

Controlling Reactivity and Selectivity in the Mizoroki-Heck Reaction: High Throughput Evaluation of 1,5-Diaza-3,7-diphosphacyclooctane Ligands

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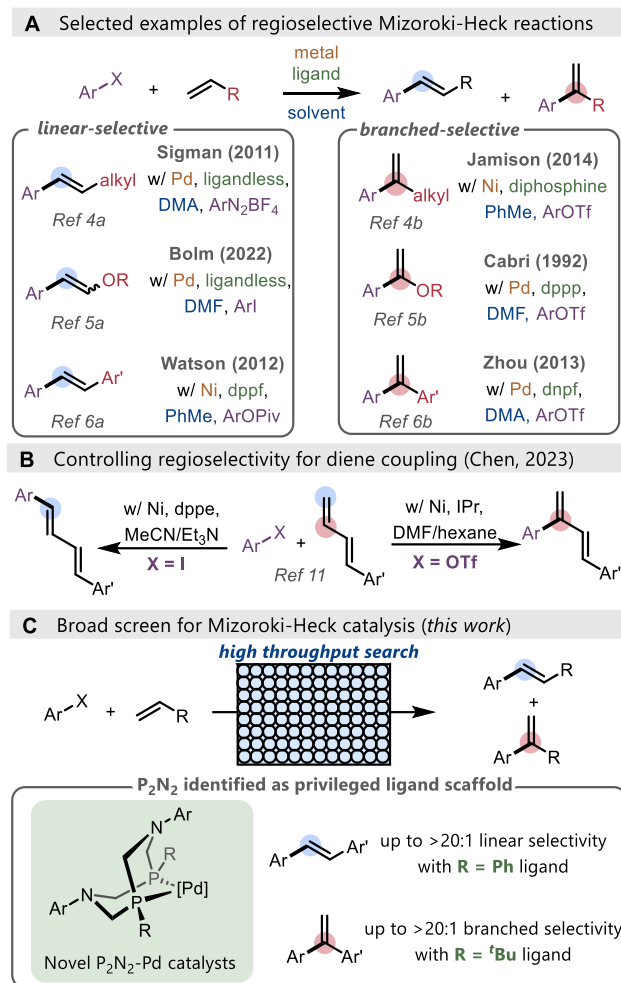
ABSTRACT: We report a high throughput evaluation of the Mizoroki-Heck reaction of diverse olefin coupling partners. Comparison of different ligands revealed the 1,5-diaza-3,7-diphosphacyclooctane (P₂N₂) scaffold to be more broadly applicable than common ‘gold standard’ ligands, demonstrating that this family of readily accessible diphosphines have unrecognized potential in organic synthesis. In particular, two structurally related P₂N₂ ligands were identified to enable the regiodivergent arylation of styrenes. By simply altering the phosphorus substituent from a phenyl to *tert*-butyl group, both the linear and branched Mizoroki-Heck products can be obtained in high regioisomeric ratios. Experimental and computational mechanistic studies were performed to further probe the origin of selectivity, which suggests that both ligands coordinate to the metal in a similar manner, but that rigid positioning of the phosphorus substituent forces contact with the incoming olefin in a π - π interaction (for P-Ph ligands) or with steric clash (for P-*t*-Bu ligands), dictating the regiocontrol.

■ **Introduction** Transition metal-catalyzed cross-couplings are a cornerstone family of reactions in synthetic organic chemistry. The growth of this field is closely tied to the development of new ligands that enable reactions with novel coupling partners, expanded scope, milder conditions, lowered catalyst loading, and improved selectivity. The search for readily available and powerful ligands continues today, seeking to overcome the many unsolved challenges in catalysis. The Mizoroki-Heck reaction is among the most seminal and fundamental coupling reactions.^{1,2} However, despite its prominence in textbooks, Heck-type reactions are rarely used in routine organic synthesis. In one survey of the medicinal chemistry literature, 0.4% of C–C bond-forming experiments were reported to be Mizoroki-Heck reactions, compared to 40.2% that were Suzuki-Miyaura reactions.³ Given the broad commercial availability of olefins and the value of substituted alkenes in medicinal chemistry, this contrast may seem surprising. One explanation is that, despite decades of research, the intermolecular Mizoroki-Heck reactions remain challenging compared to traditional biaryl-forming cross-coupling. While issues with selectivity or reactivity are common, many landmark reports have demonstrated that high-yielding, regioselective, intermolecular Mizoroki-Heck reactions are indeed possible (Scheme 1A.) For example, couplings with aliphatic alkenes,⁴ vinyl ethers,⁵ and styrenes⁶ have been achieved to selectively obtain either the branched or linear products by careful choice of catalyst, reaction conditions, and (pseudo)halide. Progress has also been made with other electron-deficient⁷ and electron-rich alkenes⁸ among other reaction

partners.⁹ Despite the many successes in the regioselective Mizoroki-Heck reaction, navigating the diverse set of available reactions is challenging, and identifying effective conditions for coupling a particular aryl(pseudo)halide and alkene can be arduous or even impossible if the reactant combination of interest has not yet been reported to provide access to the desired alkene regioisomer. Filling these holes and identifying more general catalysts are two important goals when developing site-selective methodologies. Methods which enable the synthesis of multiple regioisomers with general reaction conditions remain sparsely reported, though a recent report by Chen and co-workers on the coupling of dienes demonstrated regiocontrol (Scheme 1B).¹⁰ In this case, achieving a switch in regiochemistry involved modifying the ligand, base, solvent, and (pseudo)halide.

We hypothesized that many unresolved challenges in Mizoroki-Heck couplings could be solved by identifying more universal ligands and/or reaction conditions. One ligand family we sought to explore was the 1,5-diaza-3,7-diphosphacyclooctanes, abbreviated as P₂N₂ ligands. These are modular and readily accessible from the corresponding phosphine and amine via condensation with formaldehyde.¹¹ However, their use in organic synthesis has been sparsely reported.^{12,13} Herein we report an evaluation of diverse Mizoroki-Heck reactions that reveals this ligand class to provide both high reactivity and selectivity with a range of substrates, including surprising regiocontrol in the couplings of aryl triflates with styrenes (Scheme 1C).

Scheme 1. Regioselectivity in the Mizoroki-Heck reaction



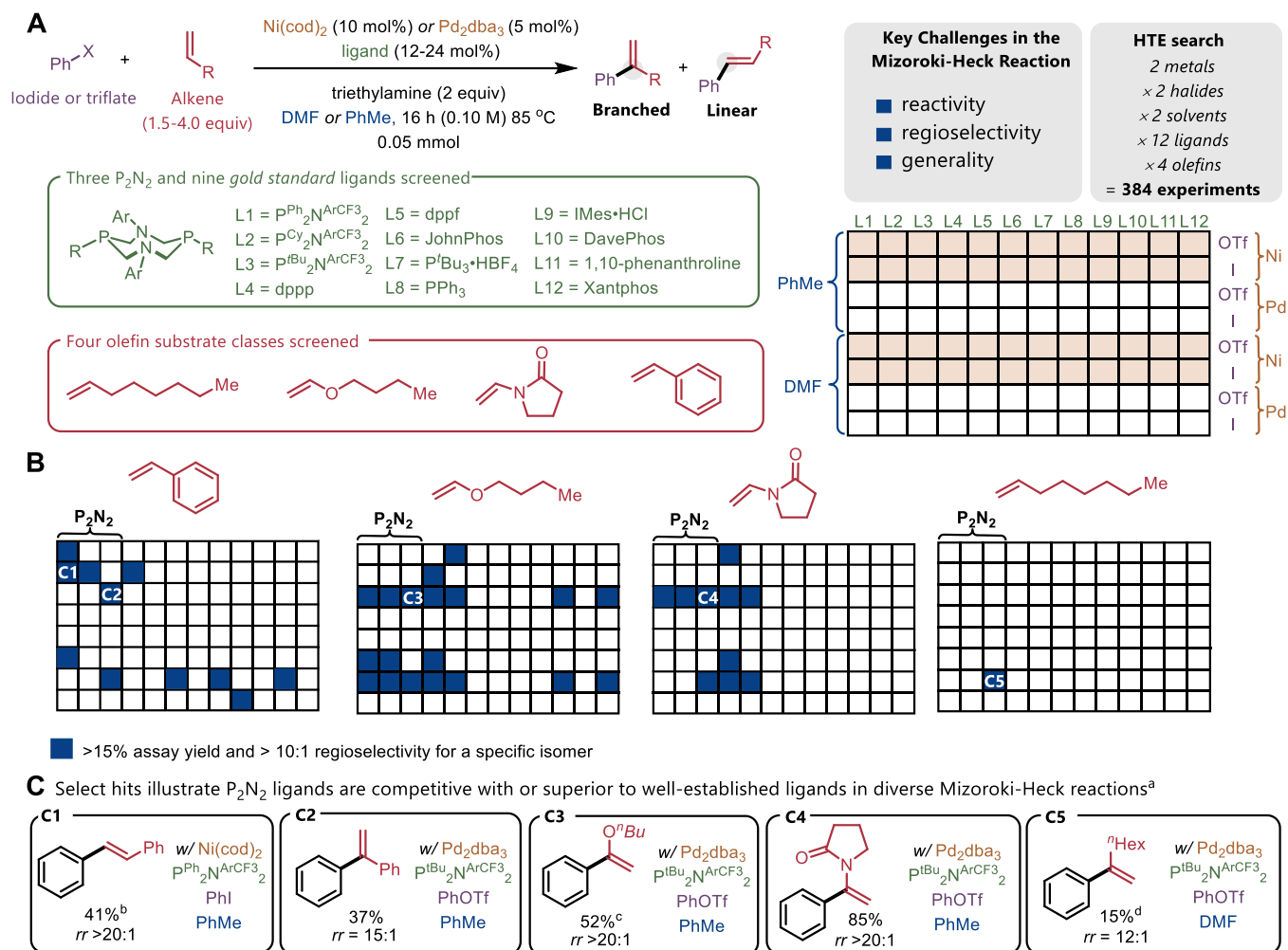
To assess if P₂N₂ ligands have any unique utility for Mizoroki-Heck reactions, a high-throughput screening campaign was carried out to compare them with well-established commercial ligands (Scheme 2A).¹⁴ Coupling with both Ni and Pd was explored using iodobenzene and phenyl triflate as differing classes of coupling partners.^{15,16} A representative substrate from four different classes of olefin coupling partners were considered. Similarly, a common polar (DMF) and non-polar (toluene) solvent were chosen for study. According to Sherwood et al., Mizoroki-Heck reactions in polar aprotic solvents are favored with aryl iodides but reactions with aryl triflates can be preferred in non-polar solvents.¹⁷ To keep the number of experiments reasonable, we elected to screen all reactions with triethylamine as a common base. Three P₂N₂ ligands with differing phosphine substituents (P^{Ph}, P^{Cy}, and P^{tBu}) were chosen for study alongside 9 'gold standard' commercially available phosphine ligands that have been demonstrated to be optimal in related methodologies: dppp,^{5b,18} dppf,^{6a,18,19} JohnPhos,²⁰ P^{tBu}Bu₃,^{5f} PPh₃,^{1g} IMes,²¹ DavePhos,²² 1,10-phenanthroline,²³ and XantPhos.²⁴ Benzotrifluoroaniline derived P₂N₂ ligands were explored as P^{Cy}N^{ArCF₃}₂ was previously found to be highly effective in nickel-catalyzed cross couplings.^{14hj}

A comprehensive screen of all conditions was carried out, representing 384 distinct experiments, the results of which are pro-

vided in the Supporting Information and are accessible in machine-readable format via the Open Reaction Database.²⁵ As discussed, Mizoroki-Heck reactions can have challenges in both reactivity and regioselectivity, with each combination of aryl (pseudo)halide and olefin coupling partner having unique challenges and solutions. To identify the best hits, a threshold of both >15% assay yield and >10:1 regioselectivity was chosen for visualization (Scheme 2B). Within these parameters, P₂N₂ ligands were the only of those screened that provided hits with each different substrate class, with P^{tBu}N^{ArCF₃}₂ (L3) in particular proving to be the most broadly effective choice. Interestingly, promising results were observed with P₂N₂ ligands with both Pd and Ni as metals, both toluene and DMF as solvents, and both iodide and triflate substrates, further highlighting the generality of this ligand scaffold. The performance of gold standard ligands on the high-throughput screen generally matched precedent from the primary literature despite, confirming that key trends in reactivity can be captured in this generalized set of reaction conditions (see Section S3.18, SI). Selected hits were chosen for replication to confirm the yield and regioselectivity (Scheme 2C). The coupling of styrene, butyl vinyl ether, and *n*-vinyl pyrrolidine proceeded in 37-85% yield by using P₂N₂ ligands with regioisomeric ratios of the substituted product ranging from 15:1 to >20:1, demonstrating that synthetically viable quantities of material could be directly accessed without targeted optimization. The selective coupling with 1-octene was more challenging, with only one observed hit with a Pd/P^{tBu}N^{ArCF₃}₂ catalyst system giving 15% yield by NMR and proving difficult to scale-up or optimize (Scheme 2C; C5). This result is largely consistent with literature, which illustrates that the regioselective coupling of linear alkenes is possible but very challenging.⁴ Also notable was the coupling with styrene. When using P^{Ph}N^{ArCF₃}₂ as a ligand, the linear (i.e. stilbene) isomer was found to be the major product in all cases. In contrast, for all styrene hits identified with P^{tBu}N^{ArCF₃}₂ as a ligand, the branched 1,1-diphenylethylene was found to be the major isomer. This ligand-controlled regioselectivity was apparent with both Ni and Pd catalysts, including several experiments below the 15% yield threshold, demonstrating that the observed selectivity is general. To our knowledge, this level of regiocontrol has not been reported without drastic modification of the catalyst and reaction conditions.²⁶ Accordingly, we selected this transformation for further study.

While it is clear that a drastic change in selectivity can be achieved when switching the ligand from P^{Ph}N^{ArCF₃}₂ to P^{tBu}N^{ArCF₃}₂, the mechanistic origin of the regiodivergent reactivity was unclear. One possible explanation is that the different P₂N₂ ligands can have different modes of binding. For example, while they are most commonly observed to be bidentate ligands,^{11a} dinuclear complexes bridged by P₂N₂ ligands in a μ-(κ¹-P, κ¹-P') binding mode as well as multimetallic clusters have also been observed.²⁷ The arene ring on aniline-derived P₂N₂ ligands has also been shown to coordinate to transition metals,^{12g} while in other complexes, the nitrogen atom has been observed to directly coordinate.²⁸ Additionally, agostic bonding of pendant C-H bonds in P₂N₂ metal complexes has been reported.^{28b,29} To probe if the differing regioselectivity originated

Scheme 2. High-throughput experimentation to probe general conditions for Ni- and Pd-catalyzed Mizoroki-Heck reaction

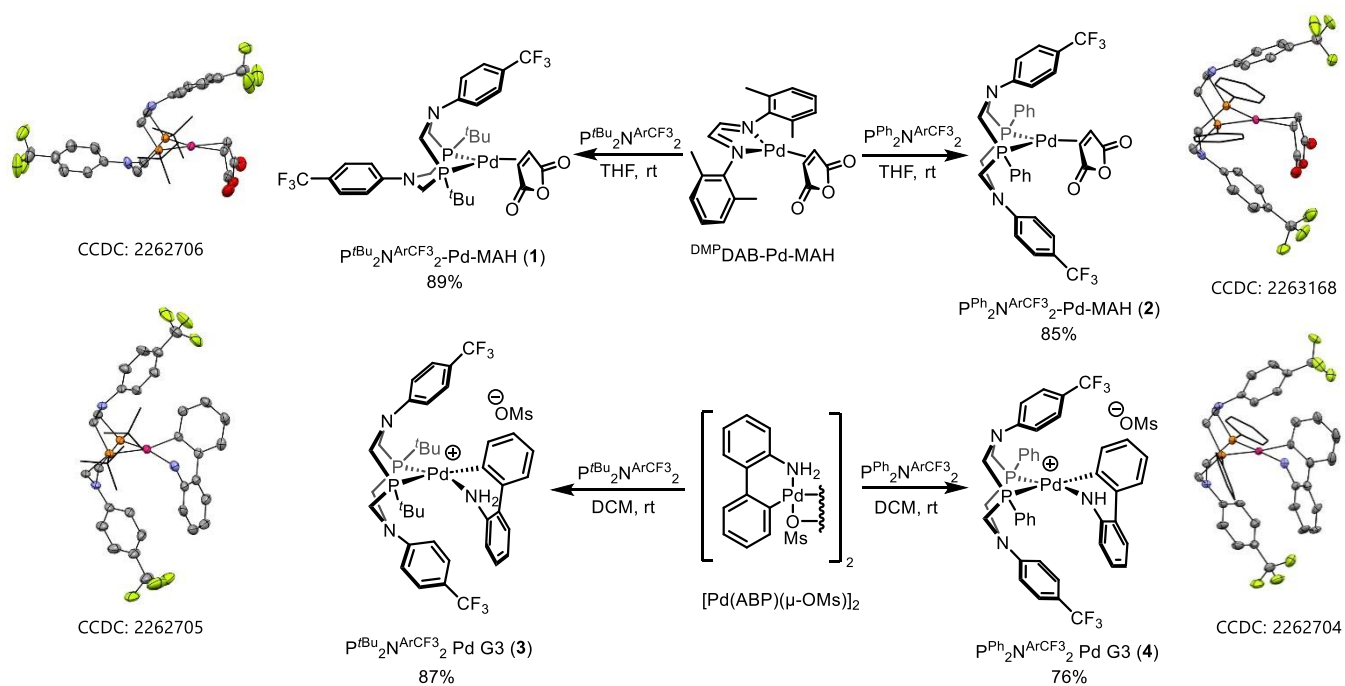


^aReplication of HTE reactions on 0.2 mmol scale. Regioisomeric ratios given were assessed by GC-FID of the crude reaction mixture. Unless otherwise indicated, isolated yields are reported. ^bWith 1 equivalent of styrene. ^cNMR yield after hydrolysis to acetophenone. ^dNMR yield.

from differing binding of the ligands, we set out to prepare and characterize some well-defined metal complexes. Although initial hits showed both Ni and Pd catalysis was promising, we elected to pursue Pd complexes because of the abundance of methods of accessing stable complexes with multidentate phosphine ligands. In particular, well-defined Pd(0) and Pd(II) complexes were targeted since these are the likely operative oxidation states in the Mizoroki-Heck mechanism. Ligand exchange with the Pd(0) species DMPDAB-Pd-MAH ($\text{DMPDAB} = N,N'$ -bis(2,6-dimethylphenyl)-diazabutadiene; MAH = maleic anhydride)³⁰ afforded $\text{P}^{\text{tBu}}_2\text{N}^{\text{ArCF}_3}_2\text{-Pd-MAH}$ (**1**) and $\text{P}^{\text{Ph}}_2\text{N}^{\text{ArCF}_3}_2\text{-Pd-MAH}$ (**2**) in 85 and 89% yields, respectively. Similarly, the Pd(II) precursor $[\text{Pd}(\text{ABP})(\mu\text{-OMs})]_2$ ($\text{ABP} = 2\text{-aminobiphenyl}$; $\text{OMs} = \text{mesylate}$)³¹ was treated with the P_2N_2 ligands to afford $\text{P}^{\text{tBu}}_2\text{N}^{\text{ArCF}_3}_2\text{-Pd G3}$ (**3**) and $\text{P}^{\text{Ph}}_2\text{N}^{\text{ArCF}_3}_2\text{-Pd G3}$ (**4**) in 87 and 76% yields, respectively. Single crystals were obtained for all four complexes and the structures confirmed a 1:1 ligand to Pd stoichiometry, and a conventional $\kappa^2\text{-P,P}$ coordination mode of the P_2N_2 ligands. The Pd to ligand bond distances and angles are consistent with related diphosphine complexes.^{30,31} However, $\text{P}^{\text{tBu}}_2\text{N}^{\text{ArCF}_3}_2\text{-Pd G3}$ (**3**) has slightly longer Pd-P bond lengths than the phenyl derivative (**4**) by ca. 0.02 Å (Table S50,

SI). The $\text{P}^{\text{tBu}}_2\text{N}^{\text{ArCF}_3}_2\text{-Pd G3}$ complex (**3**) exhibits a significantly distorted square planar geometry with a τ_4 value of 0.21 ($\tau_4 = 0$ for perfect square planar geometry).³² Conversely, the phenyl derivative (**4**) is almost perfectly square planar as evidenced by a τ_4 value of 0.06. The longer Pd-P bond lengths and geometry distortion for the ^tBu derivative (**3**) likely occurs to relieve some steric clash with the ABP moiety. The solid-state structures of the four complexes reveals that one or both of the -ArCF₃ pendent amine substituents are positioned over the palladium atom (*i.e.*, a boat metallocycle conformation), potentially blocking the axial metal site. However, neither a Pd-N nor a Pd-C_{Arene} π -interaction was observed in any of the complexes. The closest contact was the Pd-C_{ipso} distance that was >3 Å in all complexes, and this is significantly longer than Pd-C_{Arene} interactions (ca. 2.3-2.9 Å) observed for Pd(0) biaryl monophosphine complexes,³³ or a $\text{P}^{\text{Cy}}_2\text{N}^{\text{Ph}}_2\text{Ru(II)}$ complex.^{12g} Additionally, π -coordination to the aryl group would cause an upfield shift of the ¹³C resonances, and no such shift was observed for any of the complexes. The barriers for the boat/chair conformational change of nickel P_2N_2 metallocycles were previously calculated to be ca. 4–10 kcal/mol.³⁴ Therefore, in solution under catalytic conditions the interchange between conformers is likely facile,

Scheme 3. Synthesis and isolation of novel P₂N₂ Pd complexes for use in catalytic reactions



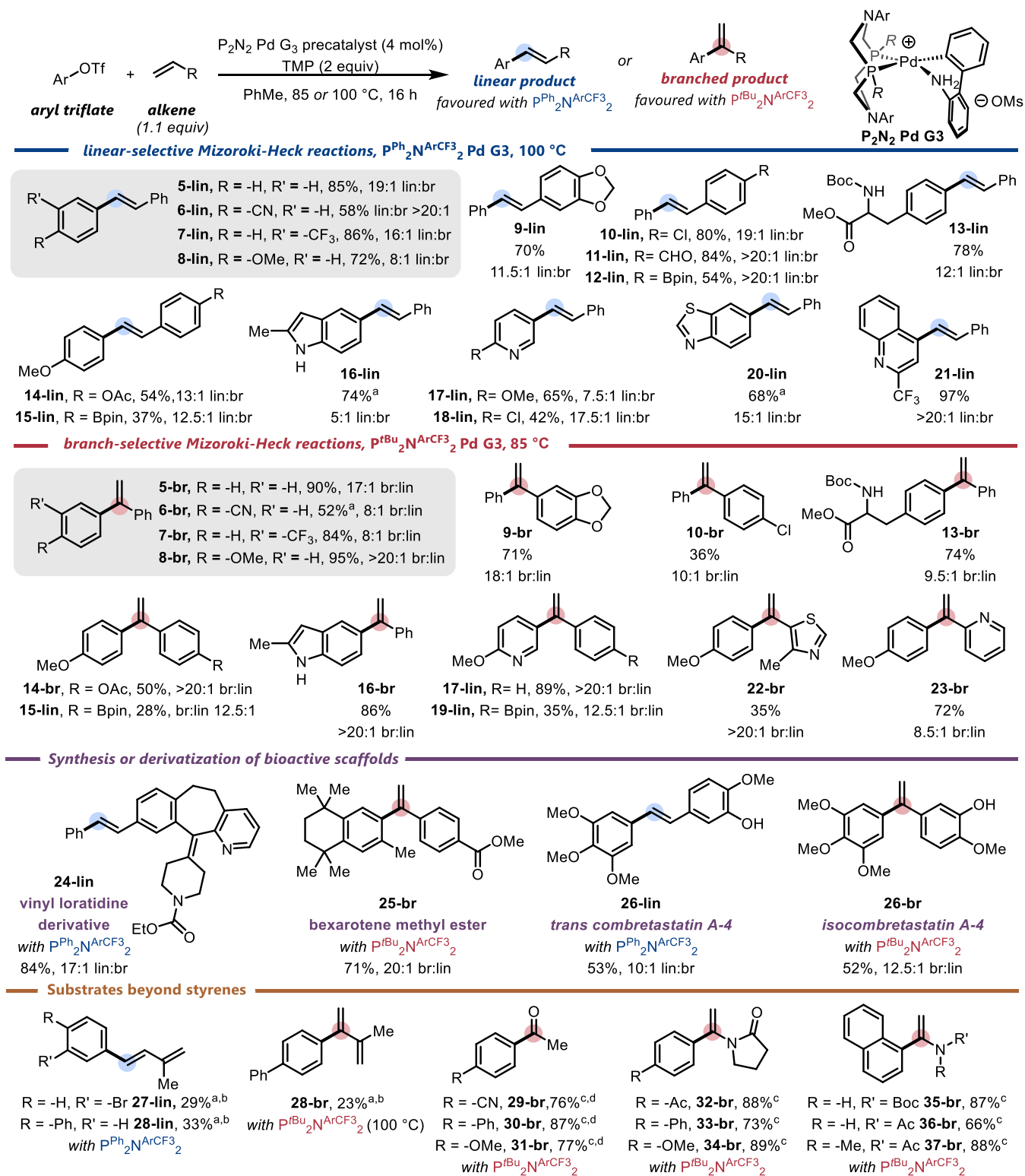
Isolated yields are reported. Thermal displacement plots are shown with ellipsoids at 50% probability. For clarity, hydrogen atoms and mesylate counterions (where relevant) were removed, and the Ph and ^tBu phosphorus substituents are depicted as wireframe. Depictions with atom labels along with tables of selected bond lengths and angles are provided in the Supporting Information (Section S6).

and the axial positions are not completely blocked by these ligands. The catalytic activity of these Pd complexes was also assessed and gave consistent trends as *in situ* formed catalysts, with complexes bearing the P^{Ph}₂N^{ArCF}₃₂ ligand being selective for the linear Mizoroki-Heck product and complexes bearing the P^{tBu}₂N^{ArCF}₃₂ ligand being branched selective. Taken together, the structures and activity of these Pd-P₂N₂ complexes strongly suggests that the difference in regioselectivity is not due to catalyst nuclearity (*i.e.*, monometallic vs. bimetallic) or ligation stoichiometry (*i.e.*, Pd : P₂N₂ = 1:1 vs 1:2). While we cannot discount that an *in situ* change in P₂N₂ coordination mode alters selectivity, these studies do not provide any positive evidence for this hypothesis. Key insight relates to the Pd(II) structures showing that the ^tBu derivatives experience significant steric clash within the square planar geometry, which may play a role in the selectivity-determining step of the catalytic cycle.

While initial HTE hits indicated that both Pd and Ni were both viable metals, the P₂N₂ Pd G3 catalysts were an appealing entry point to selective Mizoroki-Heck chemistry owing to their bench stability, ease of preparation, and consistency. Reaction optimization with 4 mol% of the P^{Ph}₂N^{ArCF}₃₂ Pd G3 precatalyst (4) revealed general, high-yielding, and regioselective conditions featuring TMP as a base in toluene at 85 °C with 1.1 equiv of the alkene coupling partner (Scheme 4). With these conditions, a selection of styrenes and aryl triflates were coupled to provide (*E*)-stilbenes **5-lin** to **15-lin** in 37-86% yield with regioselectivities ranging from 8:1 to 19:1. Unprotected indole was

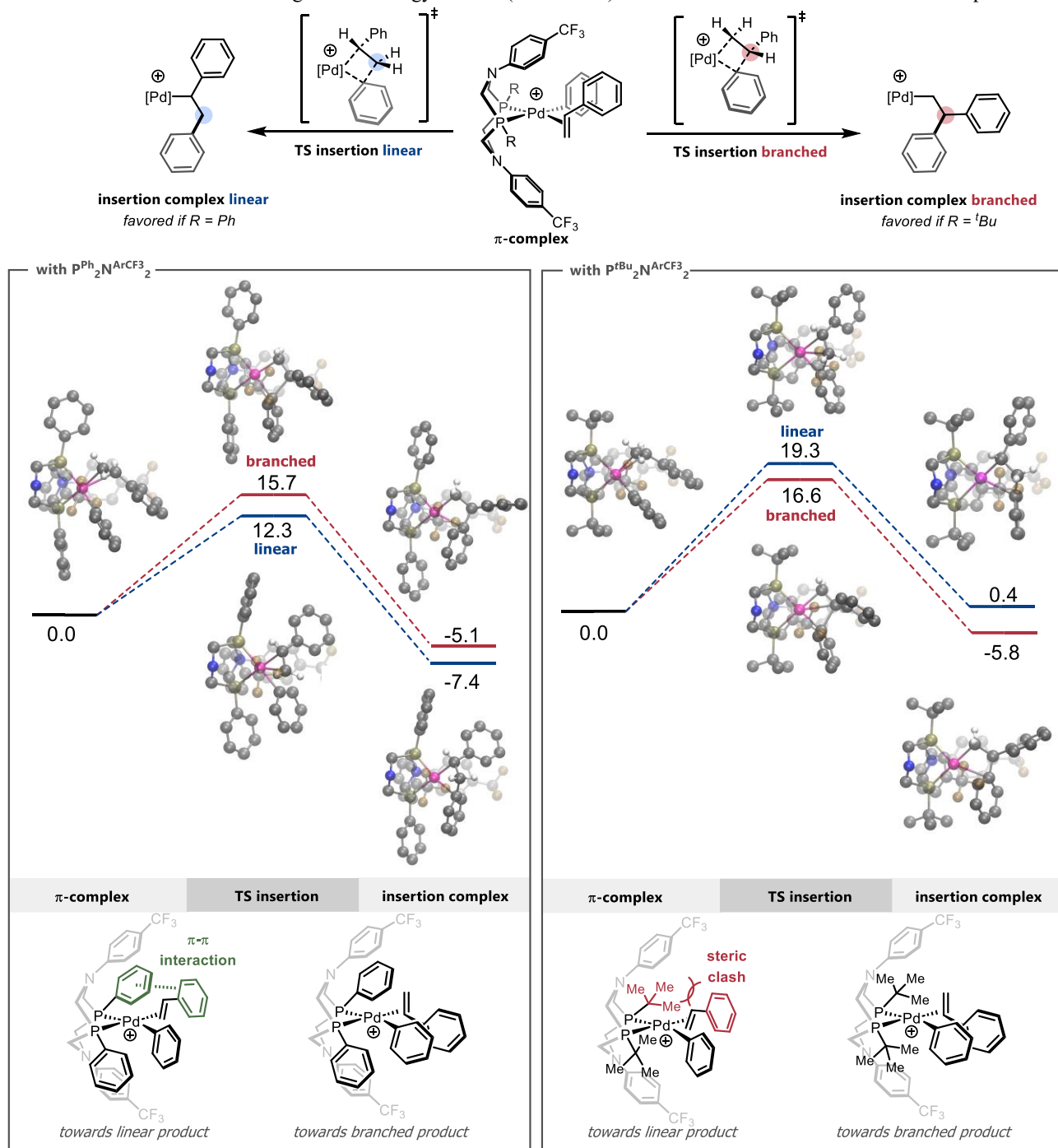
tolerated but gave a lower 5:1 regioselectivity (**16-lin**), and Lewis basic heterocyclics **17-lin**, **18-lin**, **20-lin** and **21-lin** were prepared with high linear selectivity. With the P^{tBu}₂N^{ArCF}₃₂ Pd G3 precatalyst (3), 1,1'-diarylethylenes **5-br** to **15-br** could be prepared from simple aryl triflates with regioselectivities ranging from 8:1 to >20:1 and yields between 28-95%. Unprotected indole **16-br** could also be coupled. While in most cases, the two different catalysts enabled highly selective access to both regioisomers, some exceptions were observed. For example with the P^{tBu}₂N^{ArCF}₃₂ Pd G3 (3) precatalyst, products **18-br**, **20-br** and **21-br** were not accessible in high yields or selectivity for the branched product (see Scheme S16, SI). In contrast, vinyl-substituted pyridine **22-br** and thiazole **23-br** were prepared with P^{tBu}₂N^{ArCF}₃₂ Pd G3 (3) but these substrates did not react with P^{Ph}₂N^{ArCF}₃₂ Pd G3 (4) (see Scheme S17, SI). Further scope limitations are discussed in the Supporting Information (Section S9.11). Lastly, a small selection of bioactive scaffolds and derivatives were also prepared. P^{Ph}₂N^{ArCF}₃₂ Pd G3 (4) enabled coupling of vinyl loratidine derivative to afford **24-lin**, and P^{tBu}₂N^{ArCF}₃₂ Pd G3 (3) provided access to **25-br**, the methyl ester analogue of the leukemia drug bexarotene.³⁵ *Trans* combretastatin A4 (**26-lin**), a natural product metabolite, was prepared with good yield and linear selectivity with P^{Ph}₂N^{ArCF}₃₂ Pd G3 (4)³⁶ while P^{tBu}₂N^{ArCF}₃₂ Pd G3 (3) could be used to prepare the regioisomer, isocombretastatin A4 (**26-br**), a potent bioactive non-natural analogue of combretastatin A4.³⁷ In general, low yielding reactions with both precatalysts were accompanied by substantial recovery of starting material, see Supporting Information (Section S9.15).

Scheme 4. Scope of ligand-controlled site selectivity in the coupling of aryl triflates with alkenes



Linear-selective conditions: aryl triflate (0.20 mmol), alkene (0.22 mmol), TMP (0.40 mmol), $\text{P}^{\text{Ph}}_2\text{N}^{\text{ArCF}_3}_2$ Pd G3 (4 mol%), toluene (0.1 M), 100 °C for 16 h. **Branched-selective conditions:** aryl triflate (0.20 mmol), alkene (0.22 mmol), TMP (0.40 mmol), $\text{P}^{\text{iBu}}_2\text{N}^{\text{ArCF}_3}_2$ Pd G3 (4 mol%), toluene (0.1 M), 85 °C for 16 h. Regioisomeric ratios (*rr*) are measured on the crude reaction mixtures using GC-FID analysis, or in the case of products >400 Da, by crude ¹H NMR. Isolated yields are reported as single regioisomers (*rr* ≥ 19:1). ^aWith 8 mol% P_2N_2 Pd G3 precatalyst. ^bFrom the reaction of isoprene (7.5 equiv). **27-lin** and **28-br** were formed in >20:1 regioisomeric ratio and **28-lin** formed a 9:1 regioisomeric ratio, with **28-br** representing the minor component. ^cRegioisomeric ratios measured on the crude reaction mixture were >20:1. ^dFrom the reaction of n-butyl vinyl ether (1.1 equiv). Ketone product was obtained after hydrolysis of the vinyl ether with 1M HCl.

Scheme 5. DFT calculations indicating relative energy barriers (in kcal/mol) for the π -bond insertion with P_2N_2 Pd complexes



Further details for the computational models used and for a full energy-level profile of the transformation are provided in the Supporting Information (Section S14).

Lastly, we investigated if these optimized reaction conditions were effective for the regioselective coupling or alternative alkenes. $P^{Ph}_2N^{ArCF_3}_2$ Pd G3 (**4**) was found to catalyze the site selective arylation of isoprene, a volatile feedstock diene, with two different aryl triflates to form the linear diene products **27-lin** in 29% yield as the only observed regioisomer, and **28-lin**

in 33% yield with 9:1 regioselectivity. $P^{tBu}_2N^{ArCF_3}_2$ Pd G3 (**3**) could be applied to the same coupling to afford **28-br**, a branched diene, in 23% yield. This catalyst was also broadly effective to enable access to *n*-butyl vinyl ether (**29-br** to **31-br**) and enamide derived products (**32-br** to **37-br**) with high branched selectivity (>20:1 *rr*).

Density-functional theory Since all Pd(0) and Pd(II) complexes isolated suggest both the $P^{Ph}_2N^{ArCF_3}_2$ and $P^{tBu}_2N^{ArCF_3}_2$ ligands exhibit similar binding modes and nuclearity, we surmised that the divergent selectivity must originate from subtle steric and/or electronic effects in the transition state of the alkene insertion. Accordingly, we sought to model the mechanism of the reaction between styrene and the cationic P_2N_2 Pd(II) complexes using density functional theory (Scheme 5). The calculations were performed using B3LYP-D3BJ/def2-TZVP//B3LYP-D3BJ/def2-SVP with a conductor-like polarizable continuum model (CPCM) for the toluene solvent. It was found that the styrene substrate forms a π -complex with the Pd(II) center where the C=C bond axis is perpendicular to the Pd-C_{Ar} bond. Rotation of the substrate and its migratory insertion (TS insertion) can proceed through two different pathways. The path where the styrene Ph group is in close proximity with the ligand R group will lead to the linear product (TS insertion-linear) while the path where the styrene Ph is rotated 180 degrees will lead to the branched product (TS insertion-branched). The subsequent rearrangements and β -hydride elimination were found to be lower-energy, so TS-insertion regiodetermining (see Figure S23, SI). While these steps determine the regioselectivity, we have modeled a full catalytic cycle, where the Pd-hydride intermediate is deprotonated by the solution amine, regenerating the $(P_2N_2)Pd(0)$ catalyst that can then react with another equivalent of Ph-OTf to form $(P_2N_2)Pd(Ph)(OTf)$. Exchange of OTf⁻ for styrene completes the catalytic cycle. Paths where the triflate counterion was present in either the inner or outer coordination sphere were found to be higher energy. The calculated reaction profile is described in full in Supporting Information.

To better understand the origin for the ligand-controlled differences in transition state barriers for branched and linear selectivity, we analyzed the interactions in the key migratory insertion transition state. While ligands containing P-^tBu and P-Ph substituents are known to have substantial electronic differences, the origin of the regioselective insertion step appears to derive primarily from steric effects. The rigid cyclic backbone of the P_2N_2 ligands imposes a position on the P substituent where it will have contact with the incoming styrene, particularly for in the transition state leading to the linear product (TS insertion - linear). This interaction appears critical in dictating the regioselectivity. The styrene aryl ring can interact with $P^{Ph}_2N^{ArCF_3}_2$ in a geometry with limited steric repulsion and significant compensatory dispersion and electrostatic interactions. This π - π interaction between the ligand P-Ph group and the styrene arene ring results in the linear pathway being lower in energy than the branched pathway (linear: $\Delta G^\ddagger=12.3$ kcal/mol, branched: $\Delta G^\ddagger=15.7$ kcal/mol). This trend is reversed for the $P^{tBu}_2N^{ArCF_3}_2$ transition states (branched: $\Delta G^\ddagger=16.6$ kcal/mol, linear: $\Delta G^\ddagger=19.3$ kcal/mol).

A decomposition of the interactions between these groups using Symmetry Adapted Perturbation Theory (SAPT) analysis, which allows the intermolecular interactions between two components of a chemical system to be divided into exchange (steric), dispersion, induction, and electrostatic components. At the transition state geometry (Table S64, SI). The difference in total interaction energies are consistent with the total of these interactions favoring the linear product over the branched product (-

6.9 kcal/mol vs -4.2 kcal/mol), which is reversed to favor the branched product for the R=^tBu ligand (-2.2 kcal/mol vs -2.6 kcal/mol). This is consistent with the interactions between the P_2N_2 R groups and substrate aryls determining the regioselectivity of the reaction in the migratory insertion TS. This difference in energy is primarily due to a higher steric (exchange) energy term between the ^tBu groups and the styrene phenyl ring in the transition state (TS insertion branched) than those seen in the $P^{Ph}_2N^{ArCF_3}_2$ ligand. This is consistent with the steric repulsion between the ligand *tert*-butyl groups and the styrene aromatic group destabilizing the path to the linear product, resulting in selectivity for the branched product for both ligands, although the effect is much stronger for $P^{tBu}_2N^{ArCF_3}_2$ ($\Delta E_{ex.} = -4.8$ kcal/mol for $P^{Ph}_2N^{ArCF_3}_2$ vs -9.2 kcal/mol for $P^{tBu}_2N^{ArCF_3}_2$). The electrostatic and inductive interactions are very similar for the two catalysts, but the decreased ^tBu-aryl dispersion interactions partially counter the steric preference for the branched product ($\Delta E_{disp.} = 4.0$ kcal/mol for $P^{Ph}_2N^{ArCF_3}_2$ vs 4.9 kcal/mol for $P^{tBu}_2N^{ArCF_3}_2$).³⁸

We have also performed this analysis where Ph-CF₃ groups were included in the ligand fragments and found that the predictions of the selectivity followed the same trends as for the ^tBu/Ph ligand fragments alone. This analysis is included in the Supporting Information (Section S14.5).

Conclusion Despite the prominence of the Mizoroki-Heck reaction as a powerful catalytic method to form C-C bonds, its implementation in synthetic methodologies has remained limited compared to other Pd-catalyzed couplings. In this work, a high-throughput screen identified 1,5-diaza-3,7-diphospha-cyclooctane ligands as being broadly effective towards a range of alkene substrates with comparable or superior reactivity to more well-established ligand systems. For the palladium catalyzed coupling of aryl triflates with styrenes – a challenging transformation despite its simplicity – two P_2N_2 ligands were found to enable regiodivergent outcomes, with a P-Ph ligand providing high linear selectivity and a P-^tBu ligand providing access to the branched regioisomer. Several novel P_2N_2 Pd complexes were prepared and characterized, indicating that differences in speciation or coordination of the pendant N-arene were not contributing factors in selectivity. DFT calculations uncovered a favorable π - π interaction between the styrene group and the $P^{Ph}_2N^{ArCF_3}_2$ ligand which could explain its preference for the linear pathway. Conversely, the bulky $P^{tBu}_2N^{ArCF_3}_2$ ligand destabilizes this pathway due to steric hinderance, inverting the regiochemical outcome. P_2N_2 s are well known to be powerful ligands, particularly due to the flexible, basic nitrogen atoms in the ligand's second-coordination sphere, enabling H₂ splitting and related transformations.^{11a} This work demonstrates both a new application as well as proposes a new unique feature that differentiates them from more commonly used ligand classes. The rigid positioning of the P-substituent results in close contact with incoming reactants, enabling high regiocontrol in this Pd-catalyzed cross-coupling. We suspect that further study of these P_2N_2 s may continue to reveal new applications and demonstrate that these are an underappreciated, readily accessible ligand class for organic synthesis.

ASSOCIATED CONTENT

Information regarding high-throughput experimentation, experimental procedures, optimization tables, troubleshooting, and characterization of organic molecules is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For early contributions to the Mizoroki-Heck reaction see: (a) Moritani, I. and Fujiwara, Y. Aromatic substitution of styrene-palladium chloride complex. *Tetrahedron Lett.* **1967**, 1119-1122. (b) Heck,

R. F. Acylation, methylation, and carboxyalkylation of olefins by Group VIII metal derivatives. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526. (c) Heck, R. F. The palladium-catalyzed arylation of enol esters, ethers, and halides. A new synthesis of 2-aryl aldehydes and ketones. *J. Am. Chem. Soc.* **1968**, *90*, 5535-5538. (d) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. Aromatic substitution of olefins. VI. Arylation of olefins with palladium (II) acetate. *J. Am. Chem. Soc.* **1969**, *91*, 7166-7169. (e) Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581-581. (f) Heck, R. F. and Nolley, J. P. Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides. *J. Org. Chem.* **1972**, *37*, 2320-2322. (g) Dieck, H. A. and Heck, R. F. Organophosphinepalladium complexes as catalysts for vinylic hydrogen substitution reactions. *J. Am. Chem. Soc.* **1974**, *96*, 1133-1136.

(2) For an overview of the Mizoroki-Heck reaction including historical context and applications see: (a) Heck, R. F. Palladium-Catalyzed Vinylation of Organic Halides. *Org. React.* **1982**, *27*, 345-390. (b) Davies, G. D. and Hallberg, A. 1,2-Additions to Heteroatom-Substituted Olefins by Organopalladium Reagents. *Chem. Rev.* **1989**, *89*, 1433-1445. (c) de Meijere, A. and Meyer, F. E. Fine Feathers Make Fine Birds: The Heck Reaction in Modern Garb. *Angew. Chem. Int. Ed.* **1995**, *33*, 2379-2411. (d) Beletskaya, I. P. and Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009-3066. (e) Oestreich, M. *The Mizoroki-Heck Reaction*; John Wiley & Sons, Ltd. **2009**.

(3) Roughley, S. D. and Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451-3479. .

(4) For regioselective reactions with terminal alkyl alkenes see (a) Werner, E. W.; Sigman, M. S. Operationally Simple and Highly (E)-Styrenyl-Selective Heck Reactions of Electronically Nonbiased Olefins. *J. Am. Chem. Soc.* **2011**, *133*, 9692-9695. (b) Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. Nickel-Catalyzed Mizoroki-Heck Reaction of Aryl Sulfonates and Chlorides with Electronically Unbiased Terminal Olefins: High Selectivity for Branched Products. *Angew. Chem. Int. Ed.* **2014**, *53*, 1858-1861. (c) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. Nickel-Catalyzed Heck-Type Reactions of Benzyl Chlorides and Simple Olefins. *J. Am. Chem. Soc.* **2011**, *133*, 19020-19023. (d) Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. Intermolecular Mizoroki-Heck Reaction of Aliphatic Olefins with High Selectivity for Substitution at the Internal Position. *Angew. Chem. Int. Ed.* **2012**, *51*, 5915-5919 (e) Qin, L.; Hirao, H.; Zhou, J. Regioselective Heck reaction of aliphatic olefins and aryl halides *Chem. Commun.* **2013**, *49*, 10236-10238. (f) Wang, Z.; Zhang, J.; Koh, M. J.; Shi, S. Divergent and Selective Light Alkene Cross-coupling. *Angew. Chem. Int. Ed.* **2023**, *62*, e20231020. (g) Wang, Z.-C.; Luo, X.; Zhang, J.-W.; Liu, C.-F.; Koh, M. J.; Shi, S.-L. Enantioselective C-C Cross-coupling of Unactivated Alkenes. *Nat. Catal.* **2023**, *6*, 1087-1097. For representative couplings with internal aliphatic alkenes see: (h) Zhou, J.; Huang, X.; Teng, S.; Chi, Y. R. Nickel-catalyzed Heck reaction of cycloalkenes using aryl sulfonates and pivalates. *Chem Commun.* **2021**, *57*, 3933-3936.

(5) For specific examples of vinyl ethers in Mizoroki-Heck couplings see: (a) Domzalska-Pieczyszkolan, A.; Funes-Ardoiz, I.; Furman, B.; Bolm, C. Selective Approaches to α - and β -Arylated Vinyl Ethers. *Angew. Chem. Int. Ed.* **2021**, *61*, e202109801. (b) Cabri, W.; Candiani, I.; Bedeschi, A. Ligand-Controlled -Regioselectivity in Palladium-Catalyzed Arylation

of Butyl Vinyl Ether. *J. Org. Chem.* **1990**, *55*, 3654-3655. (c) Andersson, C.-M. and Hallberg, A. Palladium-Catalyzed Vinylation of Alkyl Vinyl Ethers with Enol Triflates. A Convenient Synthesis of 2-Alkoxy 1,3-Dienes. *J. Org. Chem.* **1989**, *54*, 1502-1505. (d) Larhed, M.; Andersson, C.-M.; Hallberg, A. Chelation-controlled, palladium-catalyzed arylation of enol ethers with aryl triflates. Ligand control of selection for α - or β -arylation of [2-(dimethylamino)ethoxy]ethene. *Tetrahedron* **1994**, *50*, 285-304. (e) Jeffrey, T. and David, M. [Pd/Base/QX] catalyst systems for directing Heck-type reactions. *Tetrahedron Lett.* **1998**, *39*, 5751-5754. (f) Littke, A. F. and Fu, G. A Versatile Catalyst for Heck Reactions of Aryl Chlorides and Aryl Bromides under Mild Conditions. *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000. (g) Bengtson, A.; Larhed, M.; Hallberg, A. Protected Indanones by a Heck–Aldol Annulation Reaction. *J. Org. Chem.* **2002**, *67*, 5854-5856. (h) Mo, J. and Xiao, J. The Heck Reaction of Electron-Rich Olefins with Regiocontrol by Hydrogen-Bond Donors. *Angew. Chem. Int. Ed.* **2006**, *45*, 4152-4157. (i) Liu, S.; Berry, N.; Thomson, N.; Pettman, A.; Hyder, Z.; Mo, J.; Xiao, J. Pd–mBDPP-Catalyzed Regioselective Internal Arylation of Electron-Rich Olefins by Aryl Halides. *J. Org. Chem.* **2006**, *71*, 7467-7470. (j) Machado, A. H. L.; de Sousa, M. A.; Patto, D. C. S.; Azevedo, L. F. S.; Bombonato, F. I.; Correia, C. R. D. The scope of the Heck arylation of enol ethers with arenediazonium salts: a new approach to the synthesis of flavonoids. *Tetrahedron Lett.* **2009**, *50*, 1222-1225. (k) McConville, M.; Saidi, O.; Blacker, J.; Xiao, J. Regioselective Heck Vinylation of Electron-Rich Olefins with Vinyl Halides: Is the Neutral Pathway in Operation? *J. Org. Chem.* **2009**, *74*, 2692-2698. (l) Hartman, R. L.; Naber, J. R.; Buchwald, S. L.; Jensen, K. F. Multistep Microchemical Synthesis Enabled by Microfluidic Distillation. *Angew. Chem. Int. Ed.* **2010**, *49*, 899-903. (m) Ruan, J.; Iggo, J. A.; Berry, N. G.; Xiao, J. Hydrogen-Bonding-Promoted Oxidative Addition and Regioselective Arylation of Olefins with Aryl Chlorides. *J. Am. Chem. Soc.* **2010**, *132*, 16689-16699. (n) Gøgsig, W. M.; Kleimark, J.; Lill, S. O. N.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. Mild and Efficient Nickel-Catalyzed Heck Reactions with Electron-Rich Olefins. *J. Am. Chem. Soc.* **2012**, *134*, 443-452. (o) Becica, J.; Glaze, O. D.; Hruszkewycz, D. P.; Dobreiner, G. E.; Leitch, D. C. The influence of additives on orthogonal reaction pathways in the Mizoroki–Heck arylation of vinyl ethers. *React. Chem. Eng.*, **2021**, *6*, 1212-1219. (p) Duhamel, T.; Scaringi, S.; Leforestier, B.; Poblador-Bahamonde, A. I.; Mazet, C. Assisted Tandem Pd Catalysis Enables Regiodivergent Heck Arylation of Transiently Generated Substituted Enol Ethers. *JACS Au* **2023**, *3*, 261-274.

(6) (a) Ehle, A. R.; Zhou, Q.; Watson, M. P. Nickel(0)-Catalyzed Heck Cross-Coupling via Activation of Aryl C–OPiv Bonds. *Org. Lett.* **2012**, *14*, 1202-1205. (b) Zou, Y.; Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. Selective Arylation and Vinylation at the α Position of Vinylarenes. *Chem. Eur. J.* **2013**, *19*, 3504-3511. For specific examples of linear selective coupling with styrenes see: (c) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umami Ronchi, A. Nickel-Catalyzed Coupling of Activated Alkenes with Organic Halides. *J. Organomet. Chem.* **1986**, *301*, C62–C64. (d) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. Condensation of Organic Bromides with Vinyl Compounds Catalysed by Nickel Complexes in the Presence of Zinc. *J. Organomet. Chem.* **1988**, *344*, 253-259. (e) Bhanage, B. M.; Zhao, F.; Shirai, M.; Arai, M. Heck reaction

using nickel/TPPTS catalyst and inorganic base on supported ethylene glycol phase. *Catal. Lett.* **1998**, *54*, 195-198. (f) Walker, B. R. and Sevov, C. S. An Electrochemically Promoted, Nickel-Catalyzed Mizoroki–Heck Reaction. *ACS Catal.* **2019**, *9*, 7197-7203. For regioirregular (branched) reactions with styrenes see (g) Garnes-Portolés, F.; Greco, R.; Olivier-Meseguer, J.; Castellanos-Soriano, J.; Jiménez, M. C.; López-Haro, M.; Hernández-Garrido, J. C.; Boronat, M.; Pérez-Ruiz, R.; Levya-Pérez, A. Regioirregular and catalytic Mizoroki–Heck reactions. *Nat. Catal.* **2021**, *4*, 293-303. (j) Lui, K.; Liefert, D.; Studer, A. Cooperative triple catalysis enables regioirregular formal Mizoroki–Heck reactions. *Nat. Synth.* **2022**, 565-575.

(7) For general examples of electron rich- olefins in Mizoroki-Heck couplings: (a) Cabri, W. and Candiani, I. Recent Developments and New Perspectives in the Heck Reaction. *Acc. Chem. Res.* **1995**, *28*, 2-7. (b) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. A New Regioselective Heck Vinylation with Enamides. Synthesis and Investigation of Fluorous-Tagged Bidentate Ligands for Fast Separation. *J. Org. Chem.* **2003**, *68*, 6639-6645. (c) Tu, T.; Hou, X.-L.; Dai, L.-X. Highly Regio- and Enantioselective Heck Reaction of *N*-Methoxycarbonyl-2-pyrroline with Planar Chiral Diphosphine-oxazolone Ferrocenyl Ligands. *Org. Lett.* **2003**, *5*, 3651-3653. (d) Hansen, A. L. and Skrydstrup, T. Regioselective Heck Couplings of α,β -Unsaturated Tosylates and Mesylates with Electron-Rich Olefins. *Org. Lett.* **2005**, *7*, 5585-5587. (e) Hansen, A. L. and Skrydstrup, T. Fast and Regioselective Heck Couplings with *N*-Acyl-*N*-vinylamine Derivatives. *J. Org. Chem.* **2005**, *70*, 5997-6003. (f) Hyder, Z.; Ruan, J.; Xiao, J. Hydrogen-Bond-Directed Catalysis: Faster, Regioselective and Cleaner Heck Arylation of Electron-Rich Olefins in Alcohols. *Chem. Eur. J.* **2008**, *14*, 5555-5566. (g) Liu, Z.; Xu, D.; Tang, W.; Xu, L.; Mo, J.; Xiao, J. A general method for regioselective Heck arylation of electron-rich *N*-acyl-*N*-vinylamine with aryl halides. *Tetrahedron Lett.* **2008**, *49*, 2756-2760. (h) Pelletier, G.; Larivée, A.; Charette, A. B. Highly Regioselective Intermolecular Arylation of 1,2,3,4-Tetrahydropyridines. *Org. Lett.* **2008**, *10*, 4791-4794. (i) Gøgsig, W. M.; Lindhardt, A. T.; Dekhane, M.; Grouleff, J.; Skrydstrup, T. Heteroaromatic Tosylates as Electrophiles in Regioselective Mizoroki–Heck-Coupling Reactions with Electron-Rich Olefins. *Chem. Eur. J.* **2009**, *15*, 5950-5955. (j) Guo, Q.; Deng, B.; Zhang, H.; Qin, J. Arylations of Substituted Enamides by Aryl Iodides: Regio- and Stereoselective Synthesis of (Z)- β -Amido- β -Arylacrylates. *Org. Lett.* **2013**, *15*, 4604-4607.

(8) For general examples of electron-deficient olefins in Mizoroki-Heck couplings see: (a) Feuerstein, M.; Doucet, H.; Santelli, M. Efficient Heck Vinylation of Aryl Halides Catalyzed by a New Air-Stable Palladium–Tetraphosphine Complex. *J. Org. Chem.* **2001**, *66*, 5923-5925. (b) Fall, Y.; Doucet, H.; Santelli, M. Selective Heck reaction of aryl bromides with cyclopent-2-en-1-one or cyclohex-2-en-1-one. *Tetrahedron* **2009**, *65*, 489-495. (c) Gottumukkala, A. L.; de Vries, J. G.; Minnaard, A. J. Pd–NHC Catalyzed Conjugate Addition versus the Mizoroki–Heck Reaction. *Chem. Eur. J.* **2011**, *17*, 3091-3095. (d) Wucher, P.; Caporaso, L.; Roesle, P.; Ragone, F.; Cavallo, L.; Mecking, S.; Göttker-Schnetmann. Breaking the regioselectivity rule for acrylate insertion in the Mizoroki–Heck reaction. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 8955-8959. (e) Gowla, T. N.; Pabba, J. Selective Heck reaction of electron-rich aryl

bromides with cyclic alkenones. *Tetrahedron Lett.* **2015**, *56*, 1801-1804. (f) Canterbury, D. P.; Hesp, K. D.; Polivkova, J. Palladium-catalyzed β -(hetero)arylation of α,β -unsaturated valerolactams. *Org. Biomol. Chem.*, **2016**, *14*, 7731-7734. (g) Islam, M. S.; Nahra, F.; Tzouras, N. V.; Barakat, A.; Cazin, C. S. J.; Nolan, S. P.; Al-Majid, A. M. Mizoroki–Heck Cross-Coupling of Acrylate Derivatives with Aryl Halides Catalyzed by Palladate Pre-Catalysts. *Eur. J. Inorg. Chem.* **2019**, *2019*, 4695-4699.

(9) For a general review on regioselective couplings of electronically-unbiased alkenes see: Deb A.; Maiti, D. Emergence of Unactivated Olefins for the Synthesis of Olefinated Arenes. *Eur. J. Chem.* **2017**, *2017*, 1239-1252.

(10) Zhang, W. S.; Ji, D.-W.; Li, Y.; Zhang, X.-X.; Mei, Y.-K.; Chen, B.-Z.; Chen, Q.-A. Nickel-catalyzed divergent Mizoroki–Heck reaction of 1,3-dienes. *Nat. Commun.* **2023**, *14*, 651.

(11) (a) Wiedner, E. S.; Appel, A. M.; Raugai, S.; Shaw, W. J.; Bullock, R. M. Molecular Catalysts with Diphosphine Ligands Containing Pendant Amines. *Chem. Rev.* **2022**, *122*, 12427–12474. (b) Moiseev, D. V. and James, B. R. Phospha-Mannich Reactions of R_2PH_2 , R_2PH , and R_3P . *Phosphorus. Sulfur. Silicon Relat. Elem.* **2022**, *197*, 327–391.

(12) (a) Firhi, A.; Luart, D.; Len, C.; Solhy, A.; Chevrin, C.; Polshettiwar, V. Suzuki–Miyaura cross-coupling reactions with low catalyst loading: a green and sustainable protocol in pure water. *Dalton Trans.* **2011**, *40*, 3116-3121. (b) Bow, J.-P. P.; Boyle, P. D.; Blacquièrre, J. M. Substrate-Mediated Deactivation of a $Ru(P^{iBu_2}N^{R_2})$ Cooperative Complex. *Eur. J. Inorg. Chem.* **2015**, *2015*, 4162-4166. (c) Stubbs, J. M.; Bow, J.-P. J.; Hazlehurst, R. J.; Blacquièrre, J. M. Catalytic Cyclization and Competitive Deactivation with $Ru(P^{R_2}N^{R_2})$ Complexes. *Dalton Trans.* **2016**, *45*, 17100-17103. (d) Stubbs, J. M.; Chapple, D. E.; Boyle, P. D.; Blacquièrre, J. M. Catalyst Pendant-Base Effects on Cyclization of Alkynyl Amines. *ChemCatChem* **2018**, *10*, 4001-4009. (e) Stubbs, J. M.; Bridge, B. J.; Blacquièrre, J. M. Optimizing Ligand Structure For Low-Loading and Fast Catalysis for Alkynyl-Alcohol and Amine Cyclization. *Dalton Trans.* **2019**, *48*, 7928-7937. (f) Bridge, B. J.; Boyle, P. D.; Blacquièrre, J. M. endo-Selective Iron Catalysts for Intramolecular Alkyne Hydrofunctionalization. *Organometallics* **2020**, *39*, 2570–2574. (g) Chapple, D. E.; Boyle, P. D.; Blacquièrre, J. M. Origin of Stability and Inhibition of Cooperative Alkyne Hydrofunctionalization Catalysts. *ChemCatChem*, **2021**, *13*, 3789-3800. (h) Isbrandt, E. S.; Nasim, A.; Zhao, K.; Newman, S. G. Catalytic Aldehyde and Alcohol Arylation Reactions Facilitated by a 1,5-Diaza-3,7-diphosphacyclooctane Ligand. *J. Am. Chem. Soc.* **2021**, *143*, 14646-14656. (i) Chapple, D. E.; Hoffer, M. A.; P. D. Boyle, P. D.; Blacquièrre, J. M. Alkyne Hydrofunctionalization Mechanism Including an Off-Cycle Alkoxycarbene Deactivation Complex. *Organometallics* **2022**, *41*, 1532-1542 (j) Nasim, A.; Thomas, G. T.; Ovens, J. S.; Newman, S. G. Reductive 1,2-Arylation of Isatins. *Org. Lett.* **2022**, *24*, 7232-7236

(13) For a report of a Mizoroki–Heck reaction featuring a P,N-acetal ligand, see: Uruş, S.; Keleş, M.; Köşker, S. Synthesis and Characterization of Pd(II) and Ru(II) *Tetradentate N,N,N,N*-(diphosphinomethyl)amine Ligands: Catalytic Properties in Transfer Hydrogenation and Heck Coupling Reactions. *Heterocycles* **2020**, *100*, 1019-1034.

(14) (a) Krska, S. W.; DiRocco, D. A.; Dreher, S. D.; Shevlin, M. The Evolution of Chemical High-Throughput Experimentation To Address Challenging Problems in Pharmaceutical Synthesis. *Acc. Chem. Res.* **2017**, *50*, 2976–2985. (b) Allen, C. L.; Leitch, D. C.; Anson, M. S.; Zajac, M. A. The power and accessibility of high-throughput methods for catalysis research. *Nat. Catal.* **2019**, *2*, 2-4. (c) Isbrandt, E. S.; Sullivan, R. J.; Newman, S. G. High Throughput Strategies for the Discovery and Optimization of Catalytic Reactions. *Angew. Chem. Int. Ed.* **2019**, *58*, 7180-7191. (b) Cook, A.; Clément, R.; Newman, S. G. Re-

action screening in multiwell plates: high-throughput optimization of a Buchwald–Hartwig amination. *Nature Prot.* **2021**, *16*, 1152-1169.

(15) For discussions on the comparison of Pd and Ni in Mizoroki–Heck reactions see: (a) Liu, L. L.; Fu, Y.; Luo, S. W.; Chen, Q.; Guo, Q.-X. Comparing Nickel- and Palladium-Catalyzed Heck Reactions. *Organometallics* **2004**, *23*, 2114–2123. (b) Menezes da Silva, V. H.; Braga, A. A. C.; Cundari, T. R. N-Heterocyclic Carbene Based Nickel and Palladium Complexes: A DFT Comparison of the Mizoroki–Heck Catalytic Cycles. *Organometallics* **2016**, *35*, 3170–3181. (c) Bhakta, S. and Ghosh, T. Emerging Nickel Catalysis in Heck Reactions: Recent Developments. *Adv. Syn. Catal.* **2020**, *362*, 5257-5274. (d) Alisha, M.; Philip, R. M.; Anilkumar, G. Low-Cost Transition Metal-Catalyzed Heck-Type Reactions: An Overview. *Eur. J. Org. Chem.* **2022**, *2022*, e202101384.

(16) For discussions on the comparison of neutral and cationic Mizoroki–Heck reactions see: Bäcktorp, C. and Norrby, P.-O. A DFT comparison of the neutral and cationic Heck pathways. *Dalton Trans.*, **2011**, *40*, 11308-11314.

(17) Section 2.5.1 of: Sherwood, J.; Clark, J. H.; Fairlamb, I. J. S.; Slatery, J. M. Solvent effects in palladium catalysed cross-coupling reactions. *Green Chem.* **2019**, *21*, 2164-2213.

(18) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. Palladium-catalyzed arylation of unsymmetrical olefins. Bidentate phosphine ligand controlled regioselectivity. *J. Org. Chem.* **1992**, *57*, 3558 – 3563.

(19) Zhang, L.; Jiang, Z.; Dong, C.; Xue, X.; Qui, R.; Tang, W.; Li, H.; Xiao, J.; Xu, L. Palladium-Catalyzed Highly Regioselective Mizoroki–Heck Arylation of Allylamines with Aryl Chlorides. *ChemCatChem* **2014**, *6*, 311-318.

(20) (a) Neumann, H.; Sergeev, A. G.; Spannenberg, A.; Beller, M. Efficient Palladium-Catalyzed Synthesis of 2-Aryl Propionic Acids. *Molecules* **2020**, *25*, 3421. (b) Johnphos is marketed as a ligand for Mizoroki–Heck cross coupling by retailers (eg. Sigma Aldrich: PN 638439).

(21) (a) Yang, C. and Nolan, S. P. A Highly Efficient Palladium/Imidazolium Salt System for Catalytic Heck Reactions. *Synlett* **2001**, 1539-1542. (b) Inamoto, K.; Kuroda, J.; Danjo, T.; Sakamoto, T. Highly Efficient Nickel-Catalyzed Heck Reaction Using Ni(acac)₂/N-Heterocyclic Carbene Catalyst. *Synlett* **2005**, 1624-1626.

(22) Xu, H.-J.; Zhao, Y.-Q.; Zhou, X.-F. Palladium-Catalyzed Heck Reaction of Aryl Chlorides under Mild Conditions Promoted by Organic Ionic Bases. *J. Org. Chem.* **2011**, *76*, 8036–8041.

(23) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. Bidentate Nitrogen Ligands in Heck Type Reactions. *Synlett* **1992**, 871-872. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. 1,10-Phenanthroline derivatives: a new ligand class in the Heck reaction. Mechanistic aspects. *J. Org. Chem.* **1993**, *58*, 7421–7426.

(24) Kashani, S. K.; Jessiman, J. E.; Newman, S. G. Exploring Homogeneous Conditions for Mild Buchwald–Hartwig Amination in Batch and Flow. *Org. Process Res. Dev.* **2020**, *24*, 1948–1954.

(25) For an overview of the Open Reaction Database (ORD) see: (a) Kearnes, S. M.; Maser, M. R.; Wlekinski, M.; Kast, A.; Doyle, A. G.; Dreher, S. D.; Hawkins, J. M.; Jensen, K. F.; Coley, C. W. The Open Reaction Database. *J. Am. Chem. Soc.* **2021**, *143*, 18820-18826. The raw high-throughput data is available at <https://open-reaction-database.org/client/browse>. Data set IDs are listed below: Styrene plate: ord_dataset-0316886541d9435489859c2ad7edc863 1-octene plate: ord_dataset-1d3a1a6fb70d46c084602d0688967afc n-butyl vinyl ether plate: ord_dataset-52bd3b0ec72c443aab113bcea09bf3f4 N-Vinylpyrrolidone plate: ord_dataset-ce5045aceb214fc8bfd0ef3031e2737.

(26) For a computational analysis of the regioselectivity of Pd-catalyzed Mizoroki–Heck couplings see: (a) Ree, N.; Göller, A. H.; Jensen, J. H. What the Heck?—Automated Regioselectivity Calculations of Palladium-catalyzed Heck Reactions Using Quantum Chemistry. *ACS Omega* **2022**, *7*, 45617–45623. For selected examples of ligand controlled regiodivergency see: (b) Ke, Y.; Li, W.; Liu, W.; Kong, W. Ni-catalyzed ligand-controlled divergent and selective synthesis. *Sci. China Chem.* **2023**, *66*, 1-26. (c) Irifune, K.; Yamazaki, K.; Nakamuro,

T.; Murakami, M.; Miura, T. Ligand-Controlled Regiodivergence in Nickel-Catalyzed Vinylcyclopropane Rearrangement. *Angew. Chem. Int. Ed.* **2023**, ASAP, e202307826.

(27) (a) Strel'nik, I. D.; Musina, E. I.; Grachova, E.; Karasik, A. A.; Sinyashin, O. Luminescent copper(I) and gold(I) complexes of 1,5-diaza-3,7-diphosphacyclooctanes. *Phosphorus Sulfur Silicon Relat. Elem.* **2016**, *191*, 1518-1519. (b) Strel'nik, I. D.; Musina, E. I.; Ignatieva, S. N.; Balueva, A. S.; Gerasimova, T. P.; Katsyuba, S. A.; Krivolapov, D. B.; Dobrynin, A. B.; Bannwarth, C.; Grimme, S.; Kolesnikov, I. E.; Karasik, A. A.; Sinyashin, O. G. Pyridyl Containing 1,5-Diaza-3,7-diphosphacyclooctanes as Bridging Ligands for Dinuclear Copper(I) Complexes. *Z. Anorg. Allg. Chem.* **2017**, *643*, 895-902. (c) Strel'nik, I. D.; Dayanova, I. R.; Krivolapov, D. B.; Litvinov, I. A.; Musina, E. I.; Karasik, A. A.; Sinyashin, O. G. Unpredicted concurrency between P,P-chelate and P,P-bridge coordination modes of 1,5-diR-3,7-di(pyridine-2-yl)-1,5-diaza-3,7-diphosphacyclooctane ligands in copper(I) complexes. *Polyhedron*, **2018**, *139*, 1-6.

(28) (a) Mock, M. T.; Chen, S.; Rousseau, R.; O'Hagan, M. J.; Dougherty, W. G.; Kassel, W. S.; DuBois, D. L.; Bullock, R. M. A rare terminal dinitrogen complex of chromium. *Chem. Commun.*, **2011**, *47*, 12212-12214. (b) Hulley, E. B.; Helm, M. L.; Bullock, R. M. Heterolytic cleavage of H₂ by bifunctional manganese(i) complexes: impact of ligand dynamics, electrophilicity, and base positioning. *Chem. Sci.*, **2014**, *5*, 4729-4741. (c) Hulley, E. B.; Kumar, N.; Raugai, S.; Bullock, R. M. Manganese-Based Molecular Electrocatalysts for Oxidation of Hydrogen. *ACS Catal.* **2015**, *5*, 6838-6847. (d) Zhang, S.; Appel, A. M.; Bullock, R. M. Reversible Heterolytic Cleavage of the H-H Bond by Molybdenum Complexes: Controlling the Dynamics of Exchange Between Proton and Hydride. *J. Am. Chem. Soc.* **2017**, *139*, 7376-7387. (e) Bhattacharya, P.; Heiden, Z. M.; Chambers, G. M.; Johnson, S. I.; Bullock, R. M.; Mock, M. T. Catalytic Ammonia Oxidation to Dinitrogen by Hydrogen Atom Abstraction. *Angew. Chem. Int. Ed.* **2019**, *58*, 11618-11624.

(29) Klug, C. M.; O'Hagan, M.; Bullock, M. R.; Appel, A. M.; Wiedner, E. S. Impact of Weak Agostic Interactions in Nickel Electrocatalysts for Hydrogen Oxidation. *Organometallics* **2017**, *36*, 2275-2284.

(30) Huang, J.; Isaac, M.; Watt, R.; Becica, J.; Dennis, E.; Sadiaminov, M. I.; Sabbers, W. A.; Leitch, D. C. ^{DMP}DAB-Pd-MAH: A Versatile Pd(0) Source for Precatalyst Formation, Reaction Screening, and Preparative-Scale Synthesis. *ACS Catal.* **2021**, *11*, 5636-5646.

(31) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and preparation of new palladium precatalysts for C-C and C-N cross-coupling reactions. *Chem. Sci.* **2013**, *4*, 916-920.

(32) Yang, L.; Powell, D. R.; Houser, R. P. Structural variation in copper (I) complexes with pyridylmethylamide ligands: structural analysis with a new four-coordinate geometry index, τ_4 . *Dalton Trans.*, **2007**, 955-964.

(33) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. Structural Insights into Active Catalyst Structures and Oxidative Addition to (Biaryl)phosphine-Palladium Complexes via Density Functional Theory and Experimental Studies. *Organometallics* **2007**, *26*, 2183-2192.

(34) Franz, J. A.; O'Hagan, M.; Ho, M.-H.; Liu, T.; Helm, M. L.; Lense, S.; DuBois, D. L.; Shaw, W. J.; Appel, A. M.; Raugai, S.; Bullock, R. M. Conformational Dynamics and Proton Relay Positioning in Nickel Catalysts for Hydrogen Production and Oxidation. *Organometallics* **2013**, *32*, 7034-7042.

(35) (a) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A. Synthesis and Structure-Activity Relationships of Novel Retinoid X Receptor-Selective Retinoids. *J. Med. Chem.* **1994**, *37*, 2930-2941. (b) Farol, L. T. and Hymes, K. B. Bexarotene: a clinical review. *Expert Rev. Anticancer Ther.* **2004**, *4*, 180-188.

(36) Song, M.-Y.; He, Q.-R.; Wang, Y.-L.; Wang, H.-R.; Jiang, T.-C.; Tang, J.-J.; Gao, J.-M. Exploring Diverse-Ring Analogues on Combretastatin A4 (CA-4) Olefin as Microtubule-Targeting Agents. *Int. J. Mol. Sci.* **2020**, *21*, 1817.

(37) (a) Messaoudi, S.; Trégier, B.; Hamaze, A.; Provot, O.; Peyrat, J. -F.; De Losada, J. R.; Liu, J.-M.; Bignon, J.; Wdziczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. Isocombretastatins A versus Combretastatins A: The Forgotten isoCA-4 Isomer as a Highly Promising Cytotoxic and Antitubulin Agent. *J. Med. Chem.* **2009**, *52*, 4538-4542. (b) Hamze A.; Alami, M.; Provot, O. Developments of iso-Combretastatin A-4 derivatives as highly cytotoxic agents. *Eur. J. Med. Chem.* **2020**, *190*, 112110.

(38) Leitner and coworkers recently disclosed a related regioselective decarboxylative Mizoroki-Heck coupling, with computational results in accordance with our own findings. See: Jenthra, S.; Mondal, T.; Kemper, G.; Lantzius-Beninga, M.; Hölscher, M.; Leitner, W. Ligand-controlled Palladium-catalyzed Decarboxylative Heck Coupling for Regioselective Access to Branched Olefins. *ACS Catal.* **2023**, *13*, 10085-10093.

