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Aerobic C–H Olefination of Indoles via a Cross-Dehydrogenative Coupling in Continuous Flow

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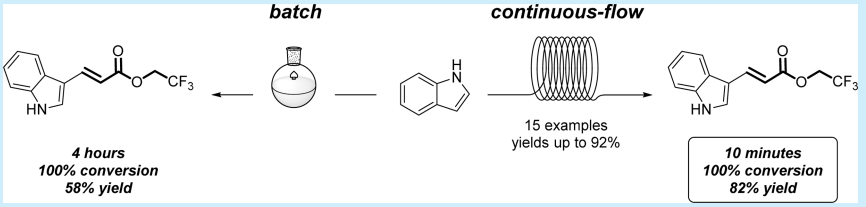
Supporting Information



ABSTRACT: Herein, we report the first site-selective, Pd(II)-catalyzed, cross-dehydrogenative Heck reaction of indoles in micro flow. By use of a capillary microreactor, we were able to boost the intrinsic kinetics to accelerate former hour-scale reaction conditions in batch to the minute range in flow. The synergistic use of microreactor technology and oxygen, as both terminal oxidant and mixing motif, highlights the sustainable aspect of this process.

3-Vinylindole motifs play a prominent role in active pharmaceutical ingredients (API) as they impart interesting biological properties, such as anticarcinogenic, antiviral, antibacterial, and antidepressant activities (Figure 1).[1−8] Consequently, reliable methods to prepare such compounds are of great importance. One appealing approach to prepare vinylindoles is via a cross-dehydrogenative Heck coupling.[9,10] Cross-dehydrogenative coupling (CDC) reactions allow the connection of two different C–H bonds under oxidative conditions. In contrast to traditional cross-coupling,[11] CDC bypasses the need for prefunctionalized coupling partners and produces, in theory, only water as a byproduct. Despite these apparent advantages, challenges still remain with regard to reactivity, selectivity, practicality, and scope.[12−15]

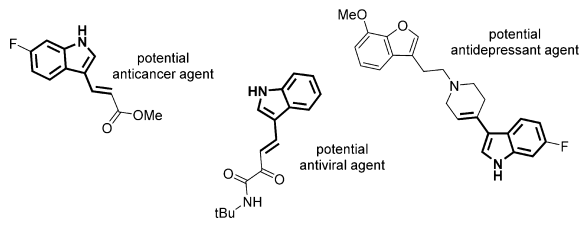


Figure 1. Examples of 3-vinylindole compounds displaying interesting biological activities.[3,5,7]

In 1967, Moritani and Fujiwara were the first to report a cross-dehydrogenative Heck reaction.[16] Their pioneering studies involved the coupling between olefins and benzene in the presence of stoichiometric amounts of $PdCl_2$. In 1999, Fujiwara described a highly efficient dehydrogenative Heck reaction of heterocycles, including (NH)-indole substrates, with olefins using catalytic amounts of $Pd(OAc)_2$ and tBuOOH as a terminal oxidant.[17] Inspired by the work of Fujiwara, several other research groups continued developing selective C-3 cross-dehydrogenative Heck reactions for (NH)-indoles, utilizing a variety of oxidants.[18−22] In 2012, Wang reported the use of gaseous oxygen as a sole terminal oxidant for this transformation.[20] Despite being the cleanest and cheapest oxidant, the use of oxygen in combination with flammable solvents raises significant safety concerns, especially on a larger scale. In addition, direct oxidation of Pd(0) by molecular oxygen is kinetically unfavored, allowing for the reduced palladium to agglomerate into inactive bulk metal.[23−30] With this in mind, the development of a safe and reliable CDC procedure to prepare 3-vinylindoles would be an attractive goal.

Due to its small dimensions, continuous-flow microreactors have received an increasing amount of attention to carry out such hazardous and challenging reactions.[31−46] Moreover, high gas–liquid mass-transfer coefficients are typically obtained in such devices which provides uniform oxygen concentration in the liquid phase. Gas–liquid flow regimes lead to a segmented flow which enables an intense contact between the liquid phase and gaseous reactants and induces small vortices inside each segment, allowing for fast mixing.[47−53] We anticipated that these features could prevent possible palladium agglomeration, ensure reoxidation of Pd(0) to Pd(II), and thus, efficiently avoid catalyst deactivation. The excellent gas–liquid mass transfer in combination with high reaction temperatures can further boost the reactivity of the catalytic system in flow. Herein, we report a minute-range protocol for the formation of 3-vinylindoles via cross-dehydrogenative Heck reaction in continuous flow using oxygen both as green oxidant and mixing motif.

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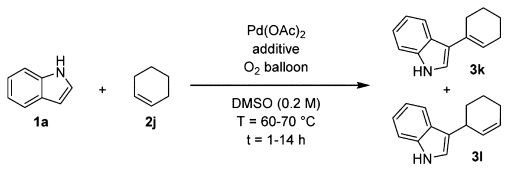
Table 1. Optimization of Reaction Conditions in Batch[a,54]



entry	additive (equiv)	temp (°C)	reaction time (h)	conversion[b] (%)
1		70	1	trace
2	TFA (8)	70	1	43
3	PivOH (8)	70	1	30
4	*p*-TsOH (8)	70	1	14
5	PhCOOH (8)	70	1	trace
6		60	14	11
7	TFA (1)	60	14	>95
8	TFA (2)	60	14	>95
9	TFA (4)	60	14	78
10	TFA (8)	60	14	69
11[c]	TFA (8)	60	14	NR
12[d]	TFA (8)	60	14	trace
13[e]	TFA (8)	60	14	21

[a]Reaction conditions: **1a** (0.5 mmol), **2j** (1.0 mmol, 2 equiv), $Pd(OAc)_2$ (0.05 mmol, 10 mol %), internal standard (0.05 mmol), and additive in DMSO (2.5 mL), O_2 balloon, specified temperature. A mixture of **3k** and **3l** was obtained. [b]Conversion of indole was determined with GC−FID and decafluorobiphenyl as the internal standard. [c]No $Pd(OAc)_2$. [d]$Pd(OAc)_2$ (0.005 mmol, 1 mol %). [e]$Pd(OAc)_2$ (0.025 mmol, 5 mol %). NR = no reaction.

We commenced our investigations by performing an initial screening of some reaction parameters in batch (Table 1). (NH)-indole (**1a**) was reacted with cyclohexene (**2j**) in the presence of 10 mol % of $Pd(OAc)_2$ as a catalyst and O_2 as sole oxidant in DMSO. From the literature, DMSO was found to be strongly coordinating, overriding any effect that acids may have on selectivity (e.g., migration to the C-2 carbon).[18,20] As a result, the reaction is characterized by excellent C-3 regioselectivity and *E* stereoselectivity. In addition, the use of such polar solvents is advantageous since they allow effective dissolution of organic products, efficiently avoiding microreactor clogging. At first, different organic acids, such as trifluoroacetic acid (TFA), pivalic acid (PivOH), benzoic acid (PhCOOH), and *p*-toluenesulfonic acid (*p*-TsOH), were tested as possible ligands to activate the Pd(II) complex (Table 1, entries 1−5). TFA was found to be the most suitable ligand (Table 1, entry 2). Next, the amount of TFA was investigated (Table 1, entries 6−10), demonstrating that 1 equiv of TFA was optimal (Table 1, entry 7). It was found that lowering the catalyst loading resulted in sluggish reaction conditions and incomplete conversion (Table 1, entries 11−13).

With optimized batch conditions in hand, a continuous-flow microreactor setup was assembled as described in Figure 2 (see the Supporting Information for a detailed description).

Initially, we investigated the temperature dependence in flow while keeping the residence/reaction time constant at 10 min (Table 2, entries 1−7). Microreactor technology offers the opportunity to accelerate reactions substantially at elevated temperatures without compromising safety aspects.[32,55,56] Moreover, by keeping the exposure time of the reaction mixture in the heated zone limited to what is kinetically required, extensive product degradation can be avoided. We found that increasing the temperature had a positive impact on the conversion, with 110 °C being the optimal temperature (Table 2, entry 4). A further increase of the temperature gave lower conversion,

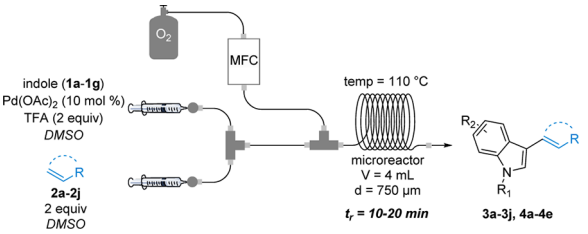
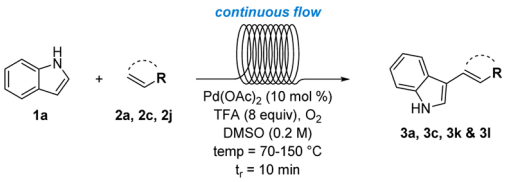


Figure 2. Schematic representation of micro flow setup. MFC = mass flow controller.

Table 2. Optimization of Reaction Conditions in Continuous Flow[a]



entry	olefin	temp (°C)	conversion[b] (%)
1	cyclohexene	70	18
2	cyclohexene	90	41
3	cyclohexene	100	57
4	cyclohexene	110	67, 43[g]
5	cyclohexene	120	67
6	cyclohexene	130	59
7	cyclohexene	150	clogging
8[c]	*tert*-butyl acrylate	110	clogging
9[d]	*tert*-butyl acrylate	110	73
10[d,e]	*tert*-butyl acrylate	110	90
11[d]	2,2,2-trifluoroethyl acrylate	110	79
12[d,f]	2,2,2-trifluoroethyl acrylate	110	100, 82,[g] 82[h]

[a]Reaction conditions: **1a** (4.0 mmol), $Pd(OAc)_2$ (0.4 mmol, 10 mol %), internal standard (0.4 mmol), and TFA (32.0 mmol, 8 equiv) in DMSO (10 mL) loaded in a 10 mL syringe. **2** (8.0 mmol, 2 equiv) in DMSO (10 mL) loaded in a 10 mL syringe. 2 mL microreactor, FEP tubing 750 μm inner diameter, t_r (residence time) = 10 min, 5:1 gas/liquid flow ratio provided a Taylor flow regime. [b]Conversion of indole was determined with GC−FID and decafluorobiphenyl as the internal standard. [c]TFA (4.0 mmol, 1 equiv). [d]TFA (8.0 mmol, 2 equiv). [e]t_r = 20 min. [f]4 mL microreactor, FEP tubing 750 μm inner diameter, t_r = 10 min, Taylor flow regime. [g]Isolated yield. [h]^{19}F NMR yield with decafluorobiphenyl as the internal standard.

presumably due to catalyst decomposition (Table 2, entries 5−7). Indeed, we observed microreactor clogging at 150 °C due to excessive Pd(0) precipitation inside the microchannels (Table 2, entry 7).[57] Next, we investigated two more activated olefins (*tert*-butyl acrylate and 2,2,2-trifluoroethyl acrylate) (Table 2, entries 9 and 11). To avoid catalyst degradation and thus microreactor clogging, we found that 2 equiv of TFA was mandatory (Table 2, entries 8−9). To achieve complete conversion, the residence time was doubled and the reactor was made twice as long (Table 2, entry 10 and 12). The latter ensured that higher flow rates could be obtained, leading to a higher degree of mixing in the segmented flow regime. This has a pronounced effect on the gas−liquid mass transfer, ensuring efficient palladium reoxidation. To our delight, this provided the conditions necessary to obtain full conversion (Table 2, entry 12).

With optimized flow conditions in hand, we explored the substrate scope for our system by varying the olefin coupling partner (Table 3) and the indole moiety (Table 4). A reaction

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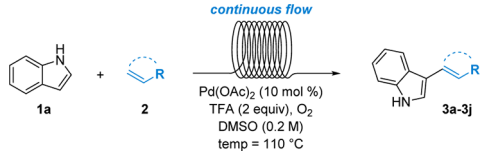
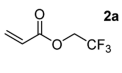
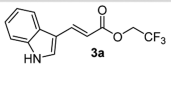
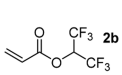
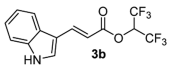
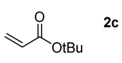
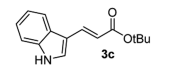
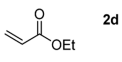
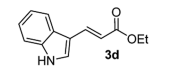
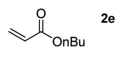
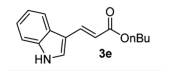
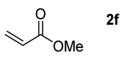
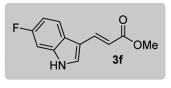
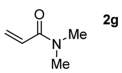
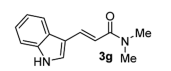
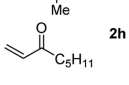
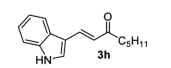
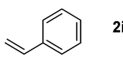
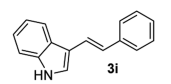
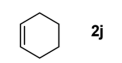
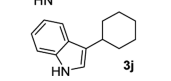
Table 3. Olefin Substrate Scope for the Pd(II)-Catalyzed Cross-Dehydrogenative Heck Reaction in Flow[a]

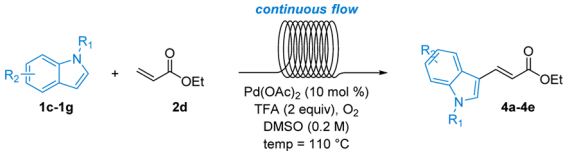


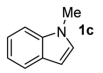
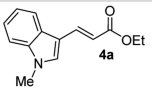
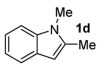
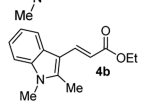
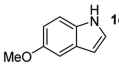
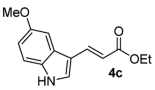
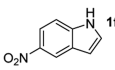
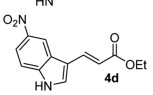
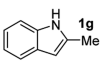
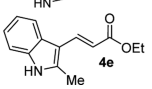
entry	olefin	product	t_r (min)	yield (%)[b]
1	 2a	 3a	10	82;58[c]
2	 2b	 3b	20	75
3	 2c	 3c	15	72
4	 2d	 3d	10	92
5	 2e	 3e	10	83
6[d]	 2f	 3f	10	67
7	 2g	 3g	20	70
8	 2h	 3h	15	49
9	 2i	 3i	20	27
10	 2j	 3j	20	43[e]

[a]Reaction conditions: **1a** (4.0 mmol), $Pd(OAc)_2$ (0.4 mmol, 10 mol %), internal standard (0.4 mmol), and TFA (8.0 mmol, 2 equiv) in DMSO (10 mL) loaded in a 10 mL syringe. **2** (8.0 mmol, 2 equiv) in DMSO (10 mL) loaded in a 10 mL syringe. 4 mL microreactor, FEP tubing 750 μm inner diameter, 5:1 gas/liquid flow ratio provided a Taylor flow regime. Conversion monitored with TLC and/or GC–MS. [b]Isolated yield. [c]Yield after 4 h batch reaction in similar conditions. [d]6-fluoroindole (**1b**) as substrate. [e]Isolated yield after hydrogenation.

between (NH)-indole and 2,2,2-trifluoroethyl acrylate (**2a**) resulted in a good isolated yield (82%) in only 10 min reaction time (Table 3, entry 1). Remarkably, a control experiment in batch showed that a 4 h reaction time was required to achieve full conversion. In addition, a drop in selectivity was observed due to prolonged exposure in the heated zone leading to a lower isolated yield of 58% (Table 3, entry 1). It is generally known that free (NH)-indoles are prone to decomposition when exposed to higher temperatures (>60 °C).[20] Next, a variety of electron-deficient olefins (acrylates, fluorinated acrylates, *N,N*-dimethylacrylamide, and 1-octen-3-one) and nonactivated olefins (styrene and cyclohexene) could be successfully coupled with free (NH)-indole in moderate to excellent yields (27–92%) within a 10–20 min residence time (Table 3, entries 2–10). C-3 olefination occurs smoothly for activated acrylates: (NH)-indole (**1a**) reacted with **2a–e** to form **3a–e** products in high yield

Table 4. Indole Substrate Scope for the Pd(II)-Catalyzed Cross-Dehydrogenative Heck Reaction in Flow[a]



entry	indole	product	t_r (min)	yield (%)[b]
1	 1c	 4a	10	84
2	 1d	 4b	20	52[c]
3	 1e	 4c	20	66
4	 1f	 4d	20	78
5	 1g	 4e	20	62[c]

[a]Reaction conditions: **1c–g** (4.0 mmol), $Pd(OAc)_2$ (0.4 mmol, 10 mol %), internal standard (0.4 mmol), and TFA (8.0 mmol, 2 equiv) in DMSO (10 mL) loaded in a 10 mL syringe. **2d** (8.0 mmol, 2 equiv) in DMSO (10 mL) loaded in a 10 mL syringe. 4 mL microreactor, FEP tubing 750 μm inner diameter, 5:1 gas/liquid flow ratio provided a Taylor flow regime. Conversion monitored with TLC and/or GC–MS. [b]Isolated yield. [c]No full conversion was observed.

(72–92%). The reaction of 6-fluoroindole (**1b**) with methyl acrylate (**2f**) produced methyl (*E*)-3-(6-fluoro-1*H*-indol-3-yl)acrylate (**3f**), a potential anticancer agent,[3] with a good yield of 67%. 1-Octen-3-one (**2h**) showed a lower reactivity (49%) toward C-3 olefination of indole, as compared to acrylates. Interestingly, within 20 min residence time, nonactivated olefins, such as styrene (**2i**) and cyclohexene (**2j**), gave the desired compounds (**3i** and **3j**), albeit in more moderate yield (27–43%).

Variation of the indole substrate was performed with ethyl acrylate as a benchmark coupling partner. The reaction proceeded smoothly with either electron-withdrawing (NO_2 and F) or electron-donating (MeO) substituents, producing, respectively, the 3-vinylindoles **3f**, **4c**, and **4d** in good yields (66–78%). Methyl substituents on the C-2 position were well tolerated (52–62%) (Table 4, entries 2 and 5). The use of *N*-methylindole (**1c**) as substrate only resulted in a small drop in yield (84%).

In summary, we have developed a fast and straightforward continuous-flow protocol for the dehydrogenative C-3 olefination of indoles using molecular oxygen as the sole oxidant. Because of the enhanced mass- and heat-transfer characteristics and the high degree of control provided by microflow processing, we were able to accelerate the intrinsic kinetics of the cross-dehydrogenative Heck coupling. Furthermore, the high surface-to-volume ratio of the oxygen phase with the liquid phase prevents catalyst degradation. Our protocol is effective to prepare a wide variety of 3-vinylindoles in good to excellent yields (27–92%) within residence times of 10–20 min. Notably, we were

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able to prepare methyl (*E*)-3-(6-fluoro-1*H*-indol-3-yl)acrylate (**3f**), a potential anticancer agent.

■ ASSOCIATED CONTENT

Supporting Information

Details on the continuous-flow microreactor setup, experimental procedures, characterization of the compounds, 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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