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One-pot Suzuki–Heck relay to prepare industrially valuable intermediates using the Pd–Cy*Phine catalyst system†

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A rare example of a one-pot, palladium-catalyzed Suzuki–Heck sequence has been developed with applicability to APIs and organoelectronic materials. High throughput screening was used to expedite development and survey strategies. Interchangeability of the coupling partners and the avoidance of intermediate isolation gives operational flexibility, which can be used to improve process efficiency and suppress by-product formation.

The installation of conjugated olefin moieties has been shown to be an important part of the synthetic process to prepare stilbene-based derivatives as key intermediates of pharmaceutical intermediates (APIs)¹ and materials used in organic light-emitting diode (OLED) technology^{2,3} (Fig. 1). As such, stilbene compounds have numerous applications in agriculture,⁴ drug discovery^{5–7} and materials science.^{8,9}

However, despite their usefulness in the synthesis of commercial products, the process by which olefin fragments are installed is step-wise and often inefficient, largely due to the complexity of the molecules. Although there are various synthetic routes to assemble these molecules, the process often requires two distinct reactions due to limited availability of commercial starting materials. The first involves the installation of a terminal, unsaturated C–C functional group to an aromatic substrate while the second involves the attachment of the unsaturated, terminal fragment to a different aryl group. In the case where alkynes are the unsaturated C–C functional group, a selective reduction step would also be necessary to form the desired olefin motif. A simpler and more direct approach to performing the assembly of the con-

jugated olefin moiety would be first to use a transition metal catalyzed Suzuki–Miyaura cross-coupling to install a terminal olefin group,^{10–18} followed by a Mizoroki–Heck reaction^{19–21} to attach the other aromatic substrate to the terminal olefin (Scheme 1). Conceptually, a single pot workflow would improve synthetic efficiency to bypass isolations, as well as alleviating the risk of intermediate instability that may arise with potentially sensitive terminal olefin functional groups.

While a one-pot sequential strategy is not a novel concept, this combination of transformations has very limited literature precedent. We are aware of only one reported example of a one-pot Suzuki/Heck sequence to prepare (*E*)-stilbenes using a heterogeneous, recyclable Pd/SiO₂ catalyst.²² However, this sequence is limited by long reaction times, moderate yields and limited substrate scope. To the best of our knowledge, there are no reports of a homogeneous metal based catalyst capable of coupling different heteroaryl substrates for both reaction types in a single pot. Thus, there exists an inherent difficulty in employing a sequential addition strategy in a single pot, despite the abundant literature precedence for both of these reaction types. To exacerbate the challenge, substrates used to prepare APIs and performance

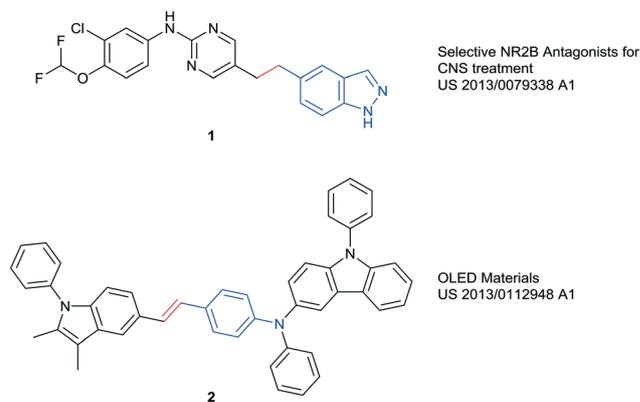


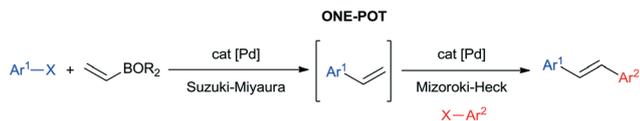
Fig. 1 Examples of patented commercial molecules that involve the installation of conjugated olefin moieties in their preparation.

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Scheme 1 Proposed one-pot Suzuki–Heck relay reaction.

materials are considerably more difficult as the functional groups can interfere with catalysis. As such, only highly capable catalysts with proven success in transforming a broad range of functionalized substrates in both reaction types using similar conditions warrant consideration; these criteria narrowed the catalyst selection pool substantially.

While the Suzuki reaction is relatively forgiving with a variety of favourable operating conditions, the Mizoroki–Heck reaction is the opposite, being very sensitive to reaction variation. In this context, one may be tempted to apply a Heck–Suzuki coupling strategy. However, one reason why the Suzuki reaction is so effective is that boronic acids react readily, suggesting they may not be stable under the harsher conditions typically required by the Heck reaction. As a result, it is more feasible to attempt a Suzuki–Heck strategy and manage the complexity of the Heck reaction sensitivity, which is challenging. For operational ease and practicality, the Suzuki–Heck sequence employed a single catalyst system as screening catalyst combinations with multiple reagents, solvents, and conditions exponentially increases the exploration space.

Several of us previously reported an extremely capable palladium-based catalyst system that incorporates an evolutionary *meta*-terarylphosphine ligand, Cy*Phine (Fig. 2). The Pd–Cy*Phine system has been shown to be very efficient in both the Suzuki and Heck reactions with notable substrate tolerability and low catalyst loading.^{23,24} Recently, we reported a related Pd(Cy*Phine)₂Cl₂ system which is used in one-pot multistep reactions including two-step borylation–Suzuki coupling and three-step borylation–Suzuki–amination (BSA) sequences.²⁵ Here, we report the development of a one-pot methodology of a sequential Pd–Cy*Phine-catalyzed Suzuki–Heck cross-coupling combination to prepare industrially valuable intermediates *via* the employment of high-throughput screening (HTS).

To carry out the one-pot Suzuki–Heck sequence using the Pd–Cy*Phine catalyst system, we initially set out to identify complementary conditions required for the Suzuki coupling step. It should be noted, however, that there is no requirement for the Suzuki step to precede the Heck reaction.

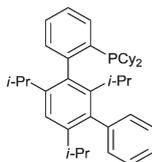


Fig. 2 Multi-arylphosphine ligand (Cy*Phine) used in one-pot Suzuki–Heck relay (SHR) sequence.

Rather, it is anticipated that the sequence should begin with Suzuki first simply due to its higher likelihood of being a quicker and more efficient transformation, in comparison to the Heck reaction. Upon literature review of relevant examples where Suzuki coupling is used as a strategy to install terminal olefin groups, we found that two palladium catalysts, Pd(PPh₃)₄ and Pd(dppf)Cl₂, are frequently used, with the former being significantly more popular. It is conceivable that the lack of other examples could be due to the Suzuki reaction being relative facile, thus obviating the need to use exotic and expensive catalyst alternatives. However, Pd(PPh₃)₄ and Pd(dppf)Cl₂ are not typically suitable for the Heck reaction, where different catalyst systems are favoured to perform the alkenylation step. Four commercially available vinylic boron-based reagents are frequently selected as the olefin source: vinylboronic acid pinacol ester, potassium vinyltrifluoroborate, vinylboronic acid dibutyl ester, and vinylboronic anhydride pyridine complex. Furthermore, a variety of solvent and base combinations are suitable for this transformation; conventional bases such as K₂CO₃, Na₂CO₃ and Cs₂CO₃ are effective when used in combination with solvent systems comprising dimethylformamide, acetonitrile, and dioxane/H₂O mixtures (10–20% H₂O v/v). Based on these findings, we hypothesized that modern catalyst systems that typically outperform Pd(PPh₃)₄ and Pd(dppf)Cl₂ in traditional Suzuki coupling reactions should be able to install the vinyl group onto aryl halide substrates *via* Suzuki coupling without significant complications. Furthermore, a favourable combination of bases and solvents may exist that are applicable for both the Suzuki transformation and the Heck reaction when the preferred Heck conditions for the Pd–Cy*Phine system are applied. In this regard, HTS should readily identify optimal conditions for both the Suzuki and the Suzuki–Heck reactions from screening arrays.

We commenced our studies by optimizing the catalytic conditions for two Suzuki coupling model reactions, HTS 1 using the Pd–Cy*Phine catalyst (Fig. S1 and S2 in ESI†). Methyl-4-chlorobenzoate (**3a**) and 5-bromo-1-(tetrahydro-pyran-2-yl)-1H-indazole (**3b**) were chosen as model substrates for HTS 1. These substrates resemble fragments of API intermediate **1**. Three solvents [DMF, MeCN, and dioxane:H₂O (9:1)], four commonly used bases [K₂CO₃, Cs₂CO₃, NaHCO₃, Cy₂NMe], and four vinylboron reagents were selected for the study. A total of 96 reactions were set up in HTS 1, consisting of 48 combinations for each substrate (see product yields in the ESI†).

In general, the Suzuki coupling of 4-methyl-chlorobenzoate (**3a**) using the Pd–Cy*Phine catalyst was fairly straight forward, giving a broad range of yields of the coupling product, **4a** in MeCN, DMF, and dioxane:H₂O (Fig. S1†). The latter combination was the best with the addition of H₂O playing an important role to achieve high conversions, especially with the less soluble inorganic bases. Both K₂CO₃ and Cs₂CO₃ in the dioxane:H₂O system afforded vinyl product **4a** nearly quantitatively with the trend: K₂CO₃ ≈ Cs₂CO₃ > NaHCO₃ > Cy₂NMe. In DMF and MeCN, only

K_2CO_3 showed good performance (trend: $K_2CO_3 > Cs_2CO_3 > NaHCO_3 > Cy_2NMe$) with only three exceptions. Direct activity comparison of the four boron coupling reagents in the three solvent systems was not clear since it showed a similar trend to that observed with the bases.

The Suzuki coupling with 5-bromo-1-(tetrahydro-pyran-2-yl)-1*H*-indazole (**3b**) was less trivial than with **3a** since favourable combinations were not obvious (Fig. S2†). However, DMF and dioxane:H₂O solvent systems performed slightly better than MeCN for all boron coupling reagents. The combination of vinylboronic acid pinacol ester with either K_2CO_3 or Cs_2CO_3 gave the best yields, leading to 70–80% of the coupling product **4b** in all three solvent systems (trend: $K_2CO_3 \approx Cs_2CO_3 > Cy_2NMe > NaHCO_3$). For all coupling reagents, $NaHCO_3$ was found to be least active in yielding **4b**, except in DMF. In contrast to the reaction of methyl 4-chlorobenzoate, Cy_2NMe produced higher yields of the coupling product **4b** in DMF and MeCN with all boron coupling reagents. It should be noted that varying amounts of vinyl boronate ester **4c** were observed using vinylboronic acid pinacol ester.

In light of these results, we set out to design a high-throughput screen for the Suzuki–Heck relay coupling using 4-methyl-chlorobenzoate and 3-chloropyridine as coupling partners. Preliminary tests established notable features such as the addition of tetra-*n*-butylammonium bromide (TBAB) that was favourable to the overall two-step reaction, and addition of Cy_2NMe that facilitated the Heck step. Conversely, the use of excess vinylic boron reagent, or the presence of water negatively affected the Heck coupling. Thus, the dioxane:H₂O combination was replaced by pure dioxane, which did not significantly impair either the Suzuki or the Heck reaction. Finally, all combinations that led to poor yields of the Suzuki product **4a**, as determined in HTS 1, were eliminated, TBAB was used in all reactions, and the boron coupling reagent equivalents were limited to 1.01.

Combinations involving the use of a single base (5.0 equivalents added initially) were matched with those in which Cy_2NMe was added at the second step with 3-chloropyridine (2.0 equivalents of base at each step). Cs_2CO_3 as a single base was eliminated because it was not a favourable base for the Heck coupling of substrates investigated previously²³ and combinations involving Cs_2CO_3/Cy_2NMe /vinylboronic dibutyl ester were eliminated due to the formation of the side-product 4-vinyl-benzoic acid butyl ester; a series of 58 combinations was thus obtained. Although it would have been ideal to add the reagents for the Heck as soon as the Suzuki was completed (observed at times to be as little as 3 hours), some of the tests revealed that the conversion of **3a** to the Suzuki product occasionally required an overnight reaction time. This incurred the risk that the catalyst's performance could be affected by longer reaction times in the presence of certain bases, which could potentially affect the second step negatively. To gain more information about these factors, the Suzuki was run overnight, followed by the Heck overnight. At this point, aliquots were taken out for analysis, but an additional 1 mol% of catalyst solution

was added to the reactions, and the plate was heated and stirred for an additional night. This protocol improved the consistency across all the reactions for a better comparison of the results.

The results of the Suzuki–Heck relay (SHR) with **3a** (HTS 2) are shown in Fig. 3 (see ESI† for details). A yield of 72% of the corresponding Suzuki–Heck product was obtained in one of the reactions, a value that increased to 93% following the addition of more catalyst – this particular reaction was conducted in dioxane using K_2CO_3/Cy_2NMe as bases, and vinylboronic anhydride pyridine complex as the olefin source. Among the three solvent systems, DMF performed the best, giving up to 70% yield and 88% after the addition of more catalyst – the general trend was DMF > MeCN > dioxane, with MeCN and dioxane becoming more similar after the addition of more catalyst. The addition of 1 mol% catalyst and longer reaction times led to significant yield increases, suggesting that addition of 1 mol% catalyst at the beginning of the second step, along with the aromatic substrate and second base, would lead to even better results. Among all base combinations surveyed, $NaHCO_3$, K_2CO_3/Cy_2NMe , and $NaHCO_3/Cy_2NMe$ demonstrated good performance with few exceptions. The general trend for single bases was $NaHCO_3 > K_2CO_3 > Cy_2NMe$ while that for combined bases was $K_2CO_3/Cy_2NMe \approx NaHCO_3/Cy_2NMe > Cs_2CO_3/Cy_2NMe$.

The efficacy of the methodology was reinforced by applying the one-pot Suzuki–Heck sequence to coupling 5-bromo-

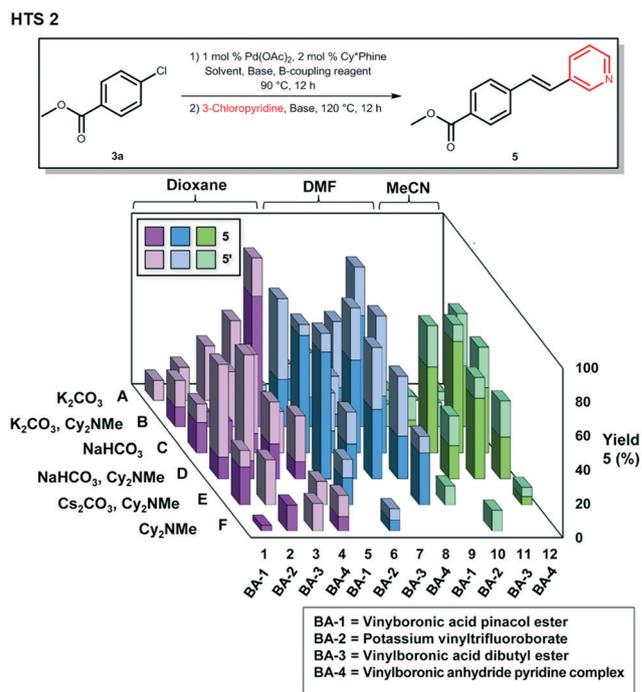
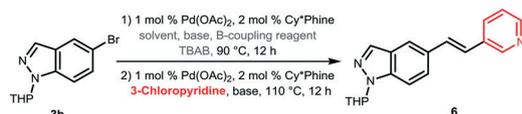


Fig. 3 Solvent, base and vinylic boron reagent optimization for HTS 2. Reaction conditions: **3a** (0.125 mmol), 3-Cl-pyridine (0.137 mmol), boron reagent (0.126 mmol), base (0.500 mmol), TBAB (0.025 mmol), solvent (475 μ L). Pd-Cy*Phine catalyst (25 μ L). Reactions were analyzed by GC/FID and quantitation was derived from previously established calibration curves.



Scheme 2 Suzuki–Heck relay reaction using 5-bromo-1-(tetrahydro-pyran-2-yl)-1H-indazole (**3b**) and 3-chloropyridine.

1-(tetrahydro-pyran-2-yl)-1H-indazole (**3b**) and 3-chloropyridine (Scheme 2) using the best combinations and conditions to afford compound **6**. The GC/MS analysis indicated a very promising 92% conversion to the expected coupling product. Intrigued by these results, the one-pot SHR sequence was attempted on a larger scale using substrates **3a** and **3b** with 3-chloropyridine as coupling partner and the products were isolated. We were able to achieve 78% isolated yield using **3a** (Table 1, entry 1). However, substrate **3b** afforded only 40% isolated yield (Table 1, entry 2). Careful investigation of this reaction after the Suzuki step revealed that **3b** produced an undesired homocoupling by-product (**4d**) along with the expected Suzuki product as identified by HPLC/MS and ^1H NMR spectroscopy (Fig. S18[†]). Interestingly, by interchanging the coupling partners (*i.e.* using 3-chloropyridine as Suzuki substrate and **3b** as Heck substrate) we achieved 82% of the coupling product (Table 1, entry 3).

Finally, using the developed protocol, the scope of this one-pot SHR method was explored by screening a diverse

range of heteroaryl chlorides and bromides to prepare industrially valuable intermediates for APIs and OLED materials (Table 1). We note that the *E*-stereoisomers are formed exclusively; none of the *Z*-isomers could be detected by GC or NMR spectroscopy. The Pd–Cy*Phine catalyst system demonstrated good performance, giving average yields of 64–91% for each step of the one-pot SHR sequence except for compound **8**, which afforded 51% average yield. The protocol was effective for installing the olefin moiety with various challenging fragments (entries 4, 7 and 8). The key benefit of this method is the flexibility to interchange the coupling partner to sidestep undesired homocoupling by-products. The avoidance of intermediate isolation likely improves process efficiency and economics with the absence of costs associated with workup, purification, isolation, drying, and waste disposal. The need to accommodate changes (*i.e.* catalysts, conditions, reagents, and solvents) to the subsequent reaction would further complicate the overall synthetic process.

In summary, a one-pot Suzuki–Heck coupling method was developed by leveraging high-throughput screening techniques and the capability of the Pd–Cy*Phine catalyst system. The synthesis of industrially important intermediates for APIs and organoelectronic materials in moderate to excellent yields demonstrated the efficacy of the protocol. Since the single-pot reaction approach is convenient and efficient, this methodology could be attractive to the synthetic, medicinal, and fine chemical industries.

Table 1 Substrate scope of the one-pot SHR cross-coupling methodology^a

Entry	Product ^{b,c}	Entry	Product ^{b,c}
1		5	
2		6	
3		7 ^d	
4		8	

^a Conditions: (Suzuki) 1 mol% Pd(OAc)₂/2 mol% Cy*Phine, 2.0 eq. K₂CO₃, 20 mol% of TBAB, 0.34 eq. vinyl boronic pyridine complex in DMF (0.25 M) at 90 °C for 12 h; (Heck) 1.1 eq. substrate, 2.0 eq. Cy₂NMe, 1 mol% Pd(OAc)₂/Cy*Phine at 110 °C for 12 h. ^b Isolated yield. ^c Bracket values indicate the average yield of each step. ^d NMR yield.

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Conflicts of interest

There are no conflicts to declare.

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