ARTICLE

Oxidative Mizoroki–Heck Reaction of Unprotected Cinnamylamines at Ambient Temperature Under Air

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Cinnamylamines make-up many important drugs that target G protein-coupled receptors. While 3,3-diarylallylamines can be prepared via existing synthetic methods, these often require poorly-selective Wittig addition to unsymmetrical ketones, and multistep sequences thereafter to reach the allylamine product. Methods that make use of direct aryl addition to *N*-protected cinnamylamines via a Mizoroki–Heck pathway are known, however, unprotected cinnamylamines are sensitive to a mixture of C–H activation and Mizoroki–Heck arylation under Pd-catalysed arylation conditions using aryl iodides. This leads to a decrease in the *trans*/*cis* selectivity that can be achieved under these reaction conditions. By reimagining the reaction and using aryl boronic acids, we have herein demonstrated how in many cases the yield and *E*/*Z* selectivity can be improved. The *in situ*-formed active catalyst is more sensitive under these conditions, and was observed to shut down at elevated temperatures.

Introduction

The cinnamylamine motif features prominently in many FDA-approved drugs **(Figure 1**),[1] while the presence of a 2nd aryl group in 3-arylcinnamylamines provides even greater opportunity to tune the properties of these drug molecules. Synthetic methods to access unsymmetrical 3,3-diarylallylamines, however, usually require either poorly-selective Wittig reactions[2] or moderate step count sequences.[3] Notably, while cinnamylamines and 3-arylcinnamylamines appear to be accessible through simple Mizoroki–Heck reactions of the free allylamine and cinnamylamine precursors respectively, the chemistry to access these reactions has not been fully developed, as most strategies have required using protected amine substrates. Using common protecting groups such as carbamates or picolinamides, numerous coupling partners have been used for the selective mono arylation of *N*-protected allylamines (**Scheme 1a**).[4] Even *trans*-1,2-disubstituted allylamine substrates can be engaged in Mizoroki–Heck reactions owing to the ability of many protected amines to coordinate to the transition metal catalyst,[5] which speeds up the otherwise sluggish addition to the alkene. Using protected amines and imines with some directing capacity, a variety of difunctionalization reactions have also been explored with good regiocontrol on alkenylamines more broadly speaking.[6] However, to make these methods more sustainable for drug synthesis, strategies are required that can facilitate functionalization using the free amine group, thus improving atom and step economy of these transformations.

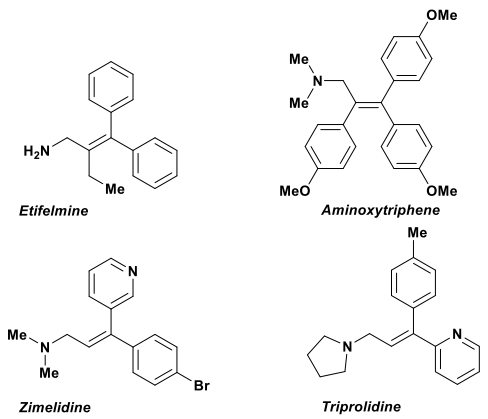

Figure 1. Representative 3-Arylcinnamylamine Drugs.

Recently the first example of a free amine-directed Mizoroki–Heck reaction of cinnamylamines was disclosed (**Scheme 1b**).[7] Notably, this reaction was proposed to occur by the action of *in situ*-formed Pd nanoparticles. Using this approach, a double Heck reaction[8] as well as a selective monoarylation of unprotected allylamines were also reported.[9] All of these reports made use of aryl iodides as coupling partners, and subsequently required the use of Ag salts.[10] Interestingly, although nanoparticles in these reports were judged to be more reactive, there was evidence of background C–H activation by homogeneous Pd^{II} which eroded the *E*:*Z* selectivity of the arylation reaction due to the stereospecific nature of each pathway. Another challenge for all of these

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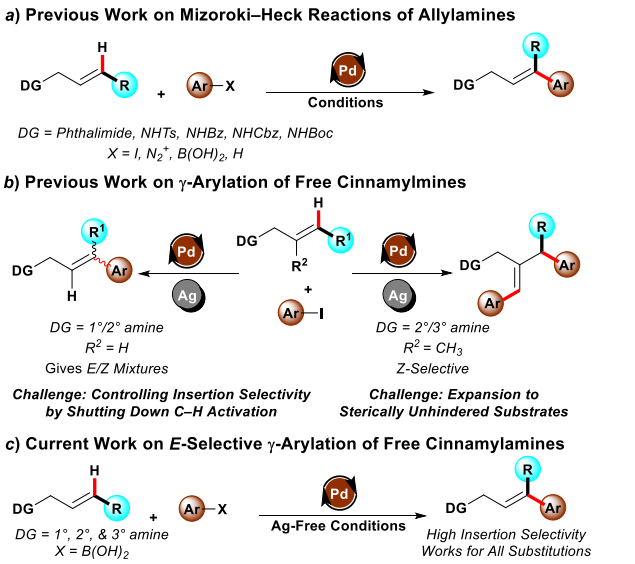
reactions was that they generally worked well for 2° amines, but struggled when applied to either 1° or 3° amines. This led us to wonder if it would be possible to reimagine these reactions as being more selective *by shutting down the background C–H activation pathway* (**Scheme 1c**), while simultaneously working well for all types of substituted amines (1°, 2°, and 3°).

Results and Discussion

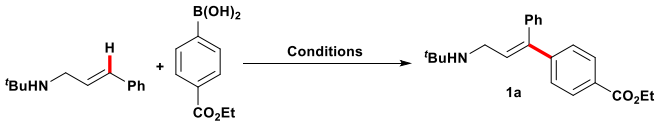
We reasoned that the rate determining step in the Mizoroki–Heck reaction of cinnamylamines would be oxidative addition to the C–I bond by the catalyst,[11] which necessitated elevated temperatures. These temperatures also allowed higher rates of C–H activation compared with the desired insertion reaction, leading to the decreased *E*/*Z*-selectivity. In addition, the use of aryl iodide as a coupling partner required the use of stoichiometric Ag salts (which are known to degrade the amine substrate over time)[12] to activate the C–I bond and to sequester the iodide by-product. To circumvent these issues, we expected that switching to a more accessible aryl source, such as an aryl boronic acid, could allow the reaction to be performed at lower temperatures, thus shutting down the background C–H activation reaction.



Scheme 1. Approaches for the Mizoroki–Heck Reaction of Allyl and Cinnamylamines.

We began by looking at the reaction of *N*-*tert*-butylcinnamylamine with 4-ethoxycarbonylphenyl boronic acid (**Table 1**). Under the conditions from our previous arylation reaction with aryl iodide as a coupling partner,[7] using 10 mol% $Pd(OAc)_2$ as catalyst and acetic acid as the solvent (but with silver omitted), the product was only observed in 6% yield (**Table 1**, **Entry 1**). What was meaningful about this result was that despite the low yield, only the *E*-isomer was observed. Based on this we next lowered the temperature to 70 °C and 50 °C, giving the desired product in 13% and 15% yield respectively (**Entries 2** and **3**). Considering the negligible difference in yields, we next looked for the effect of bases to help activate the C–B bond,[13] but did not see a significant benefit of adding metal acetate salts (**Entries 4** and **5**). Moving to 1,1,1,3,3,3-hexafluoroisopropenol (HFIP) proved to be beneficial for the reaction,[14] while a mixture of HFIP and AcOH was even better (**Entries 6** and **7**).[15] Surprisingly, we found that using a mixture of these two solvents that we could realize an increase in the yield by lowering the temperature, and could achieve an improved yield of 47% when the temperature was 40 °C (**Entry 8**) and a further improved 52% when the temperature was decreased to 25 °C (**Entry 9**).

Table 1 – Optimization of the *E*-Selective Mizoroki–Heck Reaction of Cinnamylamines.

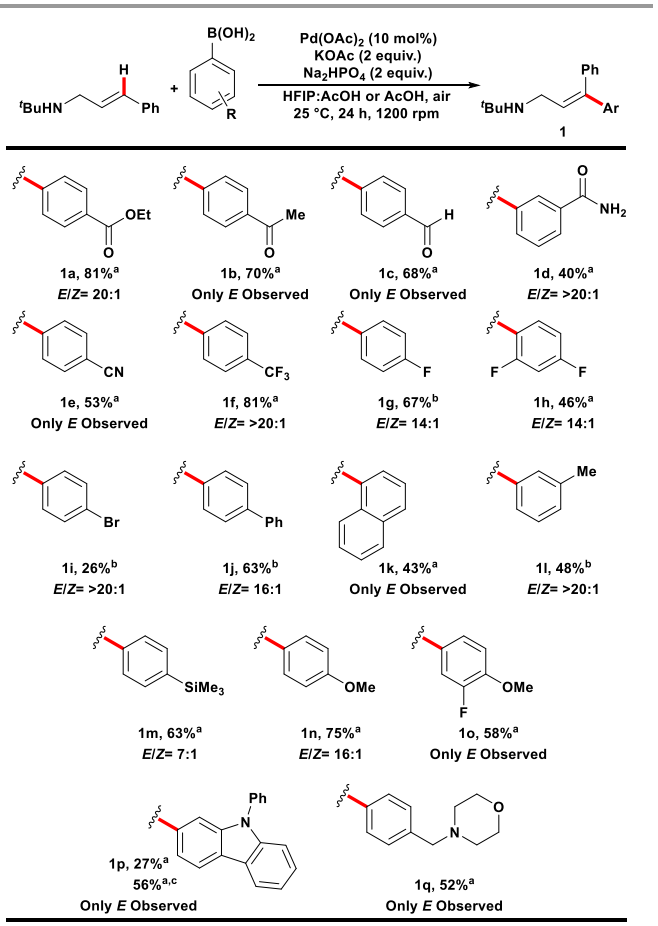


Entry	Reaction Conditions	% Yield	*E*/*Z* Ratio
1	AcOH (1 mL), 100 °C, 14h	6%	>20:1
2	AcOH (1 mL), 70 °C, 14h	13%	>20:1
3	AcOH (1 mL), 50 °C, 14h	15%	>20:1
4	LiOAc (2 equiv.), AcOH (1 mL), 50 °C, 14h	6%	>20:1
5	KOAc (2 equiv.), AcOH (1 mL), 50 °C, 14h	13%	>20:1
6	HFIP (1 mL), 50 °C, 14h	25%	>20:1
7	1:1 AcOH/HFIP (1 mL), 50 °C, 14h	40%	>20:1
8	1:1 AcOH/HFIP (1 mL), 40 °C, 14h	47%	>20:1
9	1:1 AcOH/HFIP (1 mL), 25 °C, 14h	52%	>20:1
10	$NaHCO_3$ (2 equiv.), 1:1 AcOH/HFIP (1 mL), 25 °C, 14h	49%	>20:1
11	Na_2HPO_4 (2 equiv.), 1:1 AcOH/HFIP (1 mL), 25 °C, 14h	60%	>20:1
12	Na_2HPO_4 (2 equiv.), 1:9 AcOH/HFIP (1 mL), 25 °C, 14h	67%	>20:1
13	KOAc (2 equiv.), Na_2HPO_4 (2 equiv.), 3:9 AcOH/HFIP (1.2 mL), 25 °C, 24h, 300 rpm	66%	20:1
14	KOAc (2 equiv.), Na_2HPO_4 (2 equiv.), 3:9 AcOH/HFIP (1.2 mL), 25 °C, 24h, 600 rpm	75%	20:1
15	KOAc (2 equiv.), Na_2HPO_4 (2 equiv.), 3:9 AcOH/HFIP (1.2 mL), 25 °C, 24h, 900 rpm	85%	20:1
16	KOAc (2 equiv.), Na_2HPO_4 (2 equiv.), 3:9 AcOH/HFIP (1.2 mL), 25 °C, 24h, 1200 rpm	90%	20:1
17	KOAc (2 equiv.), Na_2HPO_4 (2 equiv.), AcOH (4 mL), 25 °C, 12h, 1200 rpm, O_2 balloon	77%	20:1
18	KOAc (2 equiv.), Na_2HPO_4 (2 equiv.), AcOH (4 mL), 25 °C, 24h, 1200 rpm, deep N_2 sparge	10%	>20:1

Reactions were performed using amine (0.15 mmol) and 4-ethoxycarbonylphenyl boronic acid (0.30 mmol) in the presence of 10 mol% $Pd(OAc)_2$ in the presence of air (unless otherwise noted). All reactions were performed in triplicate and the average isolated yields reported. *E*/*Z* ratios were determined from the crude NMR using 1,1,2,2-tetrachloroethane as internal standard.

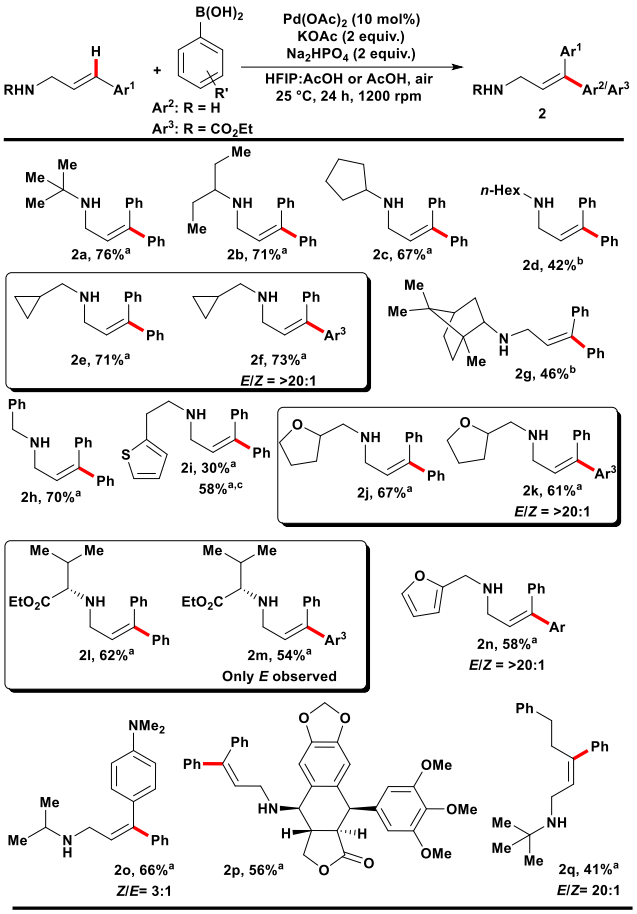
While bases such as $NaHCO_3$ were still not found to improve the reaction in the solvent mixture (**Entry 10**), Na_2HPO_4 did improve the reaction efficiency (**Entry 11**). Meanwhile, we realized that a mixture other than 1:1 HFIP/AcOH could also further increase the yield (**Entry 12**). It was at this time that we made an interesting observation – when the reaction was stirred at low spin rates, yields were generally lower. As a result, we tested the effect of spin rate, and impressively found that while the reaction yields were only around 66% when the spin rate was 300 rpm (**Entry 13**), they steadily increased with an increase in the spin rate (**Entries 13 – 16**), with the yield levelling off above 1200 rpm at 90% NMR yield. This could be evidence

of a potential gas–liquid mass transfer issue.[16] To that end we found that the reaction completed more quickly if run under an O_2 balloon (**Entry 17**, albeit with a lower overall yield), while careful control of the presence of air/oxygen by thorough sparging or under Schlenk conditions with freeze pump thawing led to only trace amount of product formation (**Entry 18**). Meanwhile, a similar effect could be achieved by running the reaction in an ultrasonication bath, although this required effectively dissipating the heat. Allowing the bath temperature to warm to 40 °C during sonication led to a decrease in the yield. Of further note – even at the increased yield, the *E*/*Z* selectivity for this transformation remained at 20:1, with essentially only trace amounts of the *Z*-product observed. In contrast, our previous conditions gave this product in 65% yield, with a 10:1 selectivity for the *E* vs. *Z*-products.[7] Notably, under the milder conditions, the addition of CO_2 was not observed to make a difference in the overall yield.



Scheme 2. Substrate Scope of Aryl Boronic Acid Coupling Partners in the *E*-Selective Mizoroki–Heck Reaction on Cinnamylamines. Reactions were performed using amine (0.15 mmol) and aryl boronic acid (0.30 mmol) under air atmosphere. All reactions were performed in triplicate and the average isolated yields reported. *E*/*Z* ratios were determined from the crude ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [a] Solvent was 0.9 mL HFIP:0.3 mL AcOH. [b] Solvent was 4.0 mL AcOH. [c] Reaction was performed under 1 atm of O_2.

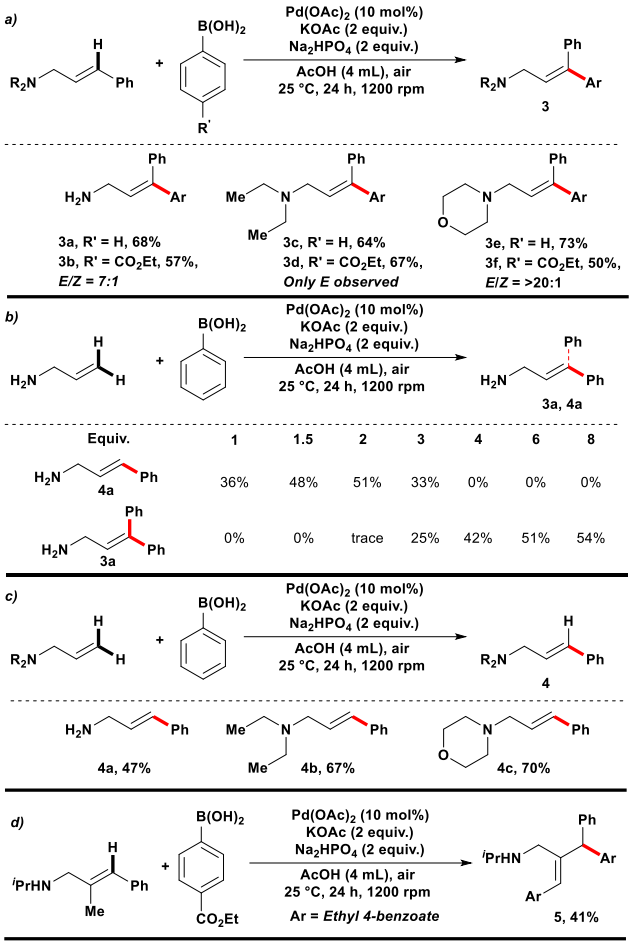
With the optimized conditions in hand, we first sought to explore the scope of the reaction (**Scheme 2**). Electron-deficient carbonyl-containing compounds bearing an ester (**1a**), ketone (**1b**), aldehyde (**1c**), amide (**1d**), and nitrile (**1e**) all worked in the reaction. Compared with the harsher conditions using ArI as a coupling partner, the nitrile could be preserved without hydrolysis under the present conditions. Because of the mild conditions, the mass balance in many of these reactions is simply unreacted amine starting material. Meaningfully, while the *E*-selectivity was generally high for all of these reactions, in several cases the *Z*-product could not even be detected by NMR or GCMS (**1b**, **1c**, and **1e**). Other electron poor substrates containing fluorides (**1f** – **1h**) and bromides (**1i**) were suitable substrates, though notably the bromide compound gave a low yield. The recovery of starting amine was reasonably high, and we determined that the low yield of **1i** comes from a complex mixture of products that give 343 fragments upon EI-MS analysis (after in-line GC separation), consistent with facile Suzuki–Miyaura cross-coupling of the brominated amine product with the boronic acid starting material.



Scheme 3. Substrate Scope of Cinnamylamine Coupling Partners in the *E*-Selective Mizoroki–Heck Reaction on Cinnamylamines. Reactions were performed using amine (0.15 mmol) and phenyl boronic acid (0.30 mmol) under air atmosphere. All reactions were performed in triplicate and the average isolated yields reported. *E*/*Z* ratios were determined from the crude ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [a] Solvent was 0.9 mL HFIP:0.3 mL AcOH. [b] Solvent was 4.0 mL AcOH. [c] Reaction was performed under 1 atm of O_2.

Conjugated systems such as biphenyl (**1j**) and naphthyl (**1k**) were suitable for the reaction, as were more electron rich groups on the arene such as Me, $SiMe_3$, and OMe (**1l**, **1m**, and **1n** respectively). Using a coupling partner with both electron

withdrawing F and donating OMe was successful (**1o**), and showed no observable *Z*-isomer from the crude reaction mixture. While we struggled to see any reactivity with several heterocycle coupling partners (see the Electronic Supplementary Information for a list of poorly reactive or unreactive substrates), a carbazole boronic acid could be coupled to give the desired product (**1p**). One issue we were concerned about was whether or not free amine functionality might compete with the desired reaction, and were delighted to find that a tertiary amine group on the coupling partner could be tolerated during the reaction (**1q**).



Scheme 4. Substrate Scope of Cinnamylamine Coupling Partners in the *E*-Selective Mizoroki–Heck Reaction on Cinnamylamines. Reactions were performed using amine (0.15 mmol) and phenyl boronic acid (0.30 mmol). All reactions were performed in triplicate and the average isolated yields reported. *E*/*Z* ratios were determined from the crude ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. *a* Study on Amine Substitution. *b* Study on Alkene Substitution for Mono/Diarylation. *C* Study on the Monoarylation of Differently Substituted Amines *d* Study on 3,3'-Diarylation of β-Methylcinnamylamine Substrate.

Regarding the amine substrate scope (**Scheme 3**), we found that a range of secondary amines could be viable substrates, including those with α-tertiary (**2a**), α-secondary (**2b** and **2c**), and α-primary (**2d**) aliphatic substituents. While a cyclopropylamine substrate was surprisingly unreactive under these conditions, adding a methylene spacer was sufficient to give access to a reactive substrate (**2e**). Considering we targeted the addition of phenyl groups for this reaction from which the *E*/*Z* selectivity cannot be determined, we spot checked this substrate and found that using 4-ethoxycarbonyl phenylboronic acid as a coupling partner, the *E*-product was favoured by >20:1 as determined from the ^{1}H NMR of the crude reaction mixture.

A sterically-conjested bornylamine derivative worked in the reaction (**2g**), as did aliphatic amines with aromatic (**2h**) and heteroaromatic (**2i**) groups. The saturated heterocycle tetrahydrofurfuryl was successfully converted to product (**2j**), and spot checking with 4-ethoxycarbonylphenyl boronic acid showed good *E*/*Z*-selectivity as well (**2k**). When we targeted an amino acid-derived substrate, we found the product (**2l**) in good yield, and similar results were obtained when the ethoxycarbonyl phenyl boronic acid coupling partner was used (**2m**), with complete *E*-selectivity based on the crude ^{1}H NMR of the reaction mixture. Based on the prepared Mosher amides of both **2l** and **2m**, the stereocenter of the amino ester was observed to have >99% *ee* after the reaction. Electron-rich furfurylamine-derived substrates were also viable in the reaction (**2n**), though pyridines were not found to be reactive.

One amine substrate that had been unsuccessful under the previous ArI conditions was *N*-*tert*-butyl-(4,4-dimethylamino)cinnamylamine,[7] which readily decomposed at the high temperatures used in the previous conditions. Using the current milder conditions, however, this substrate could give rise to the desired product (**2o**), though with a significantly decreased *Z*/*E*-selectivity (notably, the *Z*-isomer for this substrate is the insertion product). Finally, an amine derived from podophyllotoxin, with many oxygen-based functional groups, was also converted to the reaction product (**2p**). While the reaction generally works for all of the cinnamylamines sampled, one concern is whether or not chain-walking might occur with an aliphatic allylamine. When a 3-(phenethyl)-substituted allylamine was used in the reaction, the product was observed with complete control of the β-hydride elimination to give the β,γ-unsaturated allylamine product (**2q**).

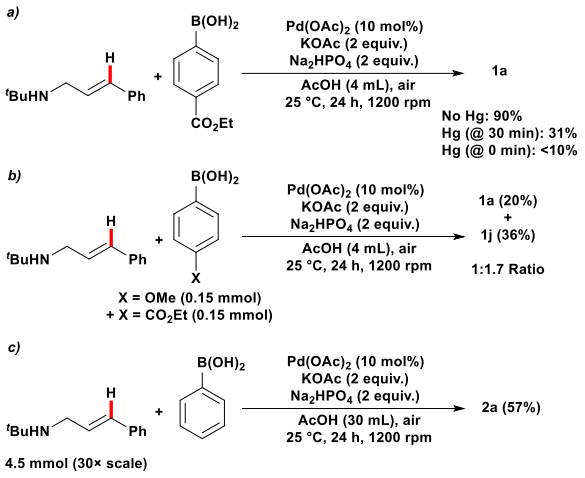
As previously mentioned, many organometallic transformations for the elaboration of amines are limited to only a specific level of amine substitution (*i.e.* 1° or 3° only), but considering this method worked for 2° amines, we wondered if the scope might be expanded to both less and more-substituted substrates. We therefore explored the scope with primary cinnamylamine, and were delighted to find the product in 68% yield (**Scheme 4a**, **3a**). In our previous work, CO_2 was required to slow the decomposition of the amine during the reaction, but this was not a viable strategy for the protection of 3° amines. However, in the milder conditions we expected that we should be able to also functionalize 3° amines without significant decomposition. Indeed, both acyclic (**3c**) and cyclic (**3e**) amine substrates could be functionalized in good yields, demonstrating the broadness of this modified approach to amine functionalization. In addition, these reactions were observed to proceed with good *trans*-selectivity when unsymmetrical 3,3-diarylallylamines were prepared (**3b**, **3d**, and **3f**).

Next we wanted to assess how well the reaction worked on terminal alkenes, and whether or not the reaction can be

achieved selectively. In previous work we had demonstrated that simple allylamine could be diarylated,[7] but monoarylation required milder conditions and increased amine substrate relative to the coupling partner.[9] With this in mind, we looked at the selectivity for *mono* versus *di* arylation as a function of the ratio of amine:aryl boronic acid (**Scheme 4b**). While the monoarylation product was observed almost exclussively when less than 2.5 equivalents of aryl boronic acid were used, further increase in the relative amount of boronic acid could push the reaction to be selective for diarylation.

With conditions for the monoarylation in hand, we briefly worked to demonstrate the efficacy on amines of different-levels of substitution. Gratifyingly, while the yields may be on the lower side for simple allylamine (**Scheme 4c**, **4a**), more substituted amines were actually more successfully-converted into cinnamylamine products. A final consideration was what would happen if a *ß*-alkyl substituent was present. The presence of *ß*-alkyl substituents has previously been shown to favour 3,3'-difunctionalization under similar conditions.[8, 17] Perhaps unsurprisingly, when a *ß*-methylcinnamylamine substrate was used under the present reaction conditions, the 3,3'-diaryl product was observed, consistent with an insertion, controlled chain-walk, and second insertion reaction (**Scheme 4d**, **5**).

Based on our previous work we recognized that allylamines can serve as ligands and reductants to produce active Pd nanoparticle (Pd NP) catalysts. However, we wanted to confirm this was occurring in the current reaction, and we turned to the mercury test (**Scheme 5a**) as a preliminary method to probe this.[18] The reaction was observed to be shut down by the addition of mercury either partway through the reaction or almost completely when it was added at the beginning of the reaction. Interestingly, the reaction initiates very quickly, and so although addition of Hg clearly stops the reaction, because Hg was added after all of the other components, a small amount of product was observed to form in the amount of time it took to measure out and then add Hg to the reaction mixture.



Scheme 5. Mechanistic and Scale-Up Experiments. [a] Reactions performed at 0.15 mmol scale of amine with 4-ethoxycarbonylphenyl boronic acid (0.30 mmol). [b] Reaction performed at 0.15 mmol scale of amine. [c] Reaction performed at 4.5 mmol scale of amine (30× scale).

Filtration of insoluble components from the reaction mixtures and analysis by scanning electron microscopy (SEM) also confirm that a variety of different nanospecies are formed throughout the reaction (see ESI). However, what is most interesting is that when the reaction is studied at intermediate points by dynamic light scattering (DLS), a fairly consistent distribution centered between approximately 200 and 400 nm is observed. When we performed a split test using a 0.22 micron filter, we found uniquely that the fraction pushed through the filter and the material that does not pass through both capable of catalysing the reaction, consistent with the work of either intermediate NP catalysts, or due to significant exchange between smaller and larger particles in solution.

While we had expected that fully-reduced Pd nanoparticles were being formed, we assumed that neutral particles would not be able to undergo transmetallation with activated aryl boronic acids in the same way as their mononuclear counterparts. We ran a competition reaction on the model amine substrate using a mixture of 1:1 4-ethoxycarbonylbenzene boronic acid and 4-methoxybenzene boronic acid (**Scheme 5b**). In this case, we found the reaction proceeded at nearly twice the rate for the more electron rich substrate. This implies nucleophilicity of the aryl boronic acid to be important in the transmetallation step, which seems inconsistent with a mechanism in which relatively more electron-rich fully-reduced Pd nanoparticles would be the active catalysts, so we considered there may be some cationic character to the *in situ*-formed nanoparticles.[19]

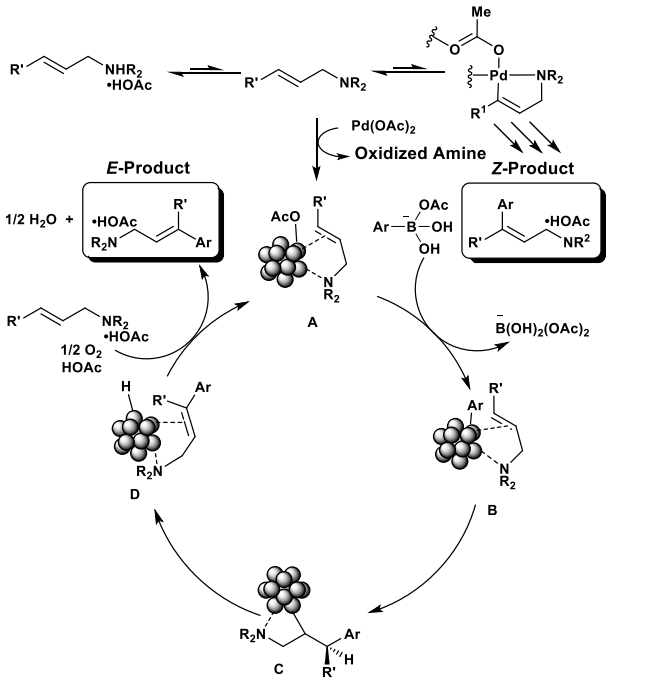


Figure 2. Proposed Catalytic Cycle.

Finally, we wanted to determine how scalable the reaction would be, especially considering the sensitivity to the stir rate. In this case, we ran the reaction in a round bottom flask rather than a sealable vial. Even at 30x the scale, however, we were able to observe the reaction occurred, with a moderate

decrease in the yield (**Scheme 5c**). As this is an unoptimized yield, we anticipate that careful control of the *in situ*-Pd nanoparticle formation or other engineering controls applied to the reaction would allow this yield to be improved.

Based on our preliminary mechanistic picture, we anticipate that the active catalyst is formed through incomplete reduction of $Pd(OAc)_2$ to Pd NPs ligated by allylamine (**Figure 2**, **A**) under the reaction conditions. Due to the charge from incomplete reduction under the mild reaction conditions, transmetallation with activated aryl boronic acid can occur through a traditional mechanism involving ligand exchange of a bound anionic ligand such as acetate to give **B**. The C–Pd bond can then insert across the alkene to give organic metallic intermediate **C**, which then undergoes facile *ß*-hydride elimination to give the desired product coordinated to the nanoparticle (**D**). Oxidation of the metal-hydride in the presence of molecular oxygen and acetic acid facilitates regeneration of the catalyst and exchange of functionalized amine for unfunctionalized substrate.

Conclusions

We have demonstrated that by making a relatively small change in the coupling partner for a free amine-directed Mizoroki–Heck reaction, we were able to achieve *trans*-selective arylation using a variety of amine and aryl boronic acids under robust oxidative conditions that use oxygen in air as the terminal oxidant. There are clear advantages to the milder conditions both in terms of selectivity, sustainability, and in many cases the overall yield. The mild conditions are also advantageous for more sensitive cinnamylamine substrates and products such as **2l**. However, the lower temperature also leads some substrates to be unreactive, while the sensitivity of the *in situ*-formed catalysts to high temperatures precludes simply increasing the temperature to enable these substrates to react. Overall, we expect that this study will prove complementary to our previous work,[7] while also providing a unique set of conditions for the *in situ*-formation of reactive Pd nanoparticles.

Author Contributions

Conceptualization was performed by O.N.F., V.G.L., S.V., and M.C.Y. Data curation, investigation, and writing – review & editing was performed by all authors. Writing – original draft was performed by O.N.F., S.V., and M.C.Y.

Conflicts of interest

There are no conflicts to declare.

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