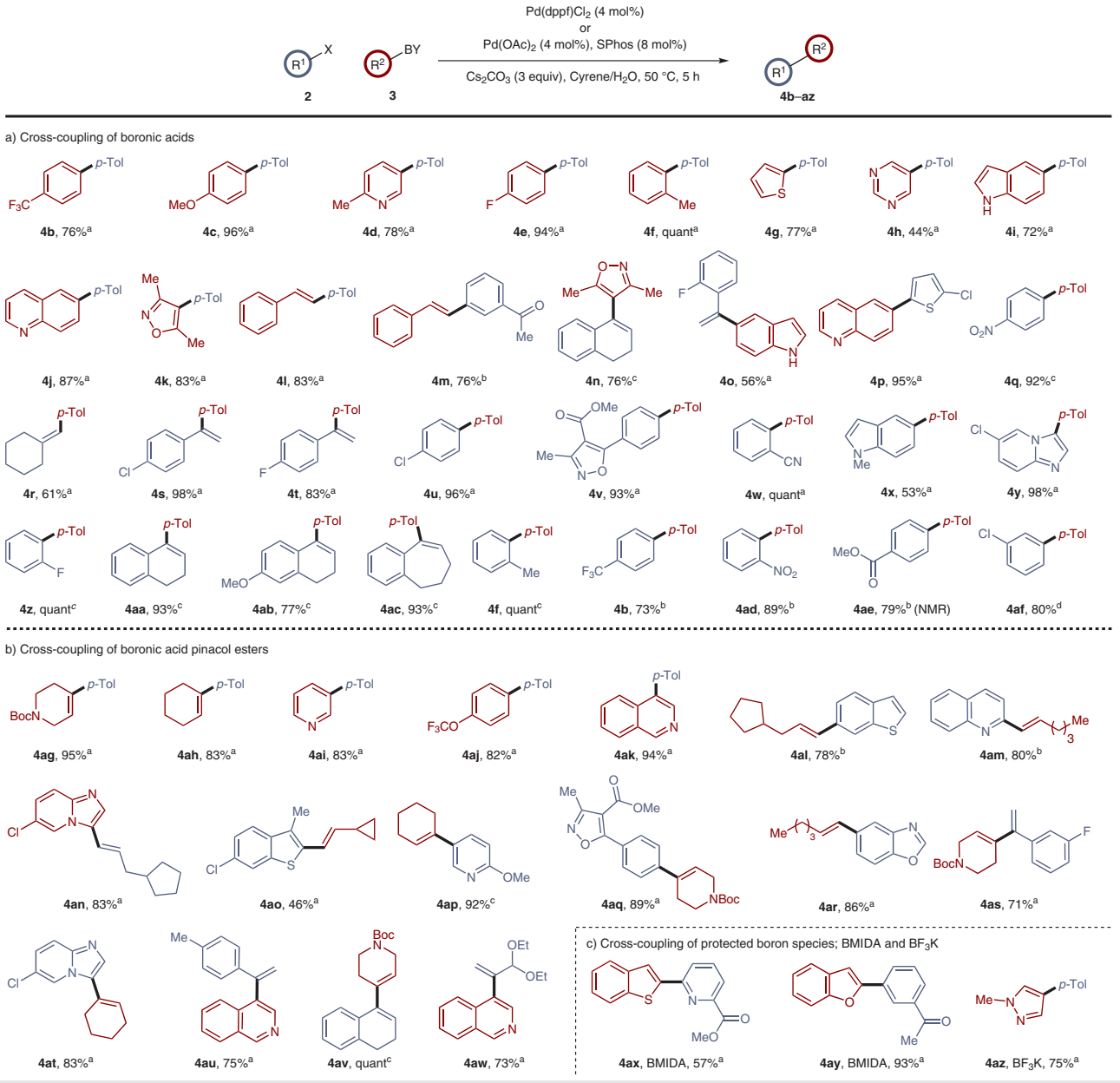
With optimized conditions developed (Table 1, entry 5) we initially assessed several classes of organoboron reagents used routinely for SM cross-coupling (Scheme 1). The Cyrene medium was broadly effective for the coupling of 4-bromotoluene with boronic acid, BPin ester, BMIDA, and BF_3K, delivering the expected product in good yield.



Scheme 1 Cyrene-based Suzuki–Miyaura cross-coupling: scope of organoboron coupling partner. *Reagents and conditions*: bromotoluene (1 equiv, 0.25 mmol), boron species (1 equiv, 0.25 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol%), Cs_2CO_3 (3 equiv, 0.75 mmol), Cyrene (1 mL), H_2O (1.8 mL, 400 equiv), 50 °C, 5 h.

The scope of the reaction manifold was then extensively explored by variation of the organoboron nucleophile and aryl electrophile (Scheme 2). Halides and pseudohalides were broadly successful, and the reaction was tolerant of wide ranging steric and electronic variation on both reaction partners as would be expected of the SM reaction in conventional media (53 examples, 44–100% isolated yield). No particular difficulties were observed and chemical yields were consistent with both literature examples as well as those from our own laboratory in previous studies.[58–62]

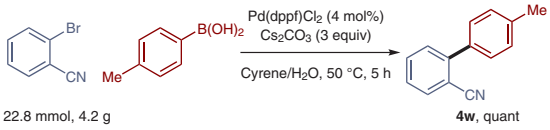
With a view to evaluate the utility of Cyrene within the context of synthesis on a more preparative scale, we selected 4′-methyl-2-biphenylcarbonitrile (OTBN, **4w**) as a target. Compound **4w** is a key intermediate in the synthesis of angiotensin II receptor antagonists (sartans), and can be easily accessed *via* the SM reaction.[63] Following the success of the discovery-scale reaction (0.25 mmol, Scheme 2) we at-



Scheme 2 Cyrene-based SM coupling: substrate scope, isolated yields; [a] X = Br, [b] X = Cl, [c] X = OTf, [d] X = I. *Reagents and conditions*: where X = Br, OTf, I, halide/pseudo halide (1 equiv, 0.25 mmol), boron species (1 equiv, 0.25 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (4 mol%), Cs_2CO_3 (3 equiv, 0.75 mmol), Cyrene (1 mL), H_2O (1.8 mL, 400 equiv), 50 °C, 5 h; where X = Cl, halide/pseudo halide (1 equiv, 0.25 mmol), boron species (1 equiv, 0.25 mmol), $Pd(OAc)_2$ (4 mol%), SPhos (8 mol%), Cs_2CO_3 (3 equiv, 0.75 mmol Cyrene (1 mL), H_2O (1.8 mL, 400 equiv), 50 °C, 5 h.

tempted the synthesis of **4w** on a four-gram (*ca.* 23 mmol) scale (Scheme 3). The overall reaction profile and yield was similar to small scale with quantitative conversion into **4w** recorded.

From a practical perspective, the production of dimer **1a** during reactions using Cyrene could engender issues during purification. Additionally, Cyrene is reported to have a high boiling point (203 °C) with no known azeotropes, which eliminates the possibility of distillation, except possibly at reduced pressure. On a small scale these issues are more easily overcome through chromatographic purification.



Scheme 3 Gram-scale synthesis of OTBN, **4w**

Chromatographic purification is less feasible at larger scales; however, the addition of a medium polarity solvent mixture (40% EtOAc in petroleum ether) facilitates the precipitation of **1a**, which can then be removed *via* filtration, while aqueous washing allows removal of residual Cyrene and enables extraction of the product. For example, in the case of **4w** above (Scheme 3), the product was isolated analytically pure using this precipitation/washing method without the requirement of chromatography. In the context of waste generation/disposal, the formation of **1a** precludes recovery and reuse of Cyrene and so this must be disposed of; safety information regarding **1a** is not currently available.

In summary, we have developed a mild method for the SM reaction, which employs Cyrene as a direct alternative to conventional solvents (DMF, THF, 1,4-dioxane).[64] The conditions developed demonstrate excellent generality and functional group tolerance with high yields obtained on both small and larger scale synthesis. Physical and chemical properties affecting recovery and disposal of Cyrene raise concerns over the impact on environmental criteria. Notwithstanding these issues, the bio-derived nature of Cyrene in addition to its innocuous attributes are attractive with respect to sustainability and safety guidelines when compared to solvents such as DMF, and should not be overlooked as a potential alternative.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589143.

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(64) **General Procedure for Suzuki–Miyaura Coupling in Cyrene**
To an oven dried 5 mL microwave vessel was added $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol%), halide/pseudohalide (1 equiv), boron coupling partner (1 equiv), and Cs_2CO_3 (3 equiv). The vessel was then capped and purged with N_2 before addition of Cyrene (1 mL, 0.25 M) and H_2O (1.8 mL). The reaction mixture was heated to 50 °C and maintained at this temperature with stirring for 5 h before the vessel was vented and decapped. The solution was then diluted with Et_2O (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (silica gel) to afford the title compound.
4-Phenyltoluene (4a)
Prepared according to the General Procedure using $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene **2a** (42.8 mg, 0.25 mmol, 1 equiv), phenylboronic acid (**3a**, 30.5 mg, 0.25 mmol, 1 equiv), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in PE) to afford the title compound as a white solid (42.9 mg, quant). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (dd, *J* = 8.3, 1.2 Hz, 2 H), 7.53 (d, *J* = 8.1 Hz, 2 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.38–7.33 (m, 1 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 2.43 (s, 3 H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 141.2, 138.4, 136.9, 129.5, 128.7, 126.9, 21.1.