

pubs.acs.org/OrgLett

#### Letter

# Sustainable and Cost-Effective Suzuki–Miyaura Couplings toward the Key Biaryl Subunits of Arylex and Rinskor Active

Balaram S. Takale,\* Ruchita R. Thakore, Nicholas M. Irvine, Abraham D. Schuitman, Xiaoyong Li, and Bruce H. Lipshutz\*



parts per million (ppm) levels of a Pd catalyst. Each coupling required a distinct set of reaction conditions to achieve maximum selectivities and chemical yields. By way of comparison, this chemistry is not only performed under environmentally responsible aqueous micellar conditions, but also involves lowering loadings (3-5 times) of endangered palladium than used previously to attain a more sustainable process.

**C** rop management is a highly challenging process, as weeds<sup>1</sup> can be very effective competitors for essential nutrients.<sup>2</sup> Moreover, control of weeds is oftentimes quite demanding, and consequently, can lead to decreased overall crop production.<sup>3</sup> As the world's population continues to increase, improved approaches to maximize crop production are essential. Corteva Agriscience has been actively involved in developing several classes of herbicides, especially those within the auxinic family, given their known effectiveness against broadleaf weeds. The discovery of "2,4-D" in 1945 propelled herbicide use as a weed killer for crop protection (Figure 1).<sup>4</sup>





Today, however, far more than just the activity of herbicides is required<sup>5</sup> and, hence, two recent herbicides, Arylex and Rinskor,<sup>6</sup> have been commercialized and studied in detail by Corteva. These offer numerous advantages, relative to previous molecules in this class (Figure 1). These new properties, in particular, include (a) dramatic reduction in residual levels of metabolites in soil due to hydrolysis, (b) reduction in use rate, and (c) an increase in their range of effectiveness toward various weeds.<sup>7</sup> These and related advances in herbicide science *in the field* by the team responsible for development of Rinskor led to an ACS Presidential Green Chemistry Challenge Award, acknowledging its favorable environmental

and toxicity profile.<sup>8</sup> Nonetheless, *in the laboratory*, syntheses of Rinskor, as well as that of its predecessor, Arylex, are continuously evolving, with efforts aimed at exploring improvements most notably with regard to sustainability.

micellar catalysis

The route to Arylex first disclosed in 2016 uses microwave heating at 110 °C in a 1:1 mixture of acetonitrile and water,<sup>6</sup> or in a toluene:water:acetonitrile mixture at 65 °C.<sup>9</sup> Considering the endangered status of Pd, the loading of non-recycled palladium catalyst used for this coupling is high (2–5 mol %, or 20 000–50 000 ppm). Similarly, an earlier route involving biaryl coupling en route to Rinskor requires high levels of Pd catalyst (3 mol %) in an acetonitrile:dimethoxyethane:water mixture and affords the biaryl in a modest 58% yield.<sup>10</sup> Reducing palladium usage is of continuing interest and focus during process development and optimization.<sup>12b</sup>

Our continuing efforts to provide new technologies based on sustainable chemistry<sup>11</sup> in recyclable water, using Nature as the perfect model, utilize nanomicelles as nanoreactors.<sup>12</sup> As an integral part of these studies, we have shown that this approach enables especially valued<sup>13</sup> Pd-catalyzed cross coupling reactions to be run at the parts per million (ppm) level.<sup>14</sup> More recently, our focus has broadened to include applications to numerous target molecules of synthetic interest. Here, most, if not all, of the chemistry involved is performed in water, much of which can be telescoped (i.e., where several steps can

Received: May 12, 2020



be performed in a single pot).<sup>15</sup> In this report, we describe the "greening" of the crucial biaryl syntheses of both Arylex and Rinskor. Hence, not only can these couplings now be done using water with minimal organic cosolvent as the reaction medium, but also, with only a few thousand ppm of Pd catalyst (a 10-fold reduction), these biaryls can now be realized making these couplings far more environmentally attractive.

Initially, in our academic laboratories, the Suzuki–Miyaura coupling toward Arylex was investigated, involving an extensive screening of the associated ligands on Pd. The presence of 10% cosolvent imparted an important element, i.e., facile stirring of reaction mixtures, with ethyl acetate being observed as the preferred choice (see the elecronic Supporting Information (ESI)). Unfortunately, none of the ligands generally used for SM couplings led to acceptable results (i.e., poor chemical yields; see Table 1, entries 1–5). Note that, in all of these

Table 1. Optimization toward ppm-Level Pd-CatalyzedSuzuki-Miyaura Coupling in the Synthesis of Arylex<sup>a</sup>

	CI F C CI	Pd(OAc) <sub>2</sub> (2500 ppm) Ligand (5000 ppm) base (2.0 equiv) 2 wt % TPGS-750-M/H <sub>2</sub> O (0. EtOAc (10%), 45 °C	
entry	Ligand/cat	base	yield (%) <sup>b</sup>
1	SPhos	$K_2CO_3$	trace
2	XPhos	$K_2CO_3$	23
3	EvanPhos	$K_2CO_3$	6
4	XPhos	K <sub>3</sub> PO <sub>4</sub>	14
5	XPhos	Et <sub>3</sub> N	28
6	XPhos	KF	67
7	$Pd(PPh_3)_2Cl_2$	KF	69
8°	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	KF	87
9 <sup>d</sup>	$Pd(PPh_3)_2Cl_2$	KF	57
	MeO OMe	<sup><i>i</i>,Pr</sup> , <sup><i>i</i>,Pr</sup> , <sup><i>i</i>,Pr</sup> , <sup><i>i</i>,Pr</sup>	OMe OMe OMe
	SPhos	XPhos E	vanPhos

<sup>*a*</sup>Reaction conditions, unless otherwise mentioned: 1 mmol of 1, 1.2 mmol of 2, 2500 ppm (0.25 mol %) of Pd(OAc)<sub>2</sub>, 5000 ppm ligand, and 2 equiv of base, stirred in 2 wt % TPGS-750-M/H<sub>2</sub>O, along with 10 vol % EtOAc at 45 °C for 12 h. <sup>*b*</sup>Isolated yield. <sup>c</sup>Reaction was performed at 70 °C. <sup>*d*</sup>Reaction was performed using the corresponding boronic acid at 70 °C.

trials, starting material was hydrolyzed, and hence, this observation indicated a need for a milder base. We eventually found that potassium fluoride  $(KF)^{10}$  supplied the required activation for an efficient coupling without hydrolyzing either amide or ester functionality (Table 1, entry 6). In addition, instead of the initially used, expensive XPhos ligand, we found that triphenylphosphine could be used to give the desired coupling product in similar yield (Table 1, entry 7). A modest increase in temperature led to excellent conversion, and thus, a very good isolated yield of biaryl **3** (Table 1, entry 8). Replacing boronic ester **2** with the corresponding boronic acid led to a significant decrease in chemical yield (Table 1, entry 9).

Both recycling and scale-up reactions were performed on a 10 mmol scale, and, as expected,<sup>15</sup> each reaction led to a similar yield. Moreover, the aqueous system could easily be recycled several times with essentially identical yields being obtained (see Scheme 1). The calculated E factor, which is

Scheme 1. Recycling and E Factor Determination for ppm-Level Pd-Catalyzed Suzuki–Miyaura Coupling toward the Biaryl Portion of  $Arylex^a$ 



based on the amount of product (given in grams) divided by the amount of waste generated (including water) (also given in grams) was found to be 2.4, which was well below Sheldon's<sup>16</sup> E factor associated with the pharmaceutical industry.

The analogous Suzuki–Miyaura coupling involved in the synthesis of the biaryl portion of Rinskor was studied next. Typically, a trichloropicolinic acid (4) is the electrophilic coupling partner used in this step. Previously optimized conditions involving Arylex were applied here, albeit with twice the catalyst loading. Surprisingly, none of the desired biaryl product 9 was formed (see Scheme 2). We speculated that, under the basic conditions, the corresponding (polar) carboxylate salt might not gain entry to the inner lipophilic micellar core, presumably where the reaction generally occurs. Therefore, different esters of this acid were prepared

Scheme 2. Use of Optimized Conditions for Suzuki–Miyaura Coupling toward the Rinskor Biaryl Intermediate $^{a,b}$ 



<sup>*a*</sup>Reaction conditions unless otherwise noted: 1 mmol of 4/5/6/7, 1.2 mmol of 8, 5000 ppm of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, 2 equiv of KF, stirred in 2 wt % TPGS-750-M/H<sub>2</sub>O, along with 10 vol % EtOAc at 45 °C. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Substrate 2 was used instead of 8.

#### **Organic Letters**

(compounds 5–7) and, as anticipated, this added lipophilicity influenced reactivity, leading to some conversion (products 10–12). The most lipophilic substrate in this series, i.e., the ester derived from 2-ethyl-hexanol, gave the best results, including the observed stability of this ester toward the basic reaction conditions. This added stability allowed use of a stronger base,  $K_3PO_4$ ·H<sub>2</sub>O, relative to KF, leading to a 35% isolated yield of 12. Both the methyl and benzyl esters were partially hydrolyzed when  $K_3PO_4$ ·H<sub>2</sub>O was used as a base.

Since the previously optimized conditions for Arylex (Table 2) were seemingly not applicable to the biaryl of Rinskor, we

Table 2. Optimization of the ppm-Level Pd-Catalyzed Suzuki–Miyaura Coupling toward the Biaryl Section of Rinskor<sup>a</sup>



<sup>*a*</sup>Reaction conditions unless otherwise mentioned: 1 mmol of 7, 1.2 mmol of 8, 5000 ppm (0.50 mol %) of Pd(OAc)<sub>2</sub>, and 2 equiv of base, stirred in 2 wt % TPGS-750-M/H<sub>2</sub>O, along with 10 vol % toluene at 45 °C. <sup>*b*</sup>Isolated yield. <sup>(</sup>Reaction was performed at 55 °C. <sup>*d*</sup>Pd-(XantPhos)Cl<sub>2</sub>, 5000 ppm was used at 55 °C. <sup>(</sup>Reaction was performed using Et<sub>3</sub>N as a base at 55 °C.

were forced to perform another screening of catalysts for this SM coupling. Again, neither XPhos nor EvanPhos gave any product (Table 2, entries 1 and 2). Remarkably, bidentate ligands proved to be effective, with DPEPhos affording a 61% yield of the targeted product (Table 2, entry 4), while XantPhos increased the yield further to 73% (Table 2, entry 7). Ferrocene-based ligands diphenylphosphinoferrocene (DPPF) and di-t-butylphosphinoferrocene (DTBPF) showed moderate conversions (Table 2, entries 5 and 6); however, each led to a series of byproducts, with only DTBPF giving any of the desired product (20% yield; see Table 2, entry 6). With XantPhos, a 10 °C increase in reaction temperature improved the yield even further (Table 2, entry 8). Use of the same catalyst but in the preformed state (i.e., Pd(XantPhos)Cl<sub>2</sub>) led to similar results (Table 2, entry 9). With this same catalyst, but with a simple change in base to triethylamine, the optimized conditions were in hand, both in terms of chemical yield and cleanliness of the reaction profile (Table 2, entry 10).

Following the successful Suzuki–Miyaura coupling that provided ester **12**, its hydrolysis under aqueous conditions was performed to give intermediate acid **9** (see Scheme 3). Using 4

# Scheme 3. Hydrolysis of Ester 12 to the Desired Acid 9



equiv of NaOH at room temperature led to a 40% isolated yield, whereas, at 55  $^{\circ}$ C, run overnight, a quantitative yield of the desired acid was obtained. The reaction time could be further reduced to 5 h by increasing the temperature to 70  $^{\circ}$ C.

These individually optimized steps, each performed in an aqueous micellar medium, were then combined into a 1-pot sequence. As seen in the images below (Scheme 4), NaOH was





added to the initial, smoothly stirred reaction slurry observed in the SM coupling (Scheme 4, image a), resulting in an orange-yellow colored emulsion (Scheme 4, image b). Once saponification was complete, dilution with water: diethyl ether (4:1) (Scheme 4, images c and d) and acidification of this mixture with concentrated  $H_2SO_4$  (Scheme 4, image e) led to the formation of a white precipitate of product (Scheme 4, images f and g) which could be easily filtered to afford acid 9 in an overall yield of 82%.

Although ester 12 is an important intermediate en route to Rinskor, this target herbicide is a benzyl ester (recall Figure 1), in which case the direct use of the benzyl ester analogue of 12 in the SM coupling might avoid the in situ hydrolysis and reesterification steps. Therefore, coupling between aryl halide 6 and arylboronic acid 8 under the same conditions (55 °C for 18 h; see Scheme 5) gave biaryl 11, albeit in only 54% yield.

Scheme 5. SM Coupling of Benzyl Ester 6 to Biaryl 11



All of the aryl halide was consumed; however, most of the remaining reaction material was attributed to the hydrolysis of starting ester. By lowering the reaction temperature to 45  $^{\circ}$ C, and then to 35  $^{\circ}$ C, the hydrolysis was slower, but the desired biaryl benzyl ester 11 could be obtained in 79% yield. Under these conditions, an attempt to perform this coupling at rt led to 11 in only 60% yield.

In summary, aqueous micellar technology has been efficiently applied to Suzuki–Miyaura couplings for the syntheses of key biaryl subsections associated with Arylex and Rinskor active ingredients from Corteva Agriscience. The required catalyst loading was significantly lower than reported for the preparation of these key intermediates, suggesting that the adoption of processes akin to those described herein are not only sustainable, but are also economically attractive.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01625.

Experimental procedures, analytical data, and copies of NMR spectra for all compounds (PDF)

### AUTHOR INFORMATION

#### **Corresponding Authors**

Bruce H. Lipshutz – Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States; o orcid.org/0000-0001-9116-7049; Email: bhlipshutz@ucsb.edu

Balaram S. Takale – Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States; o orcid.org/0000-0001-8279-944X; Email: balaram takale@ucsb.edu

#### Authors

Ruchita R. Thakore – Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States Nicholas M. Irvine – Corteva Agriscience, Indianapolis, Indiana 46268, United States; orcid.org/0000-0001-6391-4721

- Abraham D. Schuitman Corteva Agriscience, Indianapolis, Indiana 46268, United States
- Xiaoyong Li Corteva Agriscience, Indianapolis, Indiana 46268, United States

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01625

## **Author Contributions**

All authors have given approval to the final version of the manuscript.

#### Notes

The authors declare no competing financial interest.

Arylex and Rinskor are trademarks of Dow AgroSciences, DuPont, or Pioneer and their affiliated companies or respective owners.

#### ACKNOWLEDGMENTS

Financial support provided by the NSF (No. 18-56406) and PHT International (via a postdoctoral fellowship to B.S.T.) is warmly acknowledged with thanks.

#### REFERENCES

(1) (a) Riar, D. S.; Norsworthy, J. K.; Steckel, L. E.; Stephenson, D. O.; Eubank, T. W.; Scott, R. C. Assessment of weed management practices and problem weeds in the midsouth United States—Soybean: A consultant's perspective. *Weed Technol.* **2013**, *27*, 612–622. (b) Miller, M. R.; Norsworthy, J. K. Row Crop Sensitivity to Low Rates of Foliar-Applied Florpyrauxifen-Benzyl. *Weed Technol.* **2018**, *32*, 398–403.

(2) Cobb, A. H.; Reade, J. P. H. *Herbicides and Plant Physiology*, 2nd Edition; Wiley–Blackwell: United Kingdom, 2010.

(3) Walsh, T. A.; Schmitzer, P. R.; Masters, R. A.; Lo, W. C.; Gast, R. E.; Claus, J. S.; Finkelstein, B. L. Chapter 5: New Auxin Mimics and Herbicides. In *Modern Crop Protection Compounds*, 2nd Edition; Wiley–VCH: Weinheim, Germany, 2012; Vol. 1, pp 277–304.

(4) Quastel, J. H. "2,4-Dichlorophenoxyacetic Acid (2,4-D) as a Selective Herbicide". Agricultural Control Chemicals. *Adv. Chem. Ser.* **1950**, *1*, 244–249.

(5) Grossmann, K. Auxin Herbicides: Current Status of Mechanism and Mode of Action. *Pest Manage. Sci.* **2009**, *66*, 113–120.

(6) Epp, J. B.; Alexander, A. L.; Balko, T. W.; Buysse, A. M.; Brewster, W. K.; Bryan, K.; Daeuble, J. F.; Fields, S. C.; Gast, R. E.; Green, R. A.; Irvine, N. M.; Lo, W. C.; Lowe, C. T.; Renga, J. M.; Richburg, J. S.; Ruiz, J. M.; Satchivi, N. M.; Schmitzer, P. R.; Siddall, T. L.; Webster, J. D.; Weimer, M. R.; Whiteker, G. T.; Yerkes, C. N. The discovery of Arylex active and Rinskor active: Two novel auxin herbicides. *Bioorg. Med. Chem.* **2016**, *24*, 362–371.

(7) Canturk, B.; Johnson, P.; Taylor, J.; Kister, J.; Balcer, J. Identification and Synthesis of a Nitrophenyl Metabolite of Rinskor Active from Terrestrial Aerobic Soil Studies. *Org. Process Res. Dev.* **2019**, *23*, 2234–2242.

(8) 2018 Green Chemistry Challenge Awards announced, https://cen. acs.org/environment/green-chemistry/2018-Green-Chemistry-Challenge-Awards/96/web/2018/10 (accessed Feb. 20, 2020).

(9) Fisk, J. S.; Li, X.; Muehlfeld, M.; Bauman, R. S.; Oppenheimer, J.; Tu, S.; Nitz, M. A.; Chakrabarti, R.; Feist, S. D.; Ringer, J. W.; Leng, R. B. Synthesis of 6-Aryl-4-Aminopicolinates and 2-Aryl-6-Aminopyrimidine-4-Carboxylates by Direct Suzuki Coupling. International Patent No. WO 2017/201377 A1 2017.

(10) (a) Zhu, Y.; Whiteker, G. T.; Renga, J. M.; Arndt, K. E.; Roth, G.; Podhorez, D. E.; West, S. P.; Cheng, Y. Process for the preparation of 4-amino-5-fluoro-3-halo-6-(substituted) picolinates. U.S. Patent No. US 2014/0206881 A1, 2014. (b) Renga, J. M.;

Cheng, Y.; Muhuhi, J. M.; Podhorez, D. E.; Roth, G. A.; West, S. P.; Whiteker, G. T.; Zhu, Y. Process for the Preparation of 4-Amino-5-Fluoro-3-Halo-6-(Substituted) Picolinates. International Patent No. WO 2014/18502 A1, 2014.

(11) (a) Bihani, M.; Ansari, T. N.; Finck, L.; Bora, P. P.; Jasinski, J. B.; Pavuluri, B.; Leahy, D. K.; Handa, S. Ultrasmall Pd Nanoparticles in Aqueous Micelles for Scalable  $\alpha$ -Arylation of Nitriles: Surprising Formation of Carbanions. ACS Catal. **2020**, 10, 6816–6821. (b) Duong, U. T.; Gade, A. B.; Plummer, S.; Gallou, F.; Handa, S. Reactivity of Carbenes in Aqueous Nanomicelles Containing Palladium Nanoparticles. ACS Catal. **2019**, *9*, 10963–10970.

(12) (a) Lipshutz, B. H. Catalyst: Imagine Doing Chemistry at No Cost to the Environment! *Chem.* **2018**, *4*, 2004–2012. (b) Lipshutz, B. H. Synthetic chemistry in a water world. New rules ripe for discovery. Current. *Opin. Green Sus. Chem.* **2018**, *11*, 1–8. (c) Lipshutz, B. H.; Ghorai, S.; Cortes-Clerget, M. The Hydrophobic Effect Applied to Organic Synthesis: Recent Synthetic Chemistry "in Water". *Chem. - Eur. J.* **2018**, *24*, 6672–6695. (d) Andersson, M. P.; Gallou, F.; Klumphu, P.; Takale, B. S.; Lipshutz, B. H. Structure of Nanoparticles Derived from Designer Surfactant TPGS-750-M in Water, As Used in Organic Synthesis. *Chem. - Eur. J.* **2018**, *24*, 6778–6786.

(13) (a) Gildner, P. G.; Colacot, T. J. Reactions of the 21st Century: Two Decades of Innovative Catalyst Design for Palladium-Catalyzed Cross-Couplings. *Organometallics* **2015**, *34*, 5497–5508. (b) Devendar, P.; Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F. Palladium-Catalyzed Cross-Coupling Reactions: A Powerful Tool for the Synthesis of Agrochemicals. *J. Agric. Food Chem.* **2018**, *66*, 8914– 8934.

(14) (a) Takale, B. S.; Thakore, R. R.; Handa, S.; Gallou, F.; Reilly, J.; Lipshutz, B. H. A new, substituted palladacycle for ppm level Pdcatalyzed Suzuki-Miyaura cross couplings in water. *Chem. Sci.* 2019, *10*, 8825–8831. (b) Thakore, R. R.; Takale, B. S.; Gallou, F.; Reilly, J.; Lipshutz, B. H. *N*,*C*-Disubstituted Biarylpalladacycles as Precatalysts for ppm Pd-Catalyzed Cross Couplings in Water under Mild Conditions. *ACS Catal.* 2019, *9*, 11647–11657. (c) Zhang, Y.; Takale, B. S.; Gallou, F.; Reilly, J.; Lipshutz, B. H. Sustainable ppm level palladium-catalyzed aminations in nanoreactors under mild, aqueous conditions. *Chem. Sci.* 2019, *10*, 10556–10561.

(15) (a) Takale, B. S.; Thakore, R. R.; Kong, F. Y.; Lipshutz, B. H. An environmentally responsible 3-pot, 5-step synthesis of the antitumor agent sonidegib using ppm levels of Pd catalysis in water. *Green Chem.* **2019**, *21*, 6258–6262. (b) Takale, B. S.; Thakore, R. R.; Mallarapu, R.; Gallou, F.; Lipshutz, B. H. A Sustainable 1-Pot, 3-Step Synthesis of Boscalid Using Parts Per Million Level Pd Catalysis in Water. Org. Process Res. Dev. **2020**, *24*, 101–105.

(16) Sheldon, R. A. The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chem.* 2017, 19, 18–43.