



Cite this: *Green Chem.*, 2024, **26**, 10115

Environmentally friendly Miyaura Borylations allowing for green, 1-pot borylation/Suzuki–Miyaura couplings†

Chandler B. Nelson, Scott J. L'Heureux, Madison J. Wong, Simone L. Kuhn, Erika Ghiglietti and Bruce H. Lipshutz *
 *Correspondence: lipshutz@chem.ucsb.edu

Current routes to boronic acids and their corresponding esters to be used in subsequent Suzuki–Miyaura (SM) cross couplings impact the cost, waste, and safety concerns associated with generating these materials. A new method for installing the ethyl pinacol boronic ester, or B(Epin) derivative leads to stable borylated products under near-neat conditions using high concentrations of a green solvent and moderate reaction temperatures, catalyzed by relatively low palladium loadings. Alternatively, the newly fashioned Ar–B(Epin) can be generated *in situ* and used directly in the same pot for SM reactions leading to aromatic and heteroaromatic residues characteristic of the biaryl products being formed. An array of complex targets, including API-related products, can be generated *via* this green and environmentally responsible methodology.

Received 27th June 2024,
 Accepted 29th August 2024
 DOI: 10.1039/d4gc03115f
rsc.li/greenchem

1 Introduction

There are few chemical processes as omnipresent as the Suzuki–Miyaura (SM) coupling in modern organic synthesis. In fact, decades after the watershed paper by Suzuki and Miyaura¹ the reaction was reported to be the second most utilized transformation in the pharmaceutical industry.² Beyond this, the SM coupling has also been extensively used in the synthesis of agrochemicals,^{3–6} natural products,^{7–10} and in organic materials.^{6,11–13} Nonetheless, in cases where such a transformation has seen such widespread use due to its value to so many chemical processes, the cost, waste, hazards, and environmental impact^{14–18} associated with its use can also be considerable. While several recent developments serve to greatly improve the efficiency and environmental responsibility of the SM coupling reaction,^{19–23} a major hurdle that remains is the traditional manner in which the required boronic acid or ester coupling partner is obtained. While the Miyaura borylation²⁴ is an attractive alternative to commonly used cryogenic lithium halogen exchange protocols,^{25,26} or C–H activation procedures involving non-sustainable levels of iridium-based catalysis,^{27–29} it often necessitates high loadings of palladium,^{24,30–32} high temperatures,^{30,32–35} and the use of relatively dilute and waste-generating organic solvents.^{30,32,33}

Moreover, the prepared boronic esters or acids can be difficult to isolate, and have varying shelf lives and stabilities.^{36–38}

Each of these factors serve to increase the expense, energy demand, reliance on petroleum feedstocks, and organic waste associated with performing critical sp^2 – sp^2 couplings, which are typically biaryl in nature. Hence, there is a definitive need for a more reliable and more environmentally responsible borylation protocol that not only allows for ease of preparation, but also is applicable to use in subsequent “green” 1-pot SM couplings that are environmentally friendly (Fig. 1).

Among the recent advances towards more efficient Miyaura borylations, installation of the boronic acid residue *via* Pd-catalyzed couplings with bis-boronic acid (BBA) are perhaps the most favored.^{39,40} This is likely due to its reliance on moderate-to-low catalyst loadings, reasonable reaction temperatures (40–80 °C), and relatively green solvents (e.g., 2-MeTHF and EtOH). However, when these newly prepared boronic acids are then applied to 1-pot SM couplings, catalytic efficiency typically drops and loadings of 1 mol% or greater tend to be

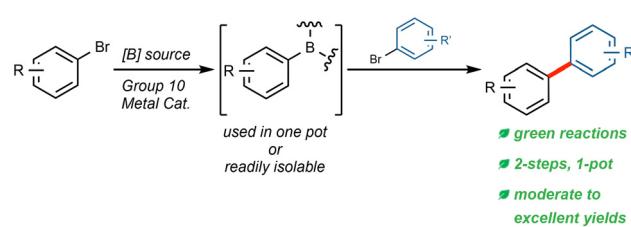


Fig. 1 Borylation/Suzuki–Miyaura couplings.

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA. E-mail: lipshutz@chem.ucsb.edu, chandernelson@chem.ucsb.edu

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4gc03115f>

required,^{39,40} especially in cases involving highly functionalized substrates. Furthermore, though seemingly more atom economical, significant excesses of BBA are employed.^{39,40} Importantly, BBA is also known to decompose readily in the presence of heat, oxygen, Pd(II) species, and moisture.^{41,42} Beyond complicating handling, such decomposition can generate hydrogen gas posing significant safety concerns at scale.^{41,42} Additionally, the use of these generated boronic acids can be prone to protodeborylation and other unwanted side products,^{43,44} thereby lowering the efficiency of the overall process and requiring a potentially tedious separation.

The effect of base on Miyaura borylations is yet another notable area where recent improvements involving use of sterically hindered and electron-rich carboxylates allow for benign reaction conditions and more attractive palladium loadings.^{45,46} Work to date using this technology, however, lacks substrate complexity, and has shown limited options for use in 1-pot carbon–carbon bond formation.^{45,46} Hence, it is apparent that there exists a need for a green (and hence, safer), benign borylation protocol that provides access to stable, and if desirable, isolable borylated products that can also be formed *in situ* and used directly in 1-pot Suzuki–Miyaura couplings.

2 Results and discussion

2.1 Optimization

Initial optimization leading to a general and green borylation protocol focused on the use of micellar catalysis, where low loadings of Pd catalysis are available and lead to highly efficient couplings, even involving challenging educts.^{20,47} Utilization of bis(ethylpinacolato)diboron ($B_2\text{Epin}_2$) was selected, as a recent communication highlights the enhanced stability (when compared to boronic acid and Bpin derivatives) of these analogous boronic esters to water, as well as their reported ease of isolation and improved yields of SM couplings under traditional reaction conditions.⁴⁴

Initial ligand screening utilized potassium acetate, which is used broadly for Miyaura borylation procedures,^{24,30} along with 4-bromoanisole as a model substrate. Both AmPhos⁴⁸ and $t\text{-Bu}_3\text{P}$ (as its $[t\text{-Bu}_3\text{PH}]BF_4$ complex)⁴⁹ emerged as effective ligands on palladium for selectively producing the borylated Epin-containing product, along with only trace amounts of undesired homocoupled material (Table 1).[‡]

A comprehensive screening of bases (Table 2)[‡] that included potassium triphosphate and potassium t -butoxide both led to significant levels of homocoupling. Use of potassium fluoride, although indicative of a good preference for the desired borylated product, led to a limited extent of conversion. Surprisingly, the electron-rich and sterically bulky potassium 2-ethylhexanoate (2-KEH), which has recently been shown to improve Miyaura borylations,^{41,46} differentiated the two

[‡] For the complete list of screened ligands and bases, see the ESI.†

Table 1 Ligand optimization

Entry ^a	Ligand	Yield ^b (A%)	
		(A)	(B)
1	QPhos	46	9
2	$[t\text{-Bu}_3\text{PH}]BF_4$	80	Trace
3	DPPF	38	Trace
4	XPhos	25	Trace
5	SPhos	26	Trace
6	DPPP	Trace	Trace
7	EvanPhos	Trace	Trace
8	AmPhos	82	Trace
9	DavePhos	42	Trace
10	RuPhos	36	Trace

^a Reactions run on a 0.25 mmol scale. ^b Yield determined *via* qNMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 2 Base optimization

Entry ^a	Ligand	Base	Yield ^b (A%)	
			(A)	(B)
1	$[t\text{-Bu}_3\text{PH}]BF_4$	KOAc	80	Trace
2	$[t\text{-Bu}_3\text{PH}]BF_4$	K_2CO_3	40	10
3	$[t\text{-Bu}_3\text{PH}]BF_4$	KF	34	Trace
4	$[t\text{-Bu}_3\text{PH}]BF_4$	K_2HPO_4	78	Trace
5	$[t\text{-Bu}_3\text{PH}]BF_4$	K_3PO_4	Trace ^c	Sig. ^c
6	$[t\text{-Bu}_3\text{PH}]BF_4$	2-KEH ^d	60	Trace
7	$[t\text{-Bu}_3\text{PH}]BF_4$	<i>t</i> BuOK	19	33
8	$[t\text{-Bu}_3\text{PH}]BF_4$	TEA	27	25
9	AmPhos	NaOAc	Trace ^c	Trace ^c
10	AmPhos	K_2HPO_4	73	8
11	AmPhos	2-KEH ^d	87	Trace

^a Reactions run on a 0.25 mmol scale. ^b Yield determined *via* qNMR using 1,3,5-trimethoxybenzene as an internal standard. ^c Qualitative assessment based off TLC of crude reaction mixture (“sig.” = significant). ^d Potassium 2-ethylhexanoate.

ligands: use of $[t\text{-Bu}_3\text{PH}]BF_4$ performed markedly worse, while the yield using the AmPhos ligand-based catalytic system improved, leading to sole employment of pre-ligated Pd (AmPhos)₂Cl₂ going forward.⁵⁰

Use of 2-KEH led to another remarkable observation: heating the reaction contents containing 2-KEH and $B_2\text{Epin}_2$ to 55 °C led to a readily stirred solution, suggesting that solvent-free, or highly concentrated reaction mixtures might be

amenable. To test such conditions, solid 5-bromo-1-methyl-1*H*-indole was selected for this study. In the event, a high level of conversion and selectivity for the borylated product was realized by simply adding small amounts of EtOAc to facilitate stirring. Notably, a Pd. catalyst loading of only 0.25 mol% was needed.

2.2 Scope of Ar-BEpin products

The application of our optimized method using AmPhos allowed for the installation of the desired BEpin boronic ester to an array of functionalized (hetero)aryl halides. The moderate temperature of 55 °C, low palladium loading of 0.25 mol%, and concentrated EtOAc [2.5 M] led to moderate to excellent yields.

Noteworthy is the application to several heteroaromatic compounds, and that each substrate was stable and isolable by column chromatography. There is no readily apparent trend between moderately electron-poor or -rich substrates; however, certain highly electron deficient substrates gave poor conversion (see compound **14** in Fig. 2). It is hypothesized that in substrates with heteroatoms that can coordinate to the catalyst (see compound **15** in Fig. 2), such coordination likely poisons the catalyst and is, thus, deleterious to conversion. Furthermore, *ortho* substitution provides significant steric hindrance towards installing the bulky ethyl pinacol boronic ester (see compound **16** in Fig. 2). Using 1-bromonaphthalene as a model for steric impedance, Fig. 3 shows that increasing reaction temperatures can overcome the activation barrier in such cases. At highly elevated temperatures (≥ 85 °C), however, competing side product (e.g. protodeborylation) formation was observed *via* proton NMR.

2.3 Highly functionalized Ar-B(Epin) products

Borylations of highly functionalized substrates, such as **X3** from the Merck Informer Library,⁵¹ indomethacin, and the precursors for abemaciclib^{52,53} and erdafitinib,⁵⁴ required somewhat extended reaction times (24–48 h), a higher palladium loading (0.5 mol%), and/or higher reaction temperatures (70 °C). Moreover, these higher molecular weight substrates often required slight dilution to maintain stirring. Nonetheless, the BEpin moiety could be installed effectively for each of these complex substrates, further highlighting this method's applicability towards APIs and late-stage functionalized molecules. The scope of functionalized substrates (Fig. 4) includes selected aryl chlorides (see products **17** and **19** in Fig. 4), although, in harmony with recent literature,^{36,40} replacement of AmPhos with XPhos proved more amenable for aryl chlorides, loratadine and perphenazine (**20** and **21**).

2.4 Comparisons with existing literature

As illustrated in Table 3, several substrates were used for comparison purposes with existing literature procedures. Products **1**, **22**, and **18** show clear improvements in terms of yield, sustainability, and potentially, cost. In general, the need for dilute environmentally egregious solvents like dioxane^{55,56} is obviated, while metal economy is amply documented, *e.g.*,

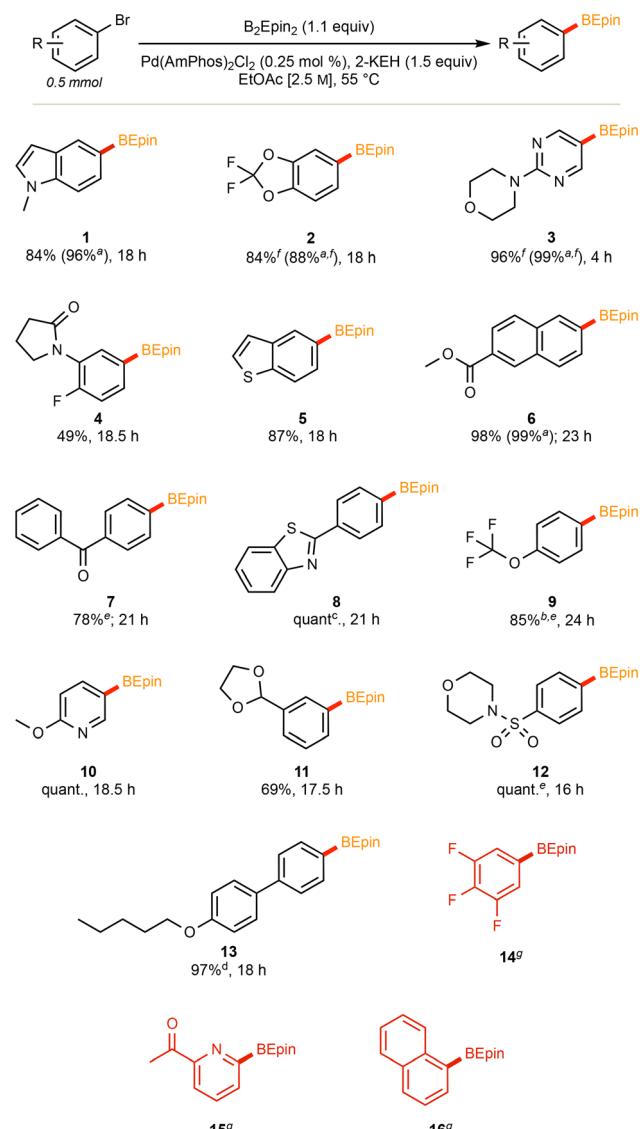


Fig. 2 Scope of Ar-BEpin products. ^a Yield determined *via* qNMR using 1,3,5-trimethoxybenzene as an internal standard. ^b Utilized 0.5 mol% of Pd. cat. (Pd : P 1 : 4). EtOAc conc. of [1.25 M]. ^c Dilution to [1.67 M] EtOAc ^d 2 mmol scale. ^e 0.3 mmol scale. ^f 0.25 mmol scale. ^g Unsuccessful substrate.

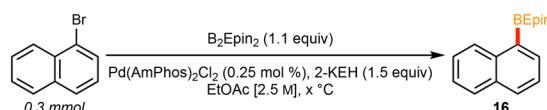
with **18** being made using twenty times less palladium than the industrial process.⁵⁷

2.5 1-Pot cross electrophile couplings

By far, access to borylated aromatics and other sp^2 -containing C–B bonds is for use in SM couplings.^{2–13} Developing a 1-pot protocol towards this goal, however, proved to be more challenging than initially anticipated.

The obvious choice regarding the medium for performing the SM coupling was the use of aqueous micellar catalysis, given procedures already in hand.^{20,47}

Best results were obtained, therefore, when a different ligand (SPhos; 0.5 mol%) was added in the second, SM step.



Effect of temperature on conversion for a sterically hindered substrate

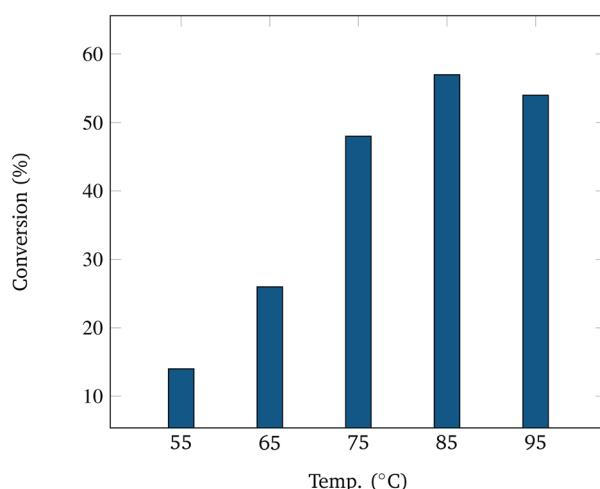


Fig. 3 Temperature study Effect of temperature on conversion for a sterically hindered substrate (^1H NMR conversions).

Unfortunately, with the exceptions noted in Fig. 5, the presence of excess B_2Epin_2 left over from the first reaction would borylate the bromide having been added in the second step, resulting in significant homocoupling of this halide.

Table 3 Comparisons with existing literature

This work	Literature
$\text{R} = \text{Et}$ 0.25 mol% 55 °C EtOAc [2.5 M] overnight (18 h) 84% (96%) ^d	$\text{R} = \text{Me}$ 1 mol% 90 °C dioxane [0.68 M] overnight (18 h) 87% ^a
$\text{R} = \text{Et}$ 0.5 mol% 55 °C EtOAc [1.5 M] 24 h 91%	$\text{R} = \text{Me}$ 5 mol% 100 °C dioxane [0.27 M] 90 min 60% ^b
$\text{R} = \text{Et}$ 0.5 mol% 55 °C EtOAc [1 M] 44 h 84%	$\text{R} = \text{Me}$ 10 mol% 100 °C DMSO [0.33 M] 16 h 73% ^c

^a Selvita Pharmaceuticals patent (2016).⁵⁵ ^b Astex Pharmaceuticals patent (2012).⁵⁶ ^c Pfizer patent (2019).⁵⁷ ^d Yield determined *via* qNMR using 1,3,5-trimethoxybenzene as an internal standard.

Increasing the equivalents of the second bromide added led to low levels of conversion. Attempts at utilizing different ligands, loadings of palladium, bases, surfactants, temperatures, and concentrations also proved to be ineffective.

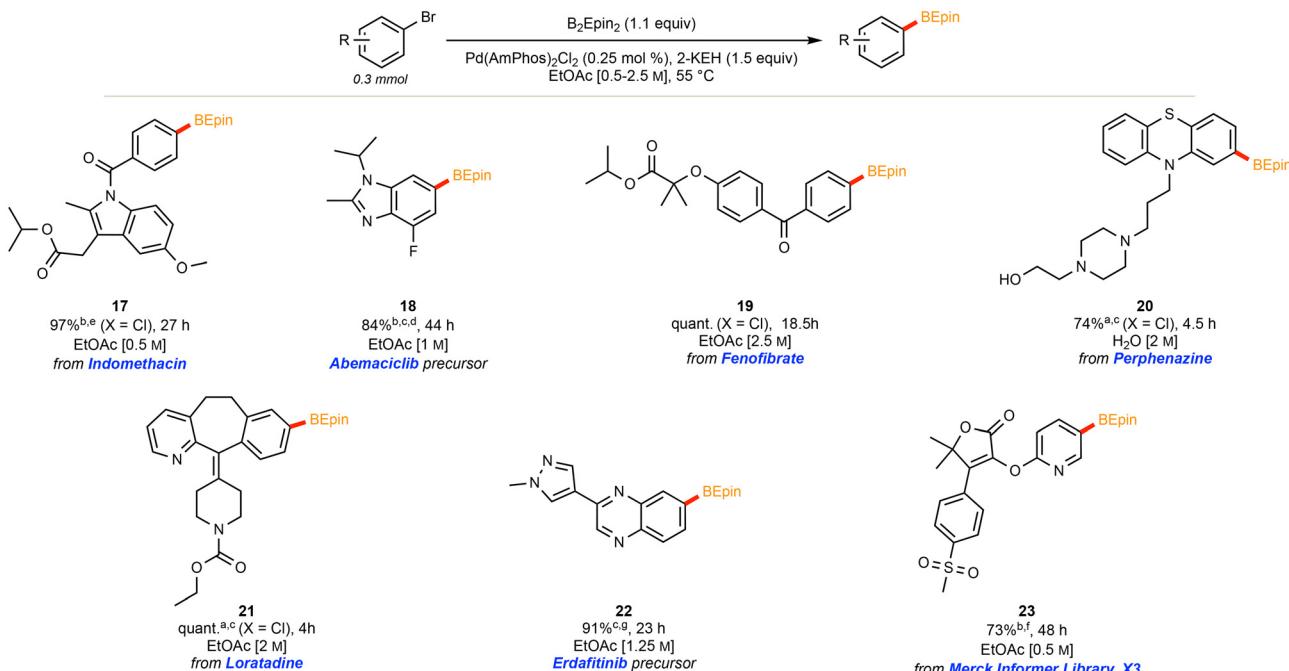


Fig. 4 Scope of highly functionalized Ar–B(Epin) products. ^a XPhos utilized. ^b Utilized 0.5 mol% of Pd. cat. ^c (Pd : P 1 : 4). ^d 70 °C. ^e 0.25 mmol scale. ^f 0.2 mmol scale. ^g 0.125 mmol scale.

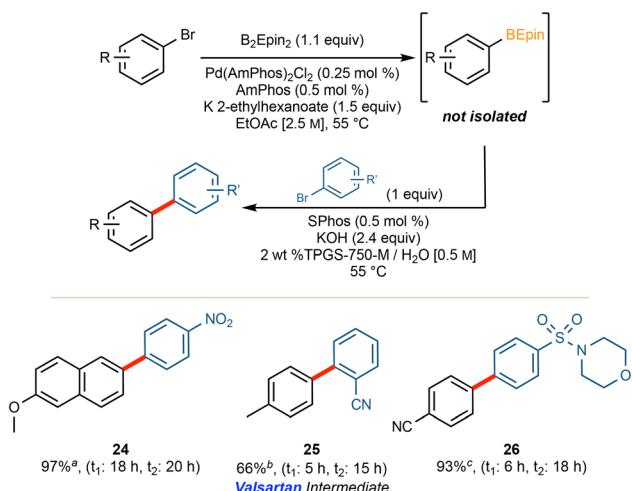


Fig. 5 Initial studies of 1-pot cross-couplings with TPGS-750-M. ^a Run on a 0.5 mmol scale with 0.8 equiv. of bromide in the SM coupling. ^b Run on 0.3 mmol scale; conc. of [0.25 M] and 3 equiv. of K_3PO_4 in SM coupling. ^c Run on a 0.25 mmol scale.

Notwithstanding these setbacks, where applicable, use of TPGS-750-M does allow for a 1-pot process that relies only on water, concentrated EtOAc, reaction temperatures of 55 °C, and an overall palladium loading of only 0.25 mol%. Nonetheless, a more generally applicable procedure was sought.

Another sustainable SM approach focused on an “on water”^{58–61} reaction utilizing tetrabutyl ammonium bromide (TBAB) as a phase transfer catalyst⁵⁸ along with an inverted stoichiometry, leading to complete consumption of the BEpin ester. Although additional Pd. catalyst had to be added for the SM coupling step, the ligated Pd bearing the same AmPhos ligand could be used. Hence, a total loading of only 0.5 mol% of the same palladium-containing catalyst is involved for the 1-pot, 2-step process. Our developed two-step one-pot method showed applicability to a diverse set of substrates, as shown in Fig. 6. Even with the overall increased catalyst loading of 0.5 mol% and temperature of 70 °C for the SM reaction, heteroaromatic halides and complex substrates can be efficiently coupled in the same reaction vessel. This observation is supported by the quantitative late-stage formation of products 37 and 38 (Fig. 6). One limitation is brought about by the need

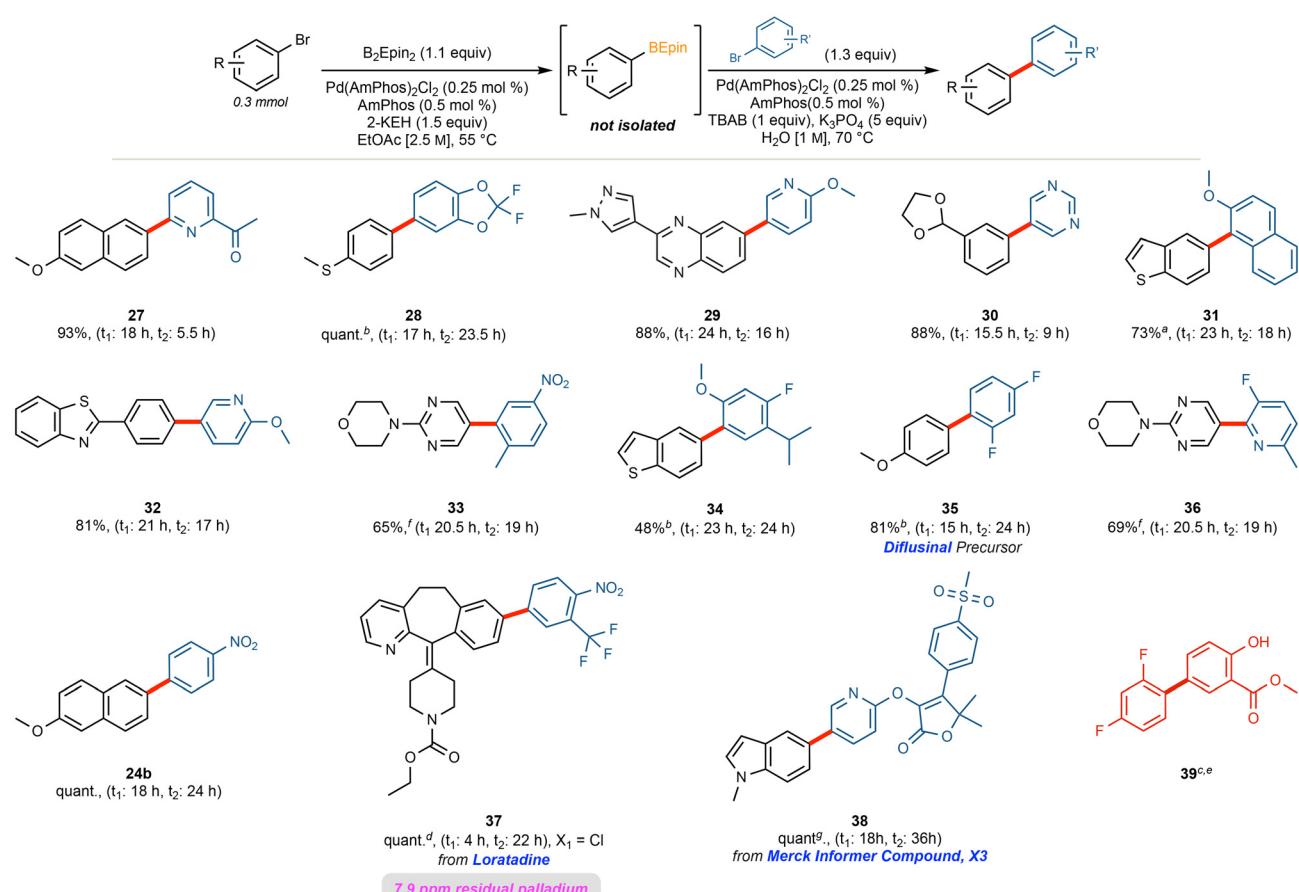


Fig. 6 General scope of 1-pot couplings. ^a 1 equiv. of bromide used in the SM coupling. ^b 1.5 equiv. of bromide used in the SM coupling. ^c 0.5 mol% of Pd at 70 °C utilized in the borylation step. ^d XPhos (Pd : P 1 : 4) utilized in the borylation step. ^e Unsuccessful coupling (first step conversion confirmed via GC). ^f Run on a 0.5 mmol scale. ^g Run on a 0.125 mmol scale.

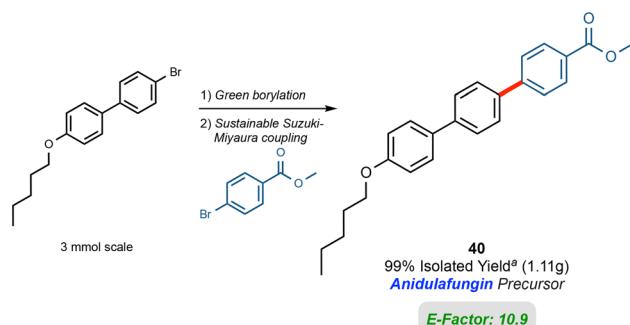


Fig. 7 Gram scale 1-pot reaction and E-factor. ^a Borylation: EtOAc [2 M] utilized; 15.5 h. Suzuki: H₂O [0.75 M] with 12.5% (v/v) 2-MeTHF; 16.5 h.

for a relatively high base loading. This is illustrated by compound **39** where there is an acidic phenol and a base sensitive methyl ester. Nonetheless, and especially relevant to the generation of APIs in the final step of a synthesis, product **38** was analyzed *via* inductively coupled plasma mass spectrometry (ICP-MS), shown to have residual palladium to the extent of 7.9 ppm. This is within the FDA guidelines limit of 10 ppm palladium per dose per day⁶² and demonstrates that complex biaryl products can be made without anticipating further investments in time and materials for metal scavenging.

2.6 Gram scale preparation of anidulafungin precursor

To show the potential scalability of this process, a gram scale preparation of compound **40**, a significant precursor to the antifungal Anidulafungin, was sought. In the borylation step, only slight dilution with EtOAc was required for stirring purposes. Once completed, the SM coupling called for addition of 2-MeTHF (10% v/v) with addition of water to aid in stirring. The product was isolated in 99% yield *via* simple filtration (see ESI†), and the calculated environmental factor (E-Factor)⁶³ of just 10.9 attests to the “greenness” of this new technology (Fig. 7).§

2.7 Multistep sequence: boscalid

A sequence that includes a borylation/SM coupling that is representative of the options now available to the community is shown in Fig. 8.

In the first step, borylation of 1-bromo-4-chlorobenzene leads to an intermediate BEpin derivative that reacts exclusively at the bromide center. Without isolation, under SM coupling conditions using newly introduced 1-bromo-2-nitrobenzene, the targeted biaryl is formed. This coupling is done within four hours, notwithstanding a 1 : 1 ratio of the Epin boronic ester and second bromide reflecting steric hindrance of the *ortho*-nitro group preventing potentially competing borylation and homocoupling. Simple workup of the biaryl product led to crude material that underwent nitro reduction *via* carbonyl iron powder (CIP)⁶⁴ in aqueous micellar media. This afforded boscalid in 65% overall yield.

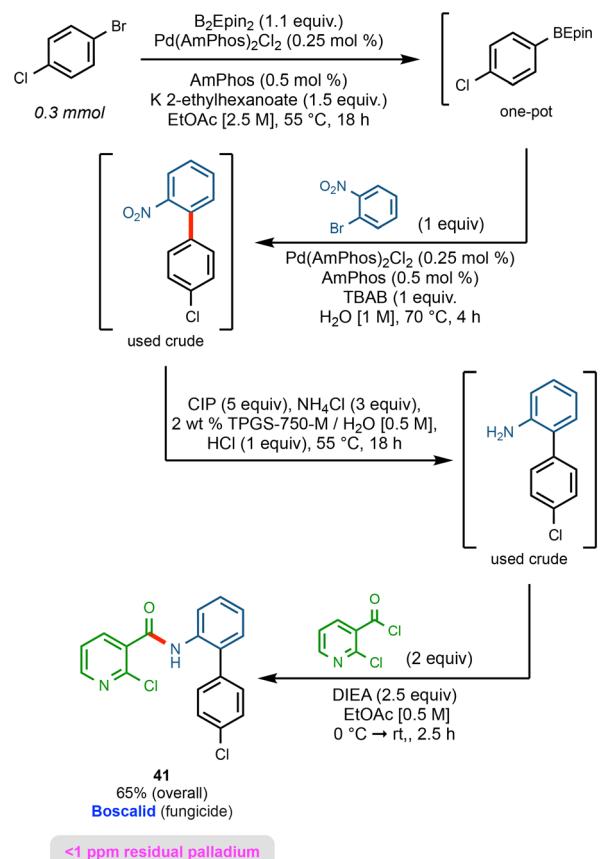


Fig. 8 Multistep sequence: boscalid.

filtration away from the CIP) in an amide coupling with 2-chloronicotinoyl chloride in EtOAc. This afforded boscalid in 65% overall yield.

2.8 Mechanistic comments

A final important observation was made with regard to the stability of these B(Epin) boronic esters. Generally, unreacted boronic esters remain stable in basic aqueous media at these reaction temperatures, which is consistent with the decomposition studies performed by Ikawa, Akai, and co-workers.⁴⁴ This stability is attributed to the ethyl “arms” of a B(Epin), that provide steric hindrance to the empty p orbital on boron, translating into hydrolytic resistance. These observations have important mechanistic considerations for Suzuki–Miyaura couplings in which B(Epin) derivatives smoothly participate. Thus, the implication is that it is not the corresponding boronic acid that undergoes transmetallation, but rather the intact aryl–B(Epin). This notion is in agreement with the findings by Denmark, *et al.*^{65,66} in which their mechanistic studies found that glycol boronic esters can transmetallate without the need to first hydrolyze to the corresponding boronic acid. Nonetheless, more sterically hindered boronic esters haven’t conclusively been determined to show similar behavior. Hence, studies to elucidate the mechanistic picture for sterically hindered Ar–B(Epins) are ongoing.

§ See ESI† for E-Factor calculations.

3 Conclusion

A sustainable and environmentally responsible borylation protocol has been developed that allows for facile installation of the B(Epin) group into a variety of aromatic/heteroaromatic substrates. These species can be utilized in subsequent Suzuki–Miyaura cross couplings. There are several additional features associated with the new technology of note:

- low loadings of Pd are involved
- green solvents/reaction media, such as recyclable EtOAc, or water, are used
- a borylation/Suzuki–Miyaura 1-pot sequence leads to both time and pot economies
- a scalable process
- low residual levels of Pd in the products, established *via* ICPMS, is to be expected
- multi-step sequences are amenable as illustrated by the synthesis of boscalid

Author contributions

All authors have given approval to the final version of the manuscript. C. B. N. conceived the project, optimized reactions conditions, carried out substrate scope, collected analytical data, and drafted the manuscript. S. J. L. assisted in optimization, substrate scope, and collecting analytical data. M. J. W. assisted in substrate scope and collecting analytical data. S. L. K. and E. G. performed early investigations into other sustainable borylation avenues. B. H. L. oversaw the work and assisted in drafting the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

Financial support provided by the NSF (CHE-2152566) is warmly acknowledged. The authors express gratitude for assistance in collecting HRMS data from the UCSB Mass Spectrometry Facility staff, Dr Desmond Bishop, and in collecting ICPMS data from the Nano and Pico Characterization Lab at the California NanoSystems Institute at UCLA, Dr Chong Hyun “Paul” Chang.

References

- 1 N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, **20**, 3437–3440.
- 2 D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458.
- 3 J. Britton and T. F. Jamison, *Eur. J. Org. Chem.*, 2017, **2017**, 6566–6574.
- 4 L. Xiong, Y.-Q. Shen, L.-N. Jiang, X.-L. Zhu, W.-C. Yang, W. Huang and G.-F. Yang, *Discovery and Synthesis of Crop Protection Products*, American Chemical Society, 2015, vol. 1204, pp. 175–194.
- 5 J. B. Epp, P. R. Schmitzer and G. D. Crouse, *Pest Manage. Sci.*, 2018, **74**, 9–16.
- 6 C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027–3043.
- 7 J. E. Zweig, D. E. Kim and T. R. Newhouse, *Chem. Rev.*, 2017, **117**, 11680–11752.
- 8 K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489.
- 9 A. Taheri Kal Koshvandi, M. M. Heravi and T. Momeni, *Appl. Organomet. Chem.*, 2018, **32**, e4210.
- 10 M. A. Selepe and F. R. Van Heerden, *Molecules*, 2013, **18**, 4739–4765.
- 11 G. Dhangan, J. L. Serrano, C. Schulzke, K. C. Gunturu and A. R. Kapdi, *ACS Omega*, 2017, **2**, 3144–3156.
- 12 S.-H. Yang and C.-S. Hsu, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 2713–2733.
- 13 H. Iino and J.-i. Hanna, *Polym. J.*, 2017, **49**, 23–30.
- 14 B. H. Lipshutz, *Is Organic Chemistry on Borrowed Time?*, 2022, <https://cen.acs.org/environment/green-chemistry/Opinion-organic-chemistry-borrowed-time/100/i34>.
- 15 C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747–800.
- 16 D. R. Joshi and N. Adhikari, *J. Pharm. Res. Int.*, 2019, 1–18.
- 17 R. Ratti, *SN Appl. Sci.*, 2020, **2**, 263.
- 18 S. Mukai and Y. Yamada, *Knowledge*, 2023, **3**, 1–17.
- 19 B. H. Lipshutz and A. R. Abela, *Org. Lett.*, 2008, **10**, 5329–5332.
- 20 J. R. A. Kincaid, M. J. Wong, N. Akporji, F. Gallou, D. M. Fialho and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2023, **145**, 4266–4278.
- 21 Y. Hu, X. Li, G. Jin and B. H. Lipshutz, *ACS Catal.*, 2023, **13**, 3179–3186.
- 22 N. Akporji, R. R. Thakore, M. Cortes-Clerget, J. Andersen, E. Landstrom, D. H. Aue, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2020, **11**, 5205–5212.
- 23 V. Singhania, C. B. Nelson, M. Reamey, E. Morin, R. D. Kavthe and B. H. Lipshutz, *Org. Lett.*, 2023, **25**, 4308–4312.
- 24 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508–7510.
- 25 J. A. Newby, L. Huck, D. W. Blaylock, P. M. Witt, S. V. Ley and D. L. Browne, *Chem. – Eur. J.*, 2014, **20**, 263–271.
- 26 D. S. Matteson, *The Metal–Carbon Bond*, John Wiley & Sons, Inc., Chichester, UK, 1987, vol. 4, pp. 307–409.

27 M. A. Larsen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 4287–4299.

28 M. M. M. Hassan, S. Guria, S. Dey, J. Das and B. Chattopadhyay, *Sci. Adv.*, 2023, **9**, eadg3311.

29 M. Liang, C. Liu, W. Ju, S. Han, J. Zhang and Y. Zhao, *Org. Lett.*, 2024, **26**, 4224–4228.

30 W. K. Chow, O. Y. Yuen, P. Y. Choy, C. M. So, C. P. Lau, W. T. Wong and F. Y. Kwong, *RSC Adv.*, 2013, **3**, 12518–12539.

31 F. D'Amico, C. Papucci, D. Franchi, G. Reginato, M. Taddei, A. Mordini, L. Zani, A. Dessì and M. Calamante, *J. Org. Chem.*, 2024, **89**, 6991–7003.

32 K. L. Billingsley, T. E. Barder and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2007, **46**, 5359–5363.

33 K. U. Rao and K. Venkateswarlu, *Synlett*, 2018, 1055–1060.

34 M. Cai, C. Luo, C. Xu and B. Huang, *Synthesis*, 2022, 1339–1346.

35 L. Xu, Z. Dong, Q. Zhang, N. Deng, S.-Y. Li and H.-J. Xu, *J. Org. Chem.*, 2022, **87**, 14879–14888.

36 K. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 3358–3366.

37 D. M. Knapp, E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2009, **131**, 6961–6963.

38 C. Achilli, A. Ciana, M. Fagnoni, C. Balduini and G. Minetti, *Cent. Eur. J. Chem.*, 2013, **11**, 137–139.

39 G. A. Molander, S. L. J. Trice, S. M. Kennedy, S. D. Dreher and M. T. Tudge, *J. Am. Chem. Soc.*, 2012, **134**, 11667–11673.

40 C. Munteanu, T. E. Spiller, J. Qiu, A. J. DelMonte, S. R. Wisniewski, E. M. Simmons and D. E. Frantz, *J. Org. Chem.*, 2020, **85**, 10334–10349.

41 S. R. Gurung, C. Mitchell, J. Huang, M. Jonas, J. D. Strawser, E. Daia, A. Hardy, E. O'Brien, F. Hicks and C. D. Papageorgiou, *Org. Process Res. Dev.*, 2017, **21**, 65–74.

42 J. R. Coombs, R. A. Green, F. Roberts, E. M. Simmons, J. M. Stevens and S. R. Wisniewski, *Organometallics*, 2019, **38**, 157–166.

43 A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2013, **43**, 412–443.

44 N. Oka, T. Yamada, H. Sajiki, S. Akai and T. Ikawa, *Org. Lett.*, 2022, **24**, 3510–3514.

45 S. Barroso, M. Joksch, P. Puylaert, S. Tin, S. J. Bell, L. Donnellan, S. Duguid, C. Muir, P. Zhao, V. Farina, D. N. Tran and J. G. de Vries, *J. Org. Chem.*, 2021, **86**, 103–109.

46 B. M. Klootwyk, J. C. Ruble, G. R. Cumming and E. M. Woerly, *J. Org. Chem.*, 2024, **89**, 5901–5904.

47 B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston and R. C. Gadwood, *J. Org. Chem.*, 2011, **76**, 4379–4391.

48 A. S. Guram, X. Wang, E. E. Bunel, M. M. Faul, R. D. Larsen and M. J. Martinelli, *J. Org. Chem.*, 2007, **72**, 5104–5112.

49 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295–4298.

50 It is noted that recent work from Woerly and colleagues showed that potassium 2-ethylhexanoate could be used catalytically with stoichiometric potassium carbonate in order to avoid work up and isolation issues associated with this base.⁴⁶ However, in our work, we were able to effectively remove the base during work up, and using the base catalytically under our conditions, led to increased homocoupling.

51 P. S. Kutchukian, J. F. Dropinski, K. D. Dykstra, B. Li, D. A. DiRocco, E. C. Streckfuss, L.-C. Campeau, T. Cernak, P. Vachal, I. W. Davies, S. W. Krska and S. D. Dreher, *Chem. Sci.*, 2016, **7**, 2604–2613.

52 M. P. Goetz, M. Toi, M. Campone, J. Sohn, S. Paluch-Shimon, J. Huober, I. H. Park, O. Trédan, S.-C. Chen, L. Manso, O. C. Freedman, G. Garnica Jaliffe, T. Forrester, M. Frenzel, S. Barriga, I. C. Smith, N. Bourayou and A. Di Leo, *J. Clin. Oncol.*, 2017, **35**, 3638–3646.

53 S. Johnston, M. Martin, A. Di Leo, S.-A. Im, A. Awada, T. Forrester, M. Frenzel, M. C. Hardebeck, J. Cox, S. Barriga, M. Toi, H. Iwata and M. P. Goetz, *npj Breast Cancer*, 2019, **5**, 1–8.

54 Y. Loriot, A. Necchi, S. H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S. T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani and A. O. Siefker-Radtke, *N. Engl. J. Med.*, 2019, **381**, 338–348.

55 C.-H. R. Y. Fabritius, M. O. Nowak, K. A. Wiklik, A. B. Sabiniarz, M. D. Bień, A. M. Buda, P. S. Guzik, A. K. Białas, H. E. Pawlik and N. F. P. Boutard, EPO WO2016180537A1, 2016.

56 G. Saxty, C. W. Murray, V. Berdini, G. E. Besong, C. C. F. Hamlett, S. J. Woodhead, Y. A. E. Ligny and P. R. Angibaud, EPO WO2012073017A1, 2012.

57 P. Chen, S. Cho-Schultz, J. G. Deal, G. M. Gallego, M. Jalaie, R. S. Kania, S. K. Nair, S. Ninkovic, S. T. M. Orr and C. L. Palmer, EPO US2019330196A1, 2019.

58 D. Badone, M. Baroni, R. Cardamone, A. Ielmini and U. Guzzi, *J. Org. Chem.*, 1997, **62**, 7170–7173.

59 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275–3279.

60 R. N. Butler and A. G. Coyne, *Org. Biomol. Chem.*, 2016, **14**, 9945–9960.

61 D. G. Blackmond, A. Armstrong, V. Coombe and A. Wells, *Angew. Chem., Int. Ed.*, 2007, **46**, 3798–3800.

62 FDA, Q3D (R1) elemental impurities guidance for industry, 2022, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/elemental-impurities-drug-products-guidance-industry>.

63 R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273–1283.

64 N. R. Lee, A. A. Bikovtseva, M. Cortes-Clerget, F. Gallou and B. H. Lipshutz, *Org. Lett.*, 2017, **19**, 6518–6521.

65 A. A. Thomas, H. Wang, A. F. Zahrt and S. E. Denmark, *J. Am. Chem. Soc.*, 2017, **139**, 3805–3821.

66 C. P. Delaney, D. P. Marron, A. S. Shved, R. N. Zare, R. M. Waymouth and S. E. Denmark, *J. Am. Chem. Soc.*, 2022, **144**, 4345–4364.