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Palladium-*meta*-Terarylphosphine Catalyst for the Mizoroki–Heck Reaction of (Hetero)Aryl Bromides and Functional Olefins

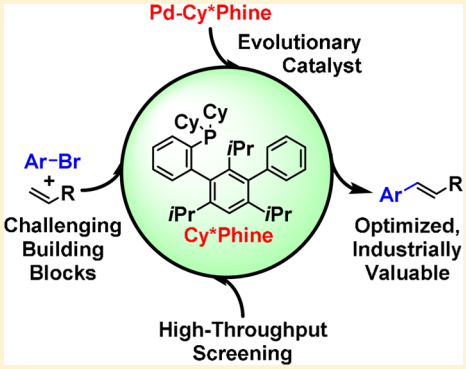
Daniel Weiliang Tay,*[†,§] Howard Jong,*[‡,§] Yee Hwee Lim,[‡] Wenqin Wu,[‡] Xinying Chew,[‡] Edward G. Robins,[†] and Charles W. Johannes[‡]

[†]Singapore Bioimaging Consortium (SBIC), Agency of Science, Technology and Research (A*STAR), 11 Biopolis Way, Helios, #01-02, Singapore 138667

[‡]Organic Chemistry, Institute of Chemical & Engineering Sciences (ICES), Agency of Science, Technology and Research (A*STAR), 11 Biopolis Way, Helios, #03-08, Singapore 138667

Supporting Information

ABSTRACT: The evolutionary *meta*-terarylphosphine ligand architecture of Cy*Phine was recently shown to be a key feature that imposed outstanding performance in palladium-catalyzed copper-free Sonogashira applications. Herein, the Pd-Cy*Phine combination has similarly proven to be a powerful catalyst system for the Mizoroki–Heck reaction. Using high-throughput screening (HTS) methodology, DMF and $NaHCO_3$ were rapidly identified as the most effective solvent and base pair for the cross-coupling catalysis of challenging and industrially valuable substrates including highly electron-rich heteroaryl bromides and unactivated olefins. Unprotected functional groups were well tolerated using low catalyst loadings, and the simple protocol produced excellent yields (up to 99%) with unprecedented substrate diversity. The Pd-Cy*Phine system broadly outperformed many state-of-the-art commercial alternatives, which demonstrated its potential as a next-generation cross-coupling catalyst.



INTRODUCTION

Since its discovery nearly a half century ago, palladium-catalyzed C–C cross-coupling reactions have become a powerful and indispensable tool for synthetic chemists in both industry and academia. Among this class of reactions, the Mizoroki–Heck reaction (MHR),[1−3] which involves the cross-coupling of an aryl halide (or pseudohalide) with an olefin, is recognized as the second most popular palladium-catalyzed reaction used in organic transformations.[4−15] The inherent usefulness of the olefin moiety in functional molecules has been broadly demonstrated in the synthesis of natural products,[14,16−18] organic materials[17,19−24] and pharmaceutical products,[6,17,25−28] such as Eletriptan[29−31] and Axitinib[32−35] (Figure 1).

In cases where the starting materials are highly reactive (e.g., aryl iodides, styrenes and acrylates), the MHR does not necessitate the use of a supporting ligand for efficient catalysis.

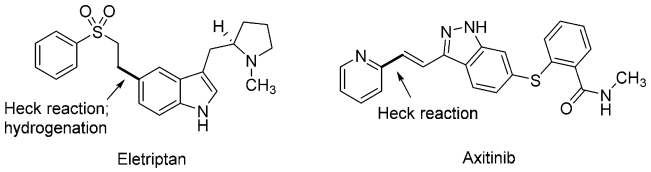


Figure 1. Application of the Mizoroki–Heck reaction in pharmaceutical products.

However, when more challenging substrates (e.g., electron-rich aryl bromides, aryl chlorides and unactivated olefins) are considered, the dependency on the ligand increases substantially and catalyst selection becomes key.[36,37] In this regard, the role of the auxiliary ligand not only affects the steric and electronic properties of the catalyst complex, but it also influences the solubility of the active species and can control the catalyst lifetime.[5,38,39] Bulky and electron-rich phosphine ligands are generally preferred as they exhibit a favorable balance of properties to facilitate a higher rate of substrate association and help promote rapid reductive elimination.[5,9,15,40,41] However, despite much evidence for accelerated catalysis using modern ligands for various cross-coupling reactions, the MHR is somewhat of an exception with many of the recent applications still employing simple monodentate phosphines, such as tri-(*o*-tolyl)phosphine and tri-*tert*-butylphosphine.[4,42,43] The former, P(*o*-Tol)$_3$, is a longstanding favorite for industrial applications, along with $Pd(OAc)_2$ as the preferred palladium source. This, in part, could be rationalized by the balance of cost, performance and predictability of the in situ catalyst prepared from $Pd(OAc)_2$ and P(*o*-Tol)$_3$.[6,25,26,28]

In terms of performance, catalyst development for the MHR was advanced when Herrmann and Beller introduced the precatalyst, cataCXium C, or better known as the Herrmann–

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Beller catalyst (HBC). The HBC palladacycle (*trans*-bis(acetate)bis[*o*-(ditolylphosphino)benzyl]dipalladium) is prepared from the combination of $P(o\text{-Tol})_3$ and $Pd(OAc)_2$, and is often considered to be a convenient alternative to its in situ $Pd(OAc)_2/P(o\text{-Tol})_3$ analogue as it has resistance to air and moisture, along with improved performance.[44−48] For the HBC, the palladation of the ligand seems to be advantageous for promoting the MHR. However, ligand cyclometalation is not a prerequisite for the design of efficient Heck catalysts. Nonpalladacycles, such as catalysts prepared from di-*tert*-butylphosphinoferrocene or QPhos (L4) in combination with $Pd_2(dba)_3$, have also shown to be excellent performers of the Heck reaction.[49,50]

Despite the considerable research effort that has been put into developing the MHR,[5,6,9,13,51] there is an obvious lack of examples in literature that broadly describes the cross-coupling of electron-rich heteroaryl halides, unactivated olefins, or substrates that contain unprotected functional groups. These compounds are of particular importance as they resemble fragments that are frequently used by the specialty chemicals and pharmaceutical industries; however, they are often recalcitrant in catalysis. Of the limited examples that are reportedly capable of transforming challenging substrates, high catalyst loadings (>5 mol %) are typically required. For palladium catalysts in particular, high loadings are especially problematic to the pharmaceutical industry as they have strict regulatory limits for the metal content allowed in the production of active pharmaceutical ingredients. Additional challenges often faced in the MHR is its sensitivity to condition changes and is easily influenced by all aspects of the catalytic system (e.g., catalyst, substrate, reaction media, bases, additives, etc.), which impedes the development of generic methods that are applicable to a diverse range of substrates.[36,38,52−54] As these obstacles still persist, the opportunity to circumvent these issues prompted our desire to contribute to this area. Herein, we report the employment of a palladium-based catalyst that contains an evolutionary *m*-terarylphosphine ligand, Cy*Phine, which efficiently promotes the cross-coupling of an extensive range of challenging (hetero)aryl bromides and functional olefins using a practical and robust protocol.

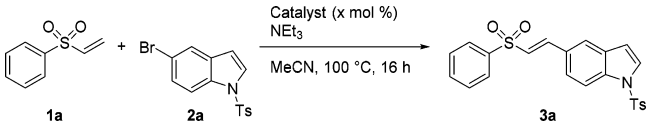
RESULTS AND DISCUSSION

Recently, our group reported the development of a *meta*-terarylphosphine ligand, Cy*Phine (**L1**), which was found to be an excellent supporting ligand for palladium-catalyzed copper-free Sonogashira cross-coupling reactions.[55] The outstanding performance that the Pd-Cy*Phine system exhibited in alkynylation catalysis spurred our interest to investigate whether the observed high activity was transferrable to other C−C cross-coupling applications. We proceeded to evaluate its efficacy in the Mizoroki−Heck reaction with a bias toward developing the catalyst technology for industrially relevant applications.

Phenyl vinyl sulfone (**1a**) and 5-bromo-1-tosyl-1*H*-indole (**2a**) were selected as the coupling partners for our model reaction as they resembled fragments that were used to prepare the triptan drug, Eletriptan (Figure 1). The initial conditions tested were adopted from industrial protocols, which included the use of acetonitrile (MeCN) and triethylamine (NEt_3) as the solvent and base, respectively. The reactions were heated to 100 °C and vigorously stirred for 16 h. Using the HBC as the benchmark, we were delighted to observe a significant performance advantage in favor of the Pd-Cy*Phine in situ generated catalyst for the coupling of **1a** with **2a**.

At a high catalyst load (6 mol %), Pd-Cy*Phine was found to perform more than 400% better than the HBC, affording a yield of 93 and 22%, respectively (Table 1, Entries 2 and 1). At lower

Table 1. Preliminary Performance Evaluation of the Pd-Cy*Phine Catalyst[a]



entry	catalyst[b]	mol % Pd	conc. (mol/L)	yield [%][c]
1	Herrmann−Beller	6	0.30	22
2	Pd-Cy*Phine	6	0.30	93
3	Pd-Cy*Phine	3	0.30	48
4	Pd-Cy*Phine	3	0.50	68
5	Pd-Cy*Phine	3	1.0	76
6	Pd-Cy*Phine	3	1.5	73
7	Pd-Cy*Phine	3	2.0	74

[a]Reaction conditions: **1a** (1.3 mmol), **2a** (1 mmol), NEt_3 (2.4 mmol), MeCN, 100 °C, 16 h. [b]The Pd-Cy*Phine catalyst is prepared in situ using a 1:2 ratio of $Pd(OAc)_2$ and Cy*Phine. [c]Yields were calculated on the basis of the ^1H NMR analysis of the crude reaction mixture using hexamethylbenzene as the internal standard.

loadings (3 mol %), the yield for Pd-Cy*Phine decreased to 48% (Table 1, entry 3). However, good performance was re-established upon increasing the reaction concentration from 0.30 to 1.0 M; operating at higher concentrations (1.5 and 2.0 M) was not found to be advantageous (Table 1).

While a higher reaction concentration enabled the Pd-Cy*Phine catalyst to achieve better activity, a more rigorous approach to reaction optimization was necessary to further enhance the catalyst's performance. In collaboration with the Centre for Catalysis Research and Innovation (CCRI), high-throughput screening (HTS) methodology was utilized to determine the optimal catalytic conditions for two model reactions, HTS 1 and 2. The coupling partners for HTS 1 and 2 were again chosen for their similarities to fragments used in the preparation of commercial drugs, Eletriptan and Montelukast,[56−59] respectively. In addition, the substrates met other selection criteria, which included having different functional groups and the opportunity to extract selectivity information (HTS 2). Various solvents were surveyed (DMF, dioxane, toluene, MeCN), which ranged in polarities along with a series of six commonly used bases for the MHR. Both organic (NEt_3, Cy_2NMe) and inorganic bases (Cs_2CO_3, K_3PO_4, AgOAc, $NaHCO_3$) were selected, which all varied in basicity strength to capture the effects of a diverse matrix of solvent and base combinations.

The screening study was carried out using 96-well reactor plates that were equipped with automated sample processors. The catalyst and starting materials were added volumetrically from stock solutions via the automated core module, as were the liquid bases and reaction solvents; the inorganic bases were dispensed manually into the plate wells. The reaction wells were sealed and heated at 120 °C on an orbital shaker for 16 h. Afterward, aliquots were withdrawn automatically and flushed through silica on a multiwelled filtration plate. The results were analyzed by HPLC (for HTS 1), or by GC-FID (for HTS 2), using phenanthrene as the internal standard. The reaction sets

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were duplicated reliably with an overall standard deviation of 2.7%.

From Figure 2, the results for HTS 1 clearly showed moderate to poor yields when the organic bases, NEt_3 and

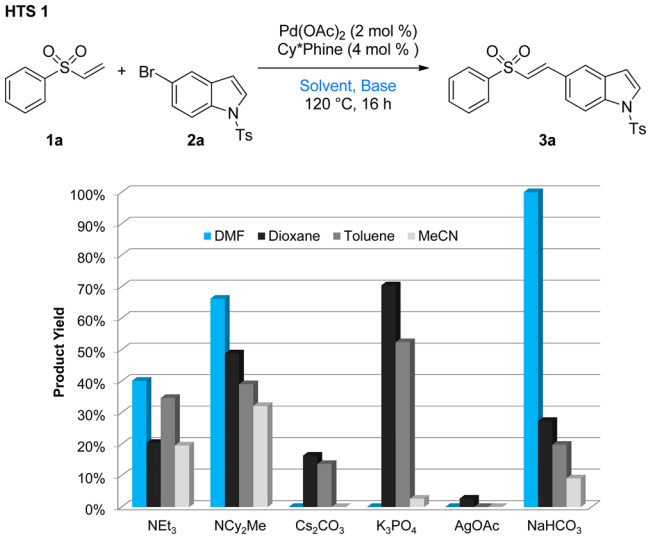

Figure 2. Solvent and base optimization for HTS 1. Reaction conditions: **1a** (0.15 mmol); **2a** (0.125 mmol), base (0.25 mmol), solvent (500 μL), 120 °C, 16 h. Yields were calculated on the basis of the analytical HPLC analysis of the crude reaction mixture using phenanthrene as the internal standard.

NCy_2Me, were used with latter being superior, in general. The inorganic bases did not fare much better with Cs_2CO_3 and AgOAc being the least effective of the series. With regards to solvent selection, the data loosely indicated an improved catalyst performance with higher-boiling, polar solvents (e.g., DMF and dioxane). As a distinct correlation between the solvent and base combinations was not palpable, the evidence further corroborates the inherent complexity and unpredictability of the MHR. Nonetheless, one solvent and base pair proved to be exceedingly effective. Using the Pd-Cy*Phine catalyst with $NaHCO_3$ in a DMF solution, outstanding performance (>99% yield) was achieved for HTS 1.

With the fundamental difficulty of predicting optimal reagent combinations and reaction conditions, a strategic combinatorial approach was found to be not only beneficial, but necessary for success, particularly for the MHR.

The benefits of using a strategic combinatorial approach via high-throughput experimentation were also evident in the evaluation of the second reaction, HTS 2. Here, many more effective combinations of solvents and bases afforded favorable outcomes. Good to excellent yields could be achieved by using organic amine bases (NEt_3 and NCy_2Me) with any of the four solvents that were evaluated. This differed from the results using inorganic bases where only $NaHCO_3$ was capable of producing good yields in either toluene, or MeCN, solutions (Figure 3). Despite having several suitable solvent and base combinations, the yields depicted in Figure 3 were measured as a total of the tautomeric products, **3f** and **3f′**. It was apparent that the solvent and base combinations had a significant impact on product selectivity, as well as an impact on substrate conversion. While the overall yields for HTS 2 were poor using K_3PO_4 and AgOAc, it was interesting to observe the reaction's preference to produce the thermodynamically less favored

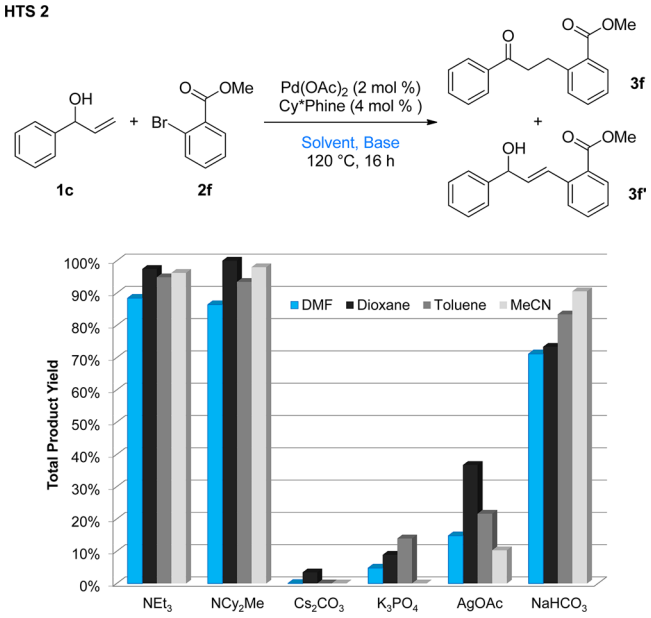

Figure 3. Solvent and base optimization for HTS 2. Reaction conditions: **1c** (0.15 mmol); **2f** (0.125 mmol), base (0.25 mmol), solvent (500 μL), 120 °C, 16 h. Yields were calculated on the basis of the analytical GC-FID analysis of the crude reaction mixture using phenanthrene as the internal standard.

product, **3f′**. Conversely, complete selectivity for product **3f** could be attained by using DMF as the solvent with NEt_3, NCy_2Me, or $NaHCO_3$ as the base (Figure 4). At this time,

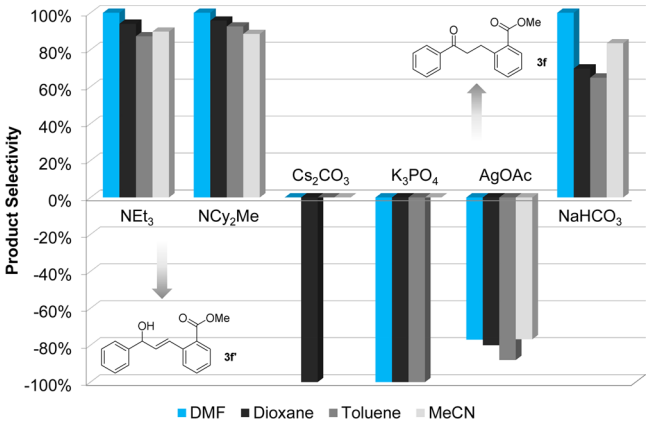

Figure 4. Selectivity profile for products **3f** and **3f′** from HTS 2. Reaction conditions: **1c** (0.15 mmol); **2f** (0.125 mmol), base (0.3 mmol), solvent (500 μL), 120 °C, 16 h. Yields were calculated on the basis of the analytical GC-FID analysis of the crude reaction mixture using phenanthrene as the internal standard.

there appears to be little evidence to support the predictability of the resultant selectivity simply based on the various solvent and base combinations. Nonetheless, a balanced combination of conversion and selectivity could be achieved with the use of dioxane and NCy_2Me, which was previously reported by Fu and co-workers to be effective for the MHR of aryl chlorides with activated olefins using $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ as an in situ catalyst.[43]

From the data collected for HTS 1 and 2, it was evident that the most generally applicable combination was DMF with $NaHCO_3$, which was capable of achieving good to excellent

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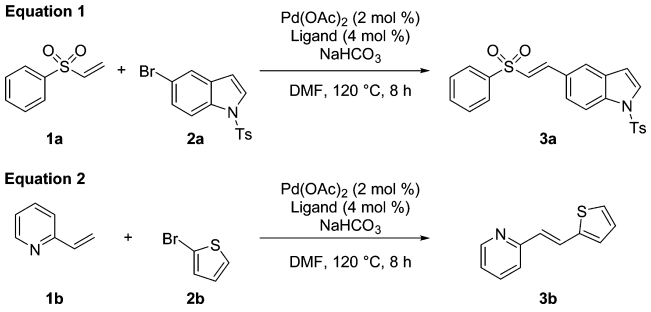
yields for both reactions. As a complementary strategy, NCy_2Me in dioxane, or MeCN, could also be considered.

After having established a favorable solvent/base pair and effective reaction conditions, a competitive study was performed to determine the performance level of Cy*Phine (**L1**) relative to other commercially available phosphine ligands that were reportedly effective for the Pd-mediated MHR. Five other candidates were selected, which included XPhos (**L2**), SPhos (**L3**), QPhos (**L4**), cataCXiumA (**L5**) and tri(*o*-tolyl)phosphine (**L6**). For more completeness, two reactions were used for measurement: the model reaction (eq 1), as well



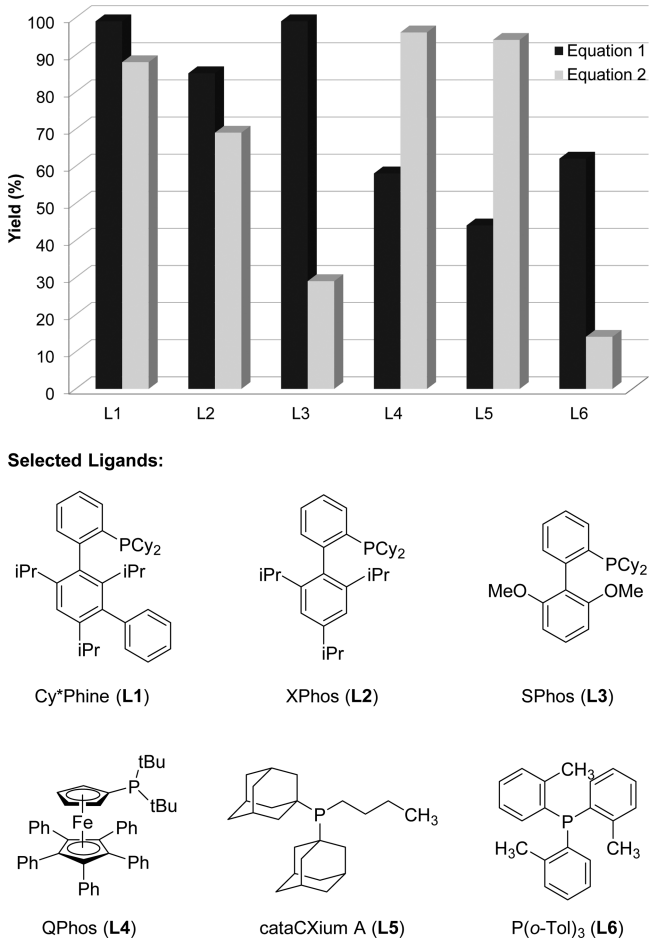
as eq 2, which involved the coupling of 2-vinylpyridine (**1b**) with 2-bromothiophene (**2b**). Purposefully, the selection criteria for the reactions included the coupling of two heteroaromatic partners as there is little precedence in the literature of these types of substrates being effectively catalyzed. Furthermore, these substrates are representative building blocks that may have industrial significance.

The outcome of the performance test was very encouraging as Cy*Phine (**L1**) achieved excellent results for both eqs 1 and 2, furnishing yields of 99 and 88%, respectively (Scheme 1). All other ligands (**L3** − **L6**), with the exception of XPhos (**L2**), were unable to achieve good results for both reactions as each of them performed significantly better in one reaction relative to the other. For instance, SPhos (**L3**) achieved comparatively excellent yields for eq 1, but was poor in eq 2; conversely, QPhos (**L4**) and cataCXium A (**L5**) showed the reverse bias with eq 2 being preferred. Under these conditions, the industrially popular tri(*o*-tolyl)phosphine (**L6**) was not a strong performer in either eq 1 or 2 giving yields of 58 and 14%, respectively. By comparison, XPhos (**L2**), produced good yields of 85 and 69% for the two respective reactions and exhibited less performance variation. However, **L2** was found to be significantly less productive than **L1** in all cases.

From the competition, it was apparent that Pd-Cy*Phine system may not have been dominant in both reactions. However, it was undoubtedly the best overall catalyst demonstrating strength in terms of consistency and generality for the MHR. Importantly, the broadly applicable performance of the Pd-Cy*Phine system addresses a persistent issue with the MHR being fastidious and reaction specific.

Upon examining the improved performance of **L1** relative to the structurally similar **L2**, the results distinctly highlight the benefits of incorporating the *m*-teraryl framework into the phosphine ligand architecture; this was consistent with our observations in palladium-catalyzed copper-free Sonogashira cross-coupling. As our effort to rationalize this effect is ongoing, it is postulated that the *m*-teraryl structure of **L1** is prolonging the active catalyst lifetime much more effectively than **L2**, which utilizes a biaryl framework.[75] While the overall effect is likely to be complex involving multiple parameters, one feature

Scheme 1. Ligand Performance Comparison[a]



[a]Reaction conditions: **1** (1.3 mmol), **2** (1 mmol), $NaHCO_3$ (2.4 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), DMF (2 mL), 120 °C. Yields were calculated on the basis of the ^1H NMR analysis of the crude reaction mixture using hexamethylbenzene as the internal standard.

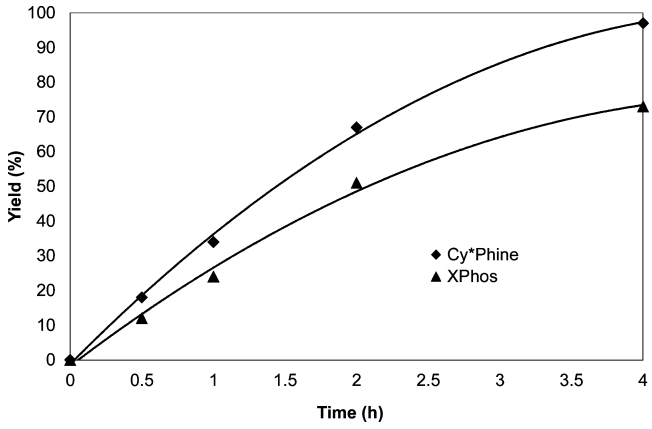


Figure 5. Performance and structural relationship between Cy*Phine (**L1**) and XPhos (**L2**). Reaction conditions: **1a** (1.3 mmol), **2a** (1 mmol), $NaHCO_3$ (2.4 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), DMF (2 mL), 120 °C. Yields were calculated on the basis of the ^1H NMR analysis of the crude reaction mixture using hexamethylbenzene as the internal standard.

that could be contributing to the improved performance of **L1** is the prevention of ligand destabilization, which is more likely

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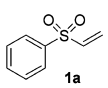
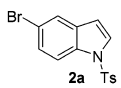
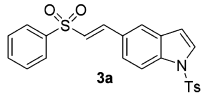
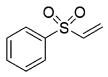
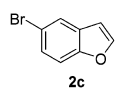
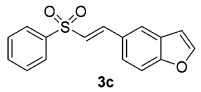
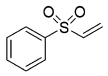
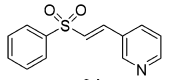
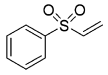
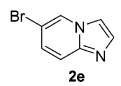
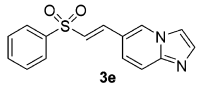
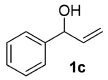
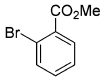
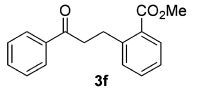
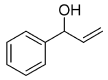
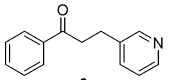
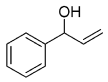
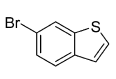
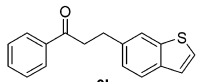
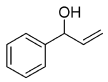
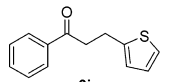
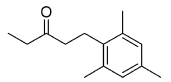
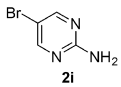
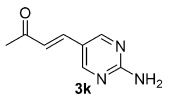
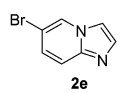
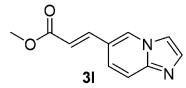
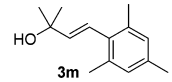
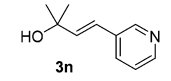
J. Org. Chem. 2015, 80, 4054−4063

Table 2. Substrate Scope[a]

Entry	Olefin	Aryl Bromide	Product	Yield (%)[b]
1	 1a	 2a	 3a	91
2		 2c	 3c	84
3		 2d	 3d	92
4		 2e	 3e	87
5	 1c	 2f	 3f	92
6		 2d	 3g	89
7		 2g	 3h	83
8		 2b	 3i	91
9	 1d	 2h	 3j	91
10	 1e	 2i	 3k	92
11	 1f	 2e	 3l	86
12	 1g	 2h	 3m	76
13		 2d	 3n	98
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15		2e	3p	89
16	1b	2d	3q	99
17		2b	3b	85
18	1d	2i	3r	89
19	1f	2a	3s	84
20		2j	3t	86

[a]Reaction conditions: **1** (1.3 mmol), **2** (1 mmol), $NaHCO_3$ (2.4 mmol), $Pd(OAc)_2$ (0.02 mmol) Cy*Phine (0.04 mmol), DMF (2 mL), 120 °C, 8 or 16 h. [b]Average yields of two runs.

to occur on **L2** via Pd-assisted dearomatization of the second aromatic ring (e.g., 2,4,6-triisopropylphenyl group of **L2**) on the biarylphosphine ligand. This dearomatization phenomenon has been previously shown to occur on biarylphosphine ligands by the Buchwald group.[60] Furthermore, the effect is potentially competitive with the catalytic cycle after oxidative addition has occurred.[61] At this point in time, neither our group nor others, have observed the dearomatization effect occurring on a *m*-terarylphosphine system. With the inhibition of competing side reactions, Cy*Phine is presumably able to maintain the Pd catalyst in its active state for longer periods of time, which ultimately increases its catalytic efficiency.

To probe the catalytic performance difference between **L1** and **L2** in more detail, eq 1 was monitored over time to extract kinetic information, which would more accurately capture the enhancement effect of the *m*-teraryl architecture relative to the biaryl analogue. In this study, Cy*Phine (**L1**) was found to produce 10% more product than XPhos (**L2**) after 1 h, to which the advantage for **L1** was further increased to 16% after 2 h and finally to 24% after 4 h (Figure 5). The reaction profile clearly exhibited an accelerative advantage of **L1** compared to **L2**, which appeared to be tiring much sooner than **L1**.

With general and effective conditions for the MHR, we proceeded to further explore the scope of the reaction by screening a diverse range of (hetero)aryl bromides and functional olefins that were reminiscent of modules of functional molecules. To our delight, the protocol for the Pd-Cy*Phine catalyst was very effective for a broad array of challenging substrates and afforded good to excellent yields (Table 2). Importantly, Pd-Cy*Phine was able to tolerate a wide variety of functional groups including unprotected alcohols (Table 2, entries 5−9, 12−15 and 18) and amines (Table 2, entries 10, 14 and 18). Electron-rich heteroaryl bromides, such as thiophenes (Table 2, entries 8 and 17), benzothiophenes (Table 2, entries 7 and 20), benzofurans (Table 2, entry 2), pyrimidines (Table 2, entries 10, 14 and 18), indoles (Table 2, entries 1 and 19), pyridines (Table 2, entries 3, 6, 13 and 16) and imidazopyridine (Table 2, entries 4, 11 and 15) all proceeded smoothly without complications. Similar to the result of HTS 2, the use of vinyl alcohols **1c** and **1d** yielded the corresponding ketone product with high selectively (Table

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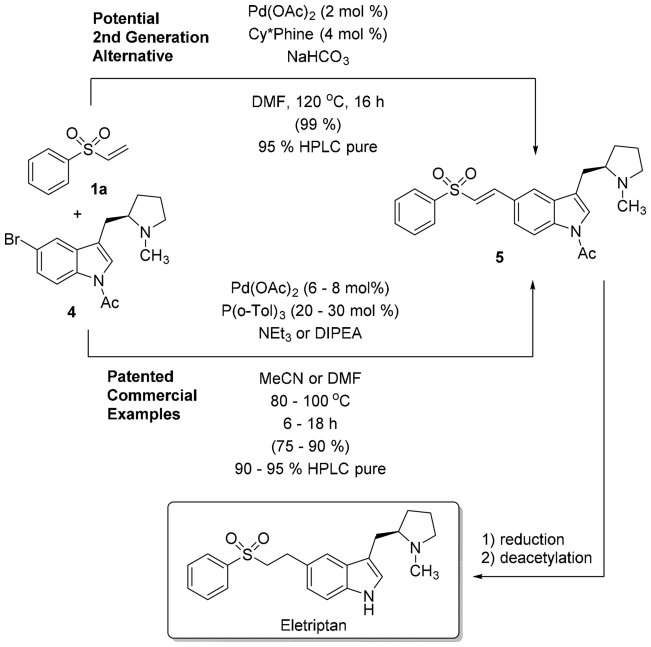
J. Org. Chem. 2015, 80, 4054−4063

2, entries 5–9 and 18). To our best knowledge, access to this breadth and scope of challenging, industrially valuable substrates is unprecedented using a single catalyst system with one reaction condition.

As our initial aim was to develop a catalyst system with methods that could be effectively applied to the synthesis of industrially valuable molecules, we pursued the preparation of a key Eletriptan intermediate using our new protocol as a potential replacement strategy for existing commercial approaches that incorporate the MHR. To prepare, **5**, 2 mol % of the Pd-Cy*Phine catalyst was used to perform the MHR achieving nearly quantitative yield (99%) of product **5** with 95% purity, as determined by HPLC.[62] These results were significant improvements to recently reported commercial methods that used much higher catalyst loads and ligand amounts (6–8 mol % of $Pd(OAc)_2$ and 20–35 mol % of P(*o*-Tol)$_3$) to achieve a lower level of performance.[29−31,63−65] Product **5** can be further manipulated in two steps (via reduction and deacetylation) to afford Eletriptan (Scheme 2).[63−66]

Scheme 2. Performance Comparison between the Pd-Cy*Phine Protocol and Patented Commercial Methods to Synthesize Key Eletriptan Intermediate, 5



CONCLUSIONS

In conclusion, we have developed a facile and efficient Mizoroki–Heck cross-coupling protocol using the evolutionary *m*-terarylphosphine ligand, Cy*Phine, in combination with $Pd(OAc)_2$. Industrially related model reactions were optimized via high-throughput screening methodology where DMF/$NaHCO_3$ was found to be the most broadly effective solvent/base combination for the reactions. A diverse array of challenging, (hetero)aryl bromides and functional olefins were cross-coupled with good to excellent yields. Moreover, the substrate breadth was found to be extensive and unprecedented. The high efficiency, functional group tolerance and versatility of the developed MHR protocol suggests that the Pd-Cy*Phine catalyst system can be an attractive and reliable tool for discovery chemists. Having successfully translated the method to improve the synthetic efficiency to produce a key Eletripan intermediate, Pd-Cy*Phine warrants consideration for its employment in industrial applications as well, and will soon be commercially available.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all reagents were purchased from commercial sources and were used as received without further purification. All operations were performed in an argon filled glovebox with Schlenk techniques. Dry tetrahydrofuran (THF), hexanes, and toluene (PhMe) were obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns, and they were further treated with dry molecular sieves. Dry *N*,*N*′-dimethylformamide (DMF), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), and 1,4-dioxane were purchased from commercial sources as sure-sealed anhydrous solvents and were used without further treatment. Reactions were monitored by thin-layer chromatography (TLC), which was performed on 0.25 mm silica gel plates by using UV light as the visualizing agent. Column chromatography was performed on silica gel (200–300 mesh) by elution with appropriate solvent, yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Gas chromatography analysis was performed with an FID detector and capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness) by using helium as the carrier gas. GC–MS analysis was performed by with triple-axis detector and capillary column by using helium as the carrier gas. NMR spectra were recorded with a 400 or 600 MHz instrument and were calibrated by using residual nondeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; C_6D_6: δ_H = 7.16 ppm, δ_C = 128.06 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.00 ppm; CD_3CN: δ_H = 1.94 ppm, δ_C = 1.32, 118.26 ppm) as an internal reference; IR spectra were recorded with FTIR spectrometer. MS and HRMS were recorded with an ESI-TOF mass spectrometer by using EI (electron ionization) or ESI (electrospray ionization). Preparation of Cy*Phine (**L1**)[55] and compound **4**[63,64,66] were in accordance to the previously reported procedures. The liquid bases (NEt_3 and NCy_2Me) used for the HTS experiments were dried and distilled prior to usage. The solid bases for the HTS experiments (Cs_2CO_3, K_3PO_4, AgOAc and $NaHCO_3$) were used as received after being evacuated overnight and stored under inert atmosphere.

General Procedure for the Mizoroki–Heck Coupling. A sealable reaction tube equipped with a stirring bar was charged with $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol %), Cy*Phine (**L1**, 22.4 mg, 0.04 mmol, 4 mol %) and $NaHCO_3$ (202 mg, 2.4 mmol), followed by the addition of the olefin (1.3 mmol), aryl bromide (1.0 mmol) and 2 mL of DMF. The tube was sealed with a Teflon-lined septum and heated to 8–16 h with vigorous stirring. The resulting suspension was cooled to room temperature, diluted with EtOAc, and filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel.

*(E)-5-(2-(Phenylsulfonyl)vinyl)-1-tosyl-1H-indole (**3a**).* Following general method, the reaction of phenyl vinyl sulfone (219 mg, 1.3 mmol) and 5-bromo-1-tosyl-1*H*-indole (350 mg, 1.0 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:1) to afford the title compound as a white solid (398 mg, 91%): mp 119–121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.7 Hz, 1 H), 7.96–7.92 (m, 2 H), 7.78–7.70 (m, 3 H), 7.65 (d, J = 1.7 Hz, 1 H), 7.63–7.57 (m, 2 H), 7.56–7.51 (m, 2 H), 7.43 (dd, J = 8.7, 1.8 Hz, 1 H), 7.25–7.19 (m, 2 H), 6.83 (d, J = 15.4 Hz, 1 H), 6.65 (dd, J = 3.7, 0.8 Hz, 1 H), 2.33 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 145.5, 142.8, 141.0, 136.2, 135.1, 133.4, 131.3, 130.1, 129.4, 127.8, 127.8, 127.7, 127.0, 126.4, 124.5, 122.8, 114.2, 109.1, 21.7 ppm; IR (film) 3343, 2945, 2833, 1659, 1448, 1413, 1113, 1025 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}NO_4S_2Na^+$ [M + Na]$^+$ 460.0637, found 460.0648.

*(E)-2-(2-(Thiophen-2-yl)vinyl)pyridine (**3b**).* Following general method, the reaction of 2-vinylpyridine (140 μL, 1.3 mmol) and 2-

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J. Org. Chem. 2015, 80, 4054–4063

bromothiophene (97 μL, 1.0 mmol) proceeded for 16 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:3) to afford the title compound as a yellow solid (159 mg, 85%): ^{1}H NMR (600 MHz, CD_3CN) δ = 8.57−8.51 (m, 1 H), 7.82 (d, J = 15.8 Hz, 1 H), 7.71 (td, J = 7.7, 1.9 Hz, 1 H), 7.41−7.34 (m, 2 H), 7.25 (d, J = 3.5 Hz, 1 H), 7.18 (ddd, J = 7.7, 4.7, 1.1 Hz, 1 H), 7.07 (dd, J = 5.1, 3.5 Hz, 1 H), 7.02 (d, J = 15.8 Hz, 1 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, CD_3CN) δ = 155.7, 150.4, 142.7, 137.4, 128.7, 128.7, 128.1, 126.6, 125.9, 122.9, 122.9 ppm. The physical data were in full accordance with the literature value.[67]

*(E)-5-(2-(Phenylsulfonyl)vinyl)benzofuran (**3c**).* Following general method, the reaction of phenyl vinyl sulfone (219 mg, 1.3 mmol) and 5-bromobenzofuran (125 μL, 1.0 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:1) to afford the title compound as a white solid (239 mg, 84%): mp 96−99 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.00−7.94 (m, 2 H), 7.82−7.77 (m, 1 H), 7.75 (d, J = 1.8 Hz, 1 H), 7.66 (d, J = 2.2 Hz, 1 H), 7.63−7.60 (m, 1 H), 7.58−7.53 (m, 2 H), 7.52−7.49 (m, 1 H), 7.44 (dd, J = 8.6, 1.8 Hz, 1 H), 6.85 (d, J = 15.3 Hz, 1 H), 6.79 (dd, J = 2.2, 0.9 Hz, 1 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 156.4, 146.4, 143.0, 140.9, 133.3, 129.3, 128.2, 127.6, 127.4, 125.9, 124.6, 122.5, 112.2, 106.8 ppm; IR (film) 3347, 2946, 2834, 158, 1449, 1115, 1027 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}O_3SNa^+$ [M + Na]$^+$ 307.0403, found 307.0399.

*(E)-3-(2-(Phenylsulfonyl)vinyl)pyridine (**3d**).* Following general method, the reaction of phenyl vinyl sulfone (219 mg, 1.3 mmol) and 3-bromopyridine (96 μL, 1.0 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:1) to afford the title compound as a yellow oil (226 mg, 92%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.71 (d, J = 2.1 Hz, 1 H), 8.61 (dd, J = 4.8, 1.6 Hz, 1 H), 7.98−7.90 (m, 2 H), 7.78 (dddd, J = 8.0, 2.3, 1.6, 0.5 Hz, 1 H), 7.69−7.64 (m, 1 H), 7.64−7.60 (m, 1 H), 7.58−7.53 (m, 2 H), 7.34−7.29 (m, 1 H), 6.97 (d, J = 15.5 Hz, 1 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 151.9, 150.0, 140.2, 138.8, 134.9, 133.8, 129.7, 129.6, 128.4, 127.9, 124.0 ppm. The physical data were in full accordance with the literature value.[68]

*(E)-6-(2-(Phenylsulfonyl)vinyl)imidazo[1,2-a]pyridine (**3e**).* Following general method, the reaction of phenyl vinyl sulfone (219 mg, 1.3 mmol) and 6-bromoimidazo[1,2-*a*]pyridine (197 mg, 1.0 mmol) proceeded for 16 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:3) to afford the title compound as a yellow solid (247 mg, 87%): mp 159−161 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.34−8.31 (m, 1 H), 7.93 (dd, J = 8.4, 1.3 Hz, 2 H), 7.65−7.53 (m, 7 H), 7.25 (dd, J = 9.5 Hz, 1.8, 1H) 6.87 (d, J = 15.3 Hz, 1 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 145.1, 140.5, 138.5, 134.9, 133.7, 129.5, 128.9, 127.8, 127.7, 121.7, 119.0, 118.5, 113.7 ppm; IR (film) 3351, 2948, 2835, 1650, 1449, 1114, 1023 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{12}N_2O_2SNa^+$ [M + Na]$^+$ 307.0512, found 307.0514.

*Methyl 2-(3-oxo-3-phenylpropyl)benzoate (**3f**).* Following general method, the reaction of α-vinyl benzyl alcohol (170 μL, 1.3 mmol) and methyl 2-bromobenzoate (140 μL, 1.0 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:1) to afford the title compound as a colorless oil (247 mg, 92%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.00−7.96 (m, 2 H), 7.92 (dt, J = 7.8, 0.9 Hz, 1 H), 7.57−7.52 (m, 1 H), 7.47−7.41 (m, 3 H), 7.36 (dd, J = 7.5, 1.2 Hz, 1 H), 7.30−7.27 (m, 1 H), 3.89 (s, 3 H), 3.38−3.33 (m, 4 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 199.5, 168.0, 143.5, 137.1, 133.1, 132.4, 131.6, 131.0, 129.6, 128.7, 128.3, 126.5, 52.2, 40.7, 29.5 ppm; IR (film) 3354, 2949, 2835, 1718, 1684, 1449, 1257, 1081, 1024 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}O_3H^+$ [M + H]$^+$ 269.1172, found 269.1176.

*1-Phenyl-3-(pyridin-3-yl)propan-1-one (**3g**).* Following general method, the reaction of α-vinyl benzyl alcohol (170 μL, 1.3 mmol) and 3-bromopyridine (96 μL, 1.0 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:3) to afford the title compound as a pale yellow solid (188 mg, 89%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.53 (d, J = 2.3 Hz, 1 H), 8.45 (dd, J = 4.8, 1.6 Hz, 1 H), 8.01−7.89 (m, 2 H), 7.61 (dt, J = 7.8, 1.8 Hz, 1 H), 7.58−7.52 (m, 1 H), 7.49−7.40 (m, 2 H), 7.23 (ddd, J = 7.8, 4.9, 0.9 Hz, 1 H), 3.32 (dd, J = 7.8, 7.0 Hz, 2 H), 3.09 (t, J = 7.4 Hz, 2 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 198.5, 149.8, 147.5, 136.9, 136.71, 136.5, 133.4, 128.8, 128.1, 123.6, 39.8, 27.2 ppm. The physical data were in full accordance with the literature value.[69]

*3-(Benzo[b]thiophen-6-yl)-1-phenylpropan-1-one (**3h**).* Following general method, the reaction of vinylbenzyl alcohol (171 μL, 1.3 mmol) and 6-bromobenzo[*b*]thiophene (213 mg, 1.0 mmol) proceeded for 16 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (4:1) to afford the title compound as a pale yellow solid (332 mg, 83%): mp 81−84 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99−7.94 (m, 2 H), 7.78−7.73 (m, 2 H), 7.59−7.53 (m, 1 H), 7.48−7.43 (m, 2 H), 7.38 (d, J = 5.4 Hz, 1 H), 7.29 (dd, J = 5.5, 0.8 Hz, 1 H), 7.27 (dd, J = 8.2, 1.6 Hz, 1 H), 3.40−3.31 (m, 2 H), 3.20 (dd, J = 8.4, 6.9 Hz, 2 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 199.2, 140.2, 138.1, 137.7, 136.9, 133.2, 128.7, 128.1, 125.8, 125.3, 123.7, 123.6, 121.9, 40.8, 30.2 ppm; IR (film) 3365, 2836, 1682, 1440, 1205, 1116, 1022 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{14}OSNa^+$ [M + Na]$^+$ 289.0663, found 289.0677.

*1-Phenyl-3-(thiophen-2-yl)propan-1-one (**3i**).* Following general method, the reaction of α-vinyl benzyl alcohol (170 μL, 1.3 mmol) and 2-bromothiophene (97 μL, 1.0 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:2) to afford the title compound as a yellow solid (197 mg, 91%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.98 (dt, J = 8.1, 1.1 Hz, 2 H), 7.60−7.54 (m, 1 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.14 (dd, J = 5.1, 1.2 Hz, 1 H), 6.94 (dd, J = 5.1, 3.5 Hz, 1 H), 6.88 (dt, J = 3.4, 1.1 Hz, 1 H), 3.37 (ddd, J = 7.8, 6.5, 1.6 Hz, 2 H), 3.34−3.28 (m, 2 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 198.5, 143.9, 136.7, 133.2, 128.7, 128.6, 128.1, 128.0, 126.9, 124.7, 123.4, 40.6, 40.5, 24.2 ppm. The physical data were in full accordance with the literature value.[70]

*1-Mesitylpentan-3-one (**3j**).* Following the general method, the reaction of 2-bromomesitylene (199.1 mg, 1 mmol) and 1-penten-3-ol (112 mg, 1.3 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum/EtOAc (9:1) as the eluent to give the title compounds as a colorless oil (186 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.83 (s, 2 H), 2.91−2.82 (m, 2 H), 2.58−2.50 (m, 2 H), 2.45 (q, J = 7.3 Hz, 2 H), 2.27 (s, 6 H), 2.25 (s, 3 H), 1.08 (t, J = 7.3 Hz, 3 H) ppm; GC−MS calcd for $C_{14}H_{20}O^+$ [M]$^+$ 204.15, found 204.2. The physical data were in full accordance with the literature value.[71]

*(E)-4-(2-Aminopyrimidin-5-yl)but-3-en-2-one (**3k**).* Following the general method, the reaction of 2-amino-5-bromopyrimidine (174 mg, 1 mmol) and methyl vinyl ketone (91.1 mg, 1.3 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using MeOH/EtOAc/CH_2Cl_2 (5:30:65) as the eluent to give the title compound as a pale yellow solid (150 mg, 92%): mp 187−189 °C; ^{1}H NMR (400 MHz, CD_3OD) δ = 8.55 (s, 2 H), 7.50 (d, J = 16.4 Hz, 1 H), 6.72 (d, J = 16.4 Hz, 1 H), 2.35 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ = 200.8, 165.1, 159.7, 139.9, 125.1, 119.2, 27.2 ppm; IR (film) 3390, 1650, 16226, 1592, 1500, 1280, 1248,1218, 992 cm^{-1}; HRMS (ESI) calcd for $C_8H_9N_3OH^+$ [M + H]$^+$ 164.0818, found 164.0823.

*Methyl (E)-3-(imidazo[1,2-a]pyridin-6-yl)acrylate (**3l**).* Following general method, the reaction of methyl acrylate (117 μL, 1.3 mmol) and 6-bromoimidazopyridine (197.0 mg, 1 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum/EtOAc (1:3) as the eluent to afford the title compound as a brown solid (173.9 mg, 86%): mp 177−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, J = 1.9 Hz, 1 H), 7.69−7.54 (m, 4 H), 7.37 (dd, J = 9.4, 1.8 Hz, 1 H), 6.40 (d, J = 15.9 Hz, 1 H), 3.80 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 167.0, 145.3, 140.6, 134.7, 127.6, 121.89, 120.9, 118.5, 118.3, 113.4, 51.9 ppm; IR (film) 3349, 2947, 1650, 1449, 1113, 1024 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}N_2O_2H^+$ [M + H]$^+$ 203.0821, found 203.0812.

*(E)-4-Mesityl-2-methylbut-3-en-2-ol (**3m**).* Following general method, the reaction of 2-methyl-3-buten-2-ol (160 μL, 1.3 mmol) and 2-bromomesitylene (153 μL, 1 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using

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J. Org. Chem. 2015, 80, 4054−4063

petroleum/EtOAc (10:1) to afford the title compound as a white solid (170 mg, 76%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.87 (s, 2 H), 6.51 (d, J = 16.4 Hz, 1 H), 5.82 (d, J = 16.4 Hz, 1 H), 2.27 (s, 3 H), 2.26 (s, 6 H), 1.44 (s, 6 H) ppm; LCMS calcd for $C_{14}H_{19}$+ $[M + H]^+ - H_2O$ 187.15, found 187.2. The physical data were in full accordance with the literature value.[72]

*(E)-2-Methyl-4-(pyridin-3-yl)but-3-en-2-ol (**3n**).* Following general method, the reaction of 2-methyl-3-buten-2-ol (136 μL, 1.3 mmol) and 3-bromopyridine (96 μL, 1.0 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (1:2) to afford the title compound as a colorless solid (160 mg, 98%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.60 (d, J = 2.3 Hz, 1 H), 8.46 (dd, J = 4.9, 1.6 Hz, 1 H), 7.78−7.67 (m, 1 H), 7.29−7.26 (m, 1 H), 6.59 (d, J = 16.1 Hz, 1 H), 6.43 (d, J = 16.1 Hz, 1 H), 1.44 (s, 6 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 148.1, 148.1, 140.4, 133.2, 132.9, 123.6, 122.7, 70.9, 29.9 ppm. The physical data were in full accordance with the literature value.[73]

*(E)-4-(2-Aminopyrimidin-5-yl)-2-methylbut-3-en-2-ol (**3o**).* Following the general method, the reaction of 2-amino-5-bromopyrimidine (174 mg, 1 mmol) and 2-methyl-3-buten-2-ol (112 mg, 1.3 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using MeOH/CH_2Cl_2 (3:97) as the eluent to give the title compound as a yellow solid (143 mg, 80%): mp 148−150 °C; ^{1}H NMR (400 MHz, CD_3OD) δ = 8.32 (s, 2 H), 6.40 (d, J = 16.3 Hz, 1 H), 6.29 (d, J = 16.2 Hz, 1 H), 1.36 (s, 6 H) ppm; ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ = 163.7, 157.3, 138.1, 122.3, 120.9, 71.6, 30.0 ppm; IR (film) 3345, 2947, 2834, 1648, 1449, 1113, 1024 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}N_3OH^+$ $[M + H]^+$ 180.1131, found 180.1140.

*(E)-4-(Imidazo[1,2-a]pyridin-6-yl)-2-methylbut-3-en-2-ol (**3p**).* Following the general method, the reaction of 6-bromoimidazo[1,2-*a*]pyridine (197 mg, 1 mmol) and 2-methyl-3-buten-2-ol (112 mg, 1.3 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using MeOH/EtOAc/CH_2Cl_2 (2−5:30:68−65) as the eluent to give the title compound as a viscous brown residue (180 mg, 89%); ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1 H), 7.78 (s, 1 H), 7.57−7.44 (m, 3 H), 6.58 (d, J = 16.1 Hz, 1 H), 6.43 (d, J = 16.1 Hz, 1 H), 1.39 (s, 6 H) ppm; ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ = 145.9, 140.1, 133.4, 125.8, 125.1, 124.9, 122.9, 117.2, 114.7, 71.5, 29.9 ppm; IR (film) 3366, 2949, 1646, 1449, 1117, 1021 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}N_2OH^+$ $[M + H]^+$ 203.1179, found 203.1177.

*(E)-2-(2-(Pyridin-3-yl)vinyl)pyridine (**3q**).* Following general method, the reaction of 2-vinylpyridine (140.2 μL, 1.3 mmol) and 3-bromopyridine (96.3 μL, 1 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using EtOAc to afford the title compound as a brown solid (180 mg, 99%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.79 (td, J = 1.7, 0.9 Hz, 1 H), 8.62 (ddt, J = 5.0, 2.0, 1.0 Hz, 1 H), 8.51 (ddt, J = 4.9, 1.8, 0.8 Hz, 1 H), 7.89 (ddt, J = 7.7, 3.0, 1.5 Hz, 1 H), 7.72−7.66 (m, 1 H), 7.63 (d, J = 16.1 Hz, 1 H), 7.40 (dq, J = 7.8, 1.2 Hz, 1 H), 7.33−7.28 (m, 1 H), 7.22 (dq, J = 16.2, 1.2 Hz, 1 H), 7.19 (ddp, J = 7.1, 4.8, 1.2 Hz, 1 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 154.9, 149.9, 149.2, 149.1, 136.9, 133.5, 132.5, 130.0, 129.2, 123.8, 122.8, 122.6 ppm. The physical data were in full accordance with the literature value.[67]

*1-(2-Aminopyrimidin-5-yl)pentan-3-one (**3r**).* Following the general method, the reaction of 2-amino-5-bromopyrimidine (174 mg, 1 mmol) and 1-penten-3-ol (112 mg, 1.3 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using MeOH/EtOAc/petroleum ether (3:47:50) as the eluent to give the title compound as a white solid (160 mg, 89%): mp 123−126 °C; ^{1}H NMR (600 MHz, CD_3OD) δ = 8.15 (s, 2 H), 2.78−2.72 (m, 2 H), 2.72−2.66 (m, 2 H), 2.45 (q, J = 7.3 Hz, 2 H), 1.00 (t, J = 7.3 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, CD_3OD) δ = 212.8, 163.3, 159.5, 124.8, 44.0, 36.8, 24.4, 8.1 ppm; IR (film) 3352, 2834, 1640, 1470, 1411, 1116, 1023 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}N_3OH^+$ $[M + H]^+$ 180.1131, found 180.1129.

*Methyl (E)-3-(1-tosyl-1H-indol-5-yl)acrylate (**3s**).* Following general method, the reaction of methyl acrylate (117 μL, 1.3 mmol) and 5-bromo-1-tosyl-1*H*-indole (350.2 mg, 1 mmol) proceeded for 8 h, of which the crude product was purified by column chromatography using petroleum/EtOAc (1:1) to afford the title compound as a cream solid (298 mg, 84%): mp 151−154 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.6 Hz, 1 H), 7.77 (d, J = 8.4 Hz, 2 H), 7.73 (s, 1 H), 7.67 (d, J = 1.7 Hz, 1 H), 7.59 (d, J = 3.7 Hz, 1 H), 7.50 (dd, J = 8.7, 1.7 Hz, 1 H), 7.25−7.21 (m, 2 H), 6.67 (dd, J = 3.7, 0.8 Hz, 1 H), 6.42 (d, J = 15.9 Hz, 1 H), 3.80 (s, 3 H), 2.34 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 167.5, 145.3, 145.0, 135.7, 135.1, 131.2, 130.0, 129.8, 127.4, 126.8, 124.1, 121.9, 117.0, 113.9, 109.1, 51.7, 21.6 ppm; IR (film) 3366, 2836, 1641, 1121, 1022 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{17}NO_4SH^+$ $[M + H]^+$ 356.0951, found 356.0940.

*Methyl (E)-3-(benzo[b]thiophen-3-yl)acrylate (**3t**).* Following general method, the reaction of methyl acrylate (117 μL, 1.3 mmol) and 3-bromobenzo[*b*]thiophene (131 μL, 1.0 mmol) proceeded for 16 h, of which the crude product was purified by column chromatography using petroleum ether/EtOAc (4:1) to afford the title compound as a yellow oil (376 mg, 86%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.02 (d, J = 8.1 Hz, 1 H), 7.98 (d, J = 16.1 Hz, 1 H), 7.96−7.82 (m, 1 H), 7.76 (d, J = 1.7 Hz, 1 H), 7.58−7.33 (m, 2 H), 6.55 (d, J = 16.1 Hz, 1 H), 3.84 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 167.7, 140.6, 137.3, 136.7, 131.7, 128.2, 125.2, 125.1, 123.2, 122.2, 118.4, 51.9 ppm. The physical data were in full accordance with the literature value.[74]

*(R,E)-1-(3-((1-Methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)-vinyl)-1H-indol-1-yl)ethan-1-one (**5**).* Following general method, the reaction of phenyl vinyl sulfone (109 mg, 0.65 mmol) and compound **4** (168 mg, 0.5 mmol) proceeded for 16 h. The reaction mixture was filtered through a pad of Celite and concentrated to dryness. The brown residue was washed with 1.0 M NaOH and extracted with EtOAc until no product was detected in the aqueous layer. The organic layer was consolidated, dried with Na_2SO_4, filtered and concentrated to give the title product as brown oil; 95% pure by HPLC (209 mg, 99%): ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.30 (d, J = 8.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.94 (dd, J = 7.2, 1.8 Hz, 2H), 7.80−7.56 (m, 7H), 3.08−2.95 (m, 2H), 2.62 (s, 3H), 2.56 (d, J = 9.2 Hz, 2H), 2.38 (s, 3H), 2.19 (dd, J = 9.9, 7.0 Hz, 1H), 1.77 (ddt, J = 12.6, 9.1, 4.5 Hz, 1H), 1.70−1.54 (m, 2H), 1.48 (tt, J = 7.5, 3.7 Hz, 1H) ppm. LCMS: calcd for $C_{24}H_{26}N_2O_3SH^+$ $[M + H]^+$ 423.17, found 423.1; HRMS calcd for $C_{22}H_{25}N_2O_2S^+$ $[M + 2H - Ac]^+$ 381.1632, found 381.1622.

General Procedure for HTS 1 and HTS 2. To the reaction wells were added the bases (Cs_2CO_3, K_3PO_4, AgOAc and $NaHCO_3$, Et_3N and Cy_2NMe), which was performed either manually for the solid reagents (est. accuracy of ±2 mg), or volumetrically via the automated core module for the liquid reagents. Eight stock solutions were also prepared (4 solvents × 2 reactions), each containing **1** (1.2 equiv), **2** (1 equiv) and phenanthrene (internal standard). The 0.26 M stock solutions (with respect to ArX) were dispensed (475 μL) into the reaction wells via the core module. Separately, a catalyst solution was prepared in toluene at room temperature and was dispensed (25 μL, 0.02 equiv) into the reaction wells after the starting materials making a total concentration of approximately 0.25 M (slight variations due to heterogeneous mixtures). Equivalently, each reaction contained **1** (0.15 mmol), **2** (0.125 mmol), base (0.25 mmol) and Pd-Cy*Phine catalyst (2 mol %). After addition of the materials, the plate was sealed and heated to 120 °C on an orbital shaker. After 16 h, the reactions were allowed to cool to room temperature and aliquots (10 μL) were flushed through silica on a multiwell filtration plate using MeCN (2 × 250 μL) as eluent. For HTS 1, reactions were further diluted to a total volume of 800 μL and analyzed by HPLC. For HTS 2, reactions were analyzed by GC-FID.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C{^{1}H} NMR of isolated compounds and HPLC of compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: daniel_tay@sbic.a-star.edu.sg.
*E-mail: howard_jong@ices.a-star.edu.sg.

Author Contributions

§D.W.T. and H.J. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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