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A Streamlined, Green, and Sustainable Synthesis of the Anticancer Agent Erdafitinib

Vani Singhania, Chandler B. Nelson, Maya Reamey, Emile Morin, Rahul D. Kavthe, and Bruce H. Lipshutz*

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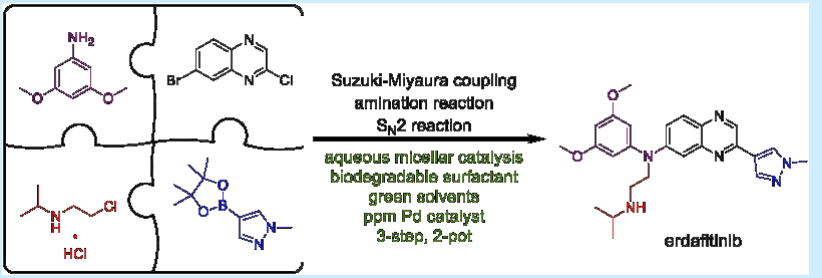

ABSTRACT: Erdafitinib, an anticancer drug, was synthesized in a three-step two-pot sequence involving ppm levels of Pd catalyst run under aqueous micellar conditions enabled by a biodegradable surfactant. This process features both pot- and time-economies and eliminates egregious organic solvents and toxic reagents associated with existing routes.

Erdafitinib, commercially sold and prescribed under the brand name Balversa, is a US Food and Drug Administration (FDA) approved (in 2019) potent anticancer agent that targets urothelial carcinoma, a type of bladder cancer, by acting as a selective small-molecule tyrosine kinase inhibitor of pan-fibroblast growth factor receptor (FGFR).[1] It was first developed by Janssen in collaboration with Astex Pharmaceuticals and received accelerated approval due to its established efficacy resulting from its oral administration in clinical trials.[2] Currently, erdafitinib is also being investigated for its potential as a therapeutic agent for bile duct, liver, prostate, lymphoma, esophageal, and non-small cell lung cancers.[3] While erdafitinib has shown considerable promise in these applications, unfortunately its current synthesis relies on several unattractive parameters, including (a) required elevated reaction temperatures, (b) unsustainable and costly loadings of the precious metal (palladium) based catalysts, and (c) reliance on toxic, flammable, and environmentally egregious organic solvents.[4−8] Herein, we report a three-step, two-pot synthesis of erdafitinib under aqueous micellar conditions using a biodegradable surfactant (Figure 1) and a green solvent.

As described by Saxty and co-workers from Astex Pharmaceuticals, a six-step convergent route and four-step linear route, among several, can be found in the original patent published in 2011 (Schemes 1 and 2, respectively).[9] Key Pd-catalyzed Suzuki−Miyaura cross-coupling and amination reactions using typical, albeit unsustainable and costly, catalyst loadings in the 1−5 mol % range are characteristic of these approaches, each of which is conducted in various waste-generating organic solvents. Hence, this chemistry is clearly amenable to more recent technologies that allow for a far more environmentally respectful use of planetary resources.

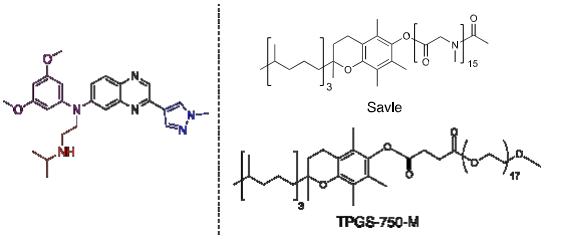

Figure 1. Structure of the anticancer agent erdafitinib (left). Structure of designer surfactants Savie and TPGS-750-M (right).

A new, improved, and far greener synthetic route to erdafitinib is outlined in Scheme 3. The synthesis involves two sequential Pd-catalyzed cross-couplings: (1) an initial Suzuki−Miyaura reaction and (2) a subsequent amination. Both can also be performed in a one-pot fashion. For the optimization of this first C−C bond-forming step, heteroaryl chloride 7-bromo-2-chloroquinoxaline (1) was treated with 1-

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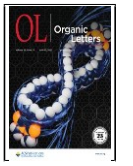

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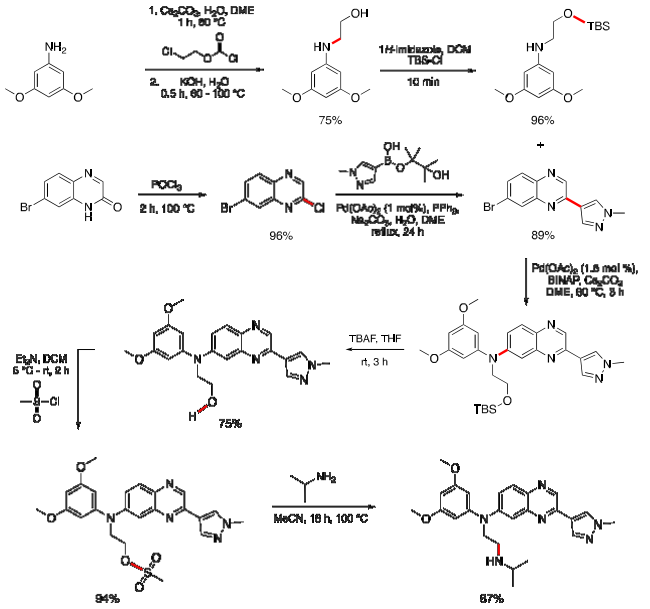
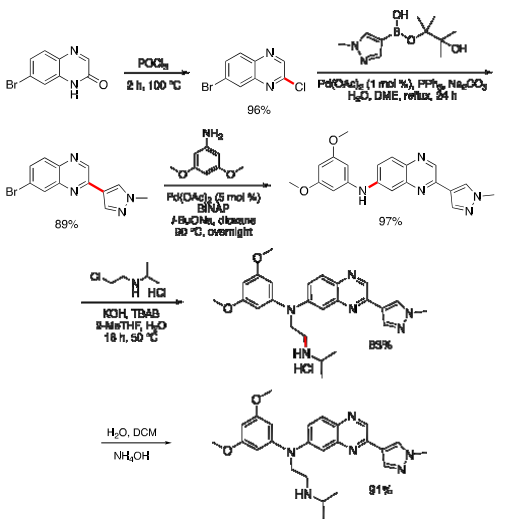
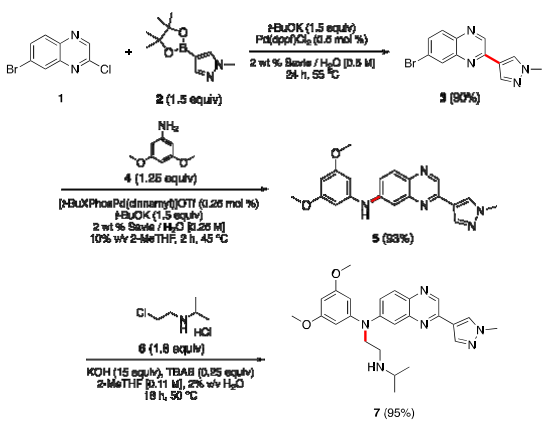
Scheme 1. A Six-Step Convergent Route to Erdafitinib (Astex Pharmaceuticals)



Scheme 2. A Four-Step Linear Route to Erdafitinib (Astex Pharmaceuticals)



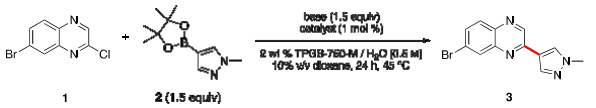
Scheme 3. Greener and Potentially Economically Attractive Route to Erdafitinib



methylpyrazole-4-boronic acid pinacol ester (2) to afford biaryl intermediate 3 in a 90% isolated yield (Scheme 3).

The reaction was performed initially at 45 °C with 1 mol % of a monomeric Pd catalyst under aqueous micellar conditions.[10,11] Optimization studies (Table 1) indicated that commercially available $Pd(dppf)Cl_2$ (entries 9−15) accompanied by KO-*t*-Bu (1.5 equiv; entries 13−15) as base is the most effective combination.

Table 1. Optimization of Catalyst and Base for the Suzuki−Miyaura reaction



entry	catalyst (ligand)*	base	NMR yield (%)
1	$Pd(PPh_3)_4$	K_3PO_4	35
2	$Pd(OAc_2)$ (SPhos)	K_3PO_4	9
3	$Pd(OAc_2)$ (EvanPhos)	K_3PO_4	19
4	[*t*-BuXPhosPd(allyl)]OTF	K_3PO_4	2
5	$(dba)_3$	K_3PO_4	2
6	$Pd(dba)_2$	K_3PO_4	2
7	Pd-G3	K_3PO_4	29
8	Pd-PEPPSI-IPent	K_3PO_4	2
10	$Pd(dppf)Cl_2$	NEt_3	86
11	$Pd(dppf)Cl_2$	K_2CO_3	79
12	$Pd(dppf)Cl_2$	*t*-BuONa	74
13	$Pd(dppf)Cl_2$		87
14	$Pd(dppf)Cl_2$	*t*-BuOK (1.0 equiv.)	67
15	$Pd(dppf)Cl_2$	*t*-BuOK (2.0 equiv.)	72

*Catalyst/ligand (1:1.8).

After thorough screening of surfactants (see the SI), the Suzuki−Miyaura coupling was successful using designer surfactants TPGS-750-M and, most recently introduced, Savie (Table 2).[12] Due to its biodegradable nature as well as its increased polarity, the polysarcosine-based surfactant (Savie) was preferred and utilized throughout this study (entries 3−5). As advertised, further experimentation using the more polar Savie demonstrated good emulsification and stirring *in the absence of a cosolvent*. Increasing the reaction temperature from 45 to 55 °C ensured complete consumption of starting material within 24 h. It is important to note that an increase in temperature to 80 °C was found to be detrimental to the reaction. A new (unidentified) byproduct was observed and hypothesized to be a compromise in chemoselectivity resulting from coupling at both the 2 and 7 positions of the quinoxaline. Product 3 was successfully obtained in 90% isolated yield relying on only 0.5 mol % (5000 ppm) of a precious metal (Pd) containing catalyst.

For optimization of the amination, aryl bromide 3 was subjected to coupling partner 3,5-dimethoxyaniline (4) to arrive at diarylamine 5 (Table 3). To increase solubility of the starting materials in this reaction mixture, a small volume (10%

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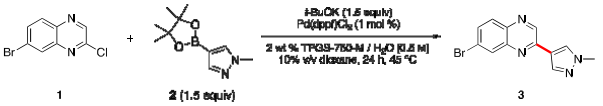
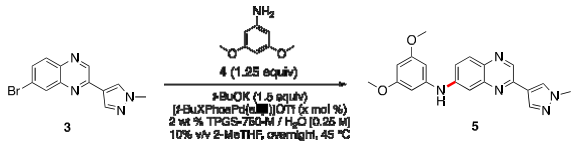
Table 2. Greener Conditions for the Suzuki−Miyaura Coupling



entry	deviation from standard conditions	NMR yield (%)
1	none	87
2	solvent	92
3	surfactant: Savie, no co-solvent	87*
4	surfactant: Savie, no co-solvent, 0.5 mol % Pd	89*
5		90*

*Isolated yield after column chromatography.

Table 3. Optimization of the Amination of Bromide 3



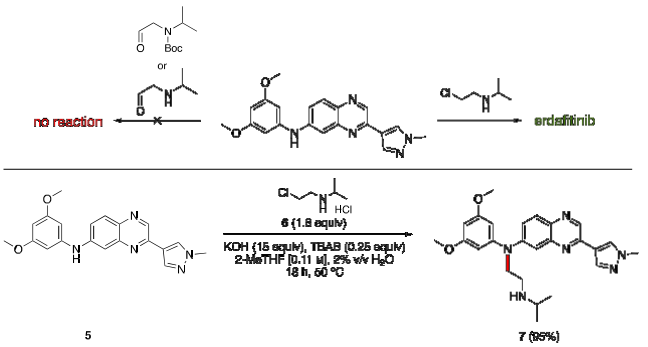
entry	catalyst loading (mol %)	deviation from standard conditions	NMR yield (%)
2	1	co-solvent: dioxane	83
3	1	0.5 M conc, co-solvent: dioxane	42
4	1	no co-solvent	72
5	-	no catalyst	trace
6	-	no catalyst, no co-solvent	trace
7	1	temperature: 60 °C	75
8	2	-	96
9	0.5	-	98
11	0.1	-	62
12	0.05	-	36
13	1		99
14	1		99
15	1		99
16	0.25		93*

*Isolated yield after filtration.

v/v) of cosolvent (2-MeTHF)[13] was added, and the reaction mixture was diluted to 0.25 M global concentration. As seen in work by Zhang and co-workers, among the *t*-BuXPhos-based Pd complexes screened, the more lipophilic precatalyst [*t*-BuXPhosPd(cinnamyl)]OTf demonstrated the greatest reactivity under micellar catalysis conditions,[14] leading to full conversion in less than two hours (entries 14−16). The biodegradable surfactant, Savie, yet again showed remarkably effective enabling properties, further strengthening the original claims associated with its potential use in sustainable drug syntheses.[12] In this case, standalone amination using water as the reaction medium was very successful, affording product 5 in two hours and with a catalyst loading of only 0.25 mol % (i.e., 2500 ppm) Pd, in stark contrast to the far higher levels of Pd typically required for such C−N bond-forming processes.[15] Moreover, and also unlike aminations in traditional Pd-catalyzed couplings in waste-generating organic solvents, this far greener approach does not require column chromatography; the water-insoluble product can be easily isolated by simple filtration, yielding product 5 in a 93% yield (see page S11 in the SI for the ^{1}H NMR spectrum to assess a rough degree of purity).

The third and final step of this streamlined route to erdafitinib was the most challenging. Attempts to perform reductive amination using amine 5 were fruitless. The use of either *N*-Boc-protected or unprotected 2-(isopropylamino)-acetaldehyde failed to provide the targeted amine (Scheme 4).

Scheme 4. Attempts at Reductive Amination and Nucleophilic Substitution Reactions (Top) and Third and Final Step of the Synthesis (Bottom)



Ultimately, as reported in the initial patent,[9] nucleophilic substitution employing 5 and the HCl salt of *N*-(2-chloroethyl)propan-2-amine (6) led to the targeted drug. Thus, with KOH as the base and tetrabutylammonium bromide (TBAB) as a phase transfer catalyst, an S_N2 reaction in 2-MeTHF gave 7 in 95% isolated yield.

Overall, comparisons between the two crucial Pd-catalyzed couplings using our method and that from the patent clearly showcase the differences in terms of both greenness and efficiency (Table 4).[16] The newly developed approach, outlined in Scheme 5, demonstrates a significantly shortened three-step process requiring only two-pots, highlighting both "time"[17] and "pot"[18] economies. Perhaps the most attractive feature, however, is the complete elimination of any workup; hence, intermediate 3 can be used directly and without isolation, leading ultimately after amination to product 5 via this two-step, one-pot tandem sequence. However, when the amination reaction is run in a one-pot fashion, a Pd catalyst loading of 0.5 mol % (5000 ppm) and increased reaction temperature (55 °C) are needed to ensure complete consumption of intermediate coupling partner 3. Notwithstanding this increase in catalyst loading, it is still an order of magnitude lower than that use in the existing literature process.

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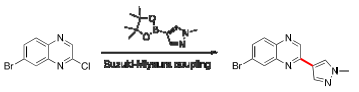
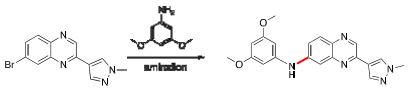
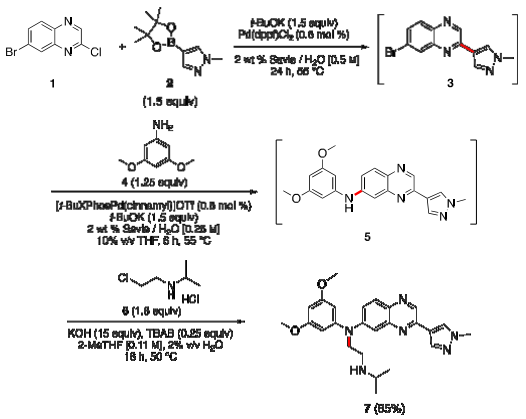
Table 4. Comparison between This Work and Literature Conditions

reaction parameters	this work	literature conditions
		
Pd loading	0.50 mol % (5000 ppm)	1 mol %
reaction temperature	55 °C	85 °C
solvent / medium	in water (with biodegradable surfactant, Savie)	DME
E Factor	8.8	11.6
		
Pd loading	0.25 mol % (2500 ppm)	5 mol %
reaction temperature	45 °C	90 °C
reaction time	2 h	overnight
solvent/medium	in water (with biodegradable surfactant, Savie)	dioxane
E Factor	12.3	128.5

Scheme 5. Three-Step, Two-Pot Sequence to Erdafitinib (7)



Product 5 can then be used directly for subsequent conversion to 7, obtained in 85% isolated yield.

In summary, an environmentally responsible, short synthetic route has been described to the drug erdafitinib, a very useful treatment for bladder cancer. The key Pd-catalyzed Suzuki–Miyaura and amination steps, in the composite, only require a total investment of 0.75 mol % of a commercially available monomeric catalyst and can be carried out in an aqueous medium using the biodegradable amphiphile Savie, thereby simplifying downstream wastewater processing. Overall, this sequence provides yet another example of designer surfactant-enabled chemistry in water that effectively replaces the use of traditional, and unsustainable, synthetic chemistry in organic solvents.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01380.

Supporting Information is available free of charge. Experimental procedures, optimization details, and analytical data (NMR and MS) (PDF)

AUTHOR INFORMATION

Corresponding Author

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

Authors

Vani Singhania − *Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States*

Chandler B. Nelson − *Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States*

Maya Reamey − *Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States*

Emile Morin − *Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States*

Rahul D. Kavthe − *Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c01380

Notes

The authors declare no competing financial interest.

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