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Transforming Suzuki–Miyaura Cross-Couplings of MIDA Boronates into a Green Technology: No Organic Solvents

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Supporting Information

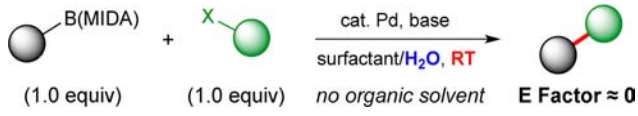
ABSTRACT: New technology has been developed that enables Suzuki–Miyaura couplings involving widely utilized MIDA boronates to be run in water as the only medium, mainly at room temperature. The protocol is such that no organic solvent is involved at any stage; from the reaction through to product isolation. Hence, using the *E* factor scale as a measure of greenness, the values for these cross-couplings approach zero.

As illustrated in a review by Snieckus and Colacot tracing the development of Pd-catalyzed cross-coupling reactions leading up to the Nobel Prizes in 2010, the Suzuki–Miyaura coupling was the most heavily used among these name reactions in the past decade, by far.[1] Notwithstanding its extraordinary popularity,[2] such highly valued C–C bond-forming processes,[3] typically run under homogeneous conditions, come with an associated heavy price from the environmental perspective. Oftentimes conditions for such couplings involve mixed, aqueous solvent systems (that make solvent recovery costly), excess of a coupling partner, and heat to drive reactions to completion. Moreover, boronic acids or their boronate derivatives may afford byproducts resulting from homocoupling or protio-quenching.[2] This material is in addition to the solvents used that make up, in general, the vast majority of organic waste produced by the chemical enterprise.[4]

One addition to the portfolio of organoboron intermediates that has found widespread acceptance[5,6] in organic synthesis involves *N*-methyliminodiacetic acid (MIDA) boronates, developed extensively by Burke.[7] They offer several positive features associated with their use, including air stability and crystallinity, two virtues that the pharmaceutical industry, in particular, finds appealing. With notoriously unstable 2-heteroaromatic substituted systems, the 2-pyridyl system in particular, slow release to their corresponding boronic acids allows for couplings that otherwise have a history of either limited utility or complete failure.[8]

Along with these properties, however, come their attendant limitations and/or associated disadvantages that are nontrivial, especially from the standpoint of "greenness".[4b] Aside from the typical conditions that rely on a large excess of base (5–7 equiv) and heat (60–100 °C) to gradually release the corresponding boronic acids and the low molarities involved (0.01–0.13 M), the solvent systems characteristic of these couplings are partially aqueous.[8,9] In some cases, the requirement for a solvent such as DMF makes the coupling highly undesirable from a safety, health, and environmental perspective.[8b] And just as certain organic solvents have been essentially removed from use (e.g., benzene and CCl_4), and others such as chlorinated solvents discouraged, so is DMF apparently destined to realize a similar fate.[10] Hence, it behooves the synthesis community to work toward not only reliance on safer solvents but also on greener solvents. Indeed, this goal is a priority in most industrial circles, including the Pharmaceutical Roundtable associated with the ACS Green Chemistry Institute.[11]

Our efforts of late have focused on development of alternative, nontraditional approaches to reactions that are heavily utilized by both academic and industrial laboratories worldwide. The goal continues to be to "get organic solvents out of organic reactions," utilizing nanoparticles composed of environmentally benign amphiphiles that allow cross-couplings and related metal-mediated reactions to take place in water and without heating or cooling.[12] In this report, we disclose new technology that enables MIDA boronates to participate in Suzuki–Miyaura couplings where the required release of boronic acids occurs in water at room temperature (RT, 23 °C). Indeed, the overall process, including workup, can be done in the complete absence of organic solvents. Based on the most commonly employed yardstick of Sheldon and co-workers as a measure of greenness, therefore, these reactions take place with associated *E* factors approaching zero.[4b,13]



An initial coupling involving a 1:1 stoichiometry of *p*-tolyl MIDA boronate **1** and 5-bromopyrimidine was performed in aqueous nanomicelles composed of commercially available designer surfactant TPGS-750-M[14] at RT (Scheme 1). In the presence of palladium catalyst Pd(dtbpf)Cl_2 (2 mol %), along with Et_3N (3 equiv), and over a 24 h period, the adduct could be isolated by diluting the reaction mixture with water and filtering off the desired product. Using this simple procedure, the coupling product could be isolated in 82% yield in >95% purity (by ^{1}H NMR); alternatively, a 90% yield could be achieved using traditional methods by filtering through a plug of silica with organic solvent. This example was conducted on a gram scale, achieving a 74% isolated yield using only 8 mL of H_2O for the

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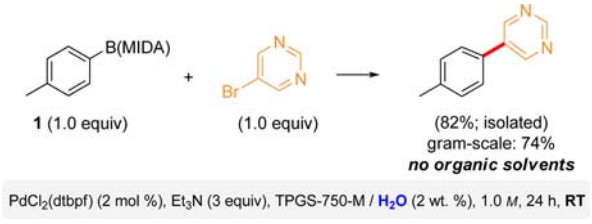
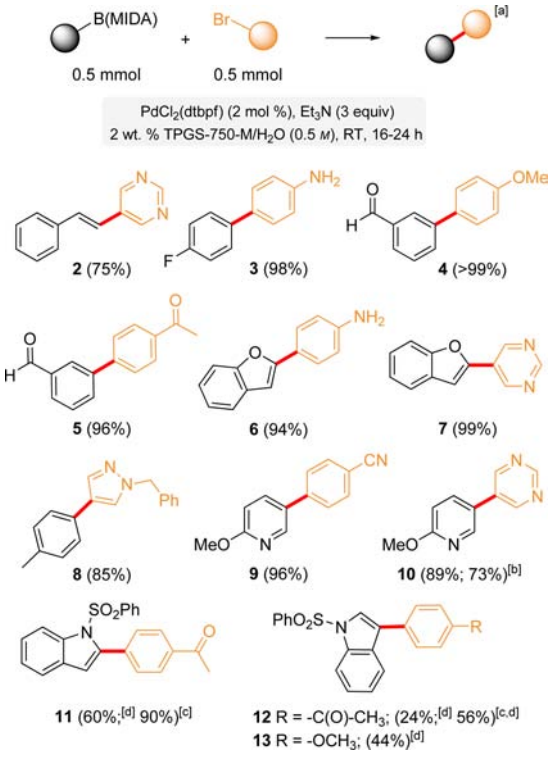
Scheme 1. Initial Coupling Between a MIDA Boronate and a Heteroaryl Bromide



filtration procedure; hence, an *E* factor of 6.5 if water is considered as waste.

Reaction variables were screened using an alkenyl MIDA boronate, where the desired product **2** was isolated in 75% yield (Scheme 2). The yield of coupling product **2** could be increased

Scheme 2. Representative Cross-Couplings of MIDA Boronates and Aryl/Heteroaryl Bromides in Water at RT



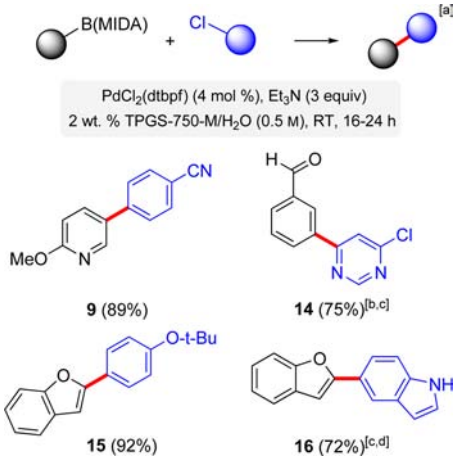
[a]Isolated yield after filtration; product determined to be >95% pure by ^{1}H NMR. [b]The free boronic acid derivative was used (1 equiv). [c]Reaction was performed in an oil bath at 40 °C. [d]Purified by column chromatography via Biotage.

to 92% using additional MIDA boronate (1.2 equiv). Inorganic bases (e.g., Na_2CO_3 or K_2CO_3) led to <5% of the product. Other organic bases such as triisobutylamine were totally unproductive. Triethylamine, therefore, was chosen for further studies given both its low cost and effectiveness. Unlike traditional MIDA boronate couplings oftentimes run in organic media at low molarities (e.g., 0.07 M),[8] a global concentration of 0.5 M was characteristic of all couplings preformed in these nanoreactors. Reactions could also be run at 1.0 M with similar yields, but on a small scale they were more difficult to monitor. Commercially available surfactants other than TPGS-750-M were evaluated, including Triton X-100, Brij 35, Solutol H15, and TPGS-1000 (vitamin E TPGS). Each led to a reasonable level of conversion under otherwise identical conditions (69−89%; see SI). Although TPGS-1000 and TPGS-750-M afforded comparable results, the former surfactant contains natural vitamin E and, therefore, is far more expensive than is TPGS-750-M.

Several combinations of aryl MIDA boronates and aryl bromides, in the same 1:1 ratio, were then exposed to these conditions to assess the scope of this mild cross-coupling process. Most biaryl products illustrated in Scheme 2 were formed in high isolated yields, regardless of the electronic nature of the substituent(s) on either ring. By contrast, use of the free boronic acid, e.g., leading to product **10**, afforded only a 73% yield vs 89% using the corresponding MIDA boronate. Coupling of an *N*-sulfonylindole bearing a MIDA boronate at the 3-position was unexpectedly sluggish, requiring mild heating to 40 °C just to form **12** in 56% yield. Changing the nature of the coupling partner with the 3-MIDA boronate to *p*-bromoanisole, likewise, led to biaryl **13** in a modest 44% yield. The corresponding 2-MIDA boronate, however, showed no such problem, leading upon filtration to the desired biaryl **11** in 90% isolated yield.

Aryl/heteroaryl chlorides are also amenable to coupling under these conditions. In some cases (**9**, **15**, **16**) an increase in catalyst loading to 4 mol % was necessary to achieve full conversion (Scheme 3). Initial trails using 2 mol % catalyst led to biaryl **15** in

Scheme 3. Representative Cross-Couplings of MIDA Boronates and Aryl/Heteroaryl Chlorides in Water at RT



[a]Isolated yield after filtration; determined to be >95% pure by ^{1}H NMR. [b]Two mol % Pd catalyst. [c]Purified by column chromatography via Biotage. [d]Performed in an oil bath at 40 °C.

only 45% yield, the remaining mass being unreacted starting materials. Attempts to use an excess of either partner leading to products **9** and **15** had little overall impact. Heterocyclic chlorides bearing electronically neutral, deactivated, and activated cases participate smoothly. A product such as biaryl **14** is attractive as it possesses two functional groups available for further manipulation.

Interestingly, there is no reported study on couplings of aryl bromides with MIDA boronates. Nonetheless, the underlying presumption is oftentimes that since aryl chlorides react to afford good isolated yields of biaryls, such will be the case with aryl bromides. However, we have previously observed, e.g., that conditions telescoped for Miyaura borylations of chlorides do not translate to bromides,[8c] and this situation appears to apply as well to MIDA boronates. As illustrated in Table 1, the coupling

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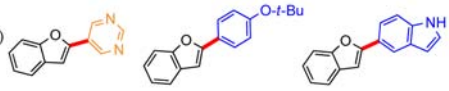
Table 1. Comparison Reactions Conducted at RT for 24 h

reaction conditions	7[a]	15[a]	16[a]
$PdCl_2$(dtbpf) (2 mol %), Et_3N (3 equiv) 2 wt. % TPGS-750-M/H_2O (0.5 *M*), rt	99%	92%[b]	53%[b]
$Pd(OAc)_2$ (2 mol %), SPhos (2 mol %) dioxane:H_2O (5:1), K_3PO_4 (3 equiv), rt	27%	12%[b]	trace[b], 82%[c]
$Pd(OAc)_2$ (5 mol %), SPhos (10 mol %) dioxane:H_2O (5:1), K_3PO_4 (7.5 equiv), rt	60%	24%	32%

[a] Isolated yield [b] 4 mol % $PdCl_2$(dtbpf) [c] Recovered Ar-Cl

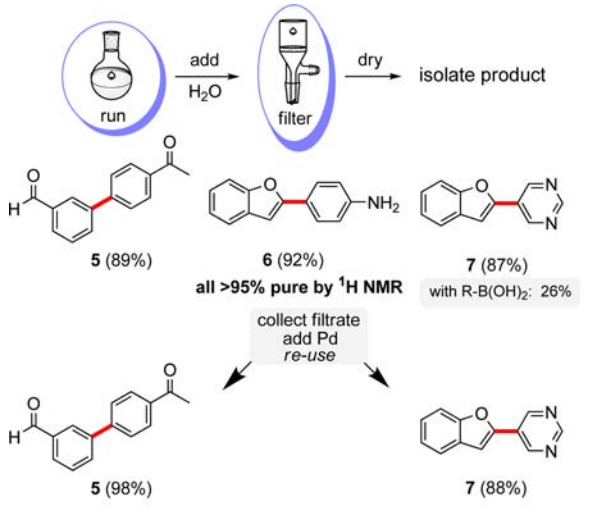


7 (from Ar-Br) **15** (from Ar-Cl) **16** (from Ar-Cl)

reaction under micellar conditions involving an aryl bromide gave a high yield of product **7**. Switching to literature conditions[8a] as to the source of Pd, ligand and solvent (aqueous dioxane) gave poor results (27%). Even by increasing the amount of Pd, ligand, and base, as prescribed for aryl chlorides in a dioxane/water mix,[8a] only a modest yield (60%) was obtained. The same trend holds with aryl chlorides, leading to biaryls **15** and **16**.

Following filtration of the diluted reaction mixture leading to product isolation, the aqueous filtrate can be recycled. As illustrated in Scheme 4, once an initial coupling is completed

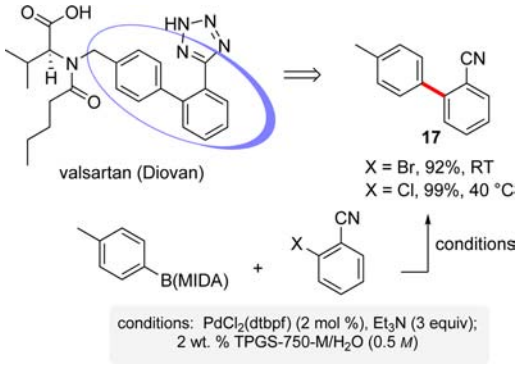
Scheme 4. Sequence for Organic Solvent-Free Suzuki–Miyaura Reactions: Couple/Filter/Recycle



(e.g., to give **5**, **6**, or **7**; additional substrates in SI), each product can be isolated by the dilution/filtration protocol. Upon addition of TPGS-750-M so as to bring its level back to 2 wt %, the aqueous solution could be recycled to regenerate biaryls **5** and **7**, which were again isolated using the same dilution/filtration sequence. Clearly, the palladium catalyst must be retained in the aqueous phase, in all likelihood assisted by the MIDA salt acting as ligand.[15,16] Each of these products was formed with an associated *E* factor close to zero.

One application of this green chemistry focuses on the sartan family of drugs, e.g., valsartan (Diovan), which is therapeutically useful in treating congestive heart failure and high blood pressure (Scheme 5).[17] The biaryl core is a common intermediate and should be derivable from a cross-coupling between 4-tolyl MIDA boronate and 2-bromobenzonitrile. Indeed, biaryl product **17**

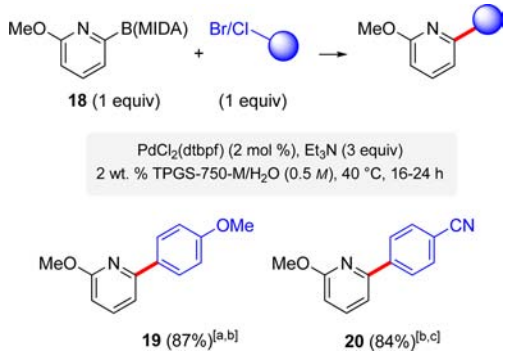
Scheme 5. Synthesis of the Biaryl Core within Valsartan



could be obtained in water at RT uneventfully in 92% isolated yield. 2-Chlorobenzonitrile can also be utilized as a coupling partner, albeit with mild heating to 40 °C, to arrive at **17** in essentially quantitative isolated yield.

Lastly, a 2-pyridyl MIDA boronate has been tested to determine whether this class of particularly challenging coupling partners might be amenable to micellar catalysis. The 2-pyridyl subunit is especially common in pharmaceuticals,[18] natural products,[19] and materials.[20] Although only a single example (**18**; Scheme 6) has as yet been screened, it reacted with remarkable

Scheme 6. Preliminary Examples Using a 2-Pyridyl MIDA Boronate in Suzuki–Miyaura Couplings in Water



[a]The coupling partner was the corresponding aryl bromide. [b]Isolated yield after filtration; product determined to be >95% pure by ^{1}H NMR. [c]The coupling partner was the corresponding aryl chloride.

facility with both an electron-rich and -poor aryl halide. Biaryls **19** and **20** were formed in good isolated yields using stoichiometric amounts of each partner, in water at 40 °C. By contrast, the traditional method includes 0.5 equiv of copper in the pot,[21] an alcohol additive, an excess of MIDA boronate, and is run in DMF at 100 °C.[8b]

In summary, nanoreactors composed of an engineered surfactant in water enable Suzuki–Miyaura couplings involving MIDA boronates to be run efficiently in the complete absence of organic solvents using a simple couple/filter/recycle sequence. The huge excesses of heavy, inorganic bases in reaction mixtures consisting of water and organic solvents that require heating in these traditional couplings can now be replaced by very mild and green conditions. Further studies on couplings involving a variety of 2-pyridyl MIDA boronates of high relevance to the pharmaceutical industry are in progress and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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