

Superseding Substrate Control with Catalyst Control to Improve Regioselectivity in Aryne Annulations

Brylon N. Denman[‡], Erin E. Plasek[‡], Courtney C. Roberts^{*}

University of Minnesota, Department of Chemistry, Minneapolis, MN 55455, USA

ABSTRACT: The utility of reactions using unsymmetrically substituted aryne intermediates is negatively impacted by issues with regioselectivity. There have been numerous reports about how to enhance or reverse this regioselectivity in metal-free aryne reactions by altering the electronics of the substrate. To the best of our knowledge, no such studies exist for systems with metal-bound aryne intermediates, which often suffer from worse regioselectivities. Herein we report a means of achieving regioselectivity in a metal catalyzed aryne difunctionalization via catalyst control. Through the use of an unsymmetrical ligand environment, selectivity can be induced (up to 9:91 r.r.). Through Charton analysis the source of regioselectivity can be attributed to the interplay of ligand effects and aryne sterics. These investigations demonstrate that catalyst design can influence selectivity in metal-catalyzed aryne reactions.

Arynes are highly reactive intermediates which have enabled the synthesis of natural products, ligands, and conjugated materials.^{1–10} A substantial challenge is posed when using unsymmetrically substituted arynes as they can produce multiple regioisomeric.^{6,11–20} This severely limits the potential of aryne intermediates towards synthetic applications.⁶ Yoshida and coworkers synthesis of the synthesis of phenoxathiins demonstrates this limitation as a 54:46 ratio of regioisomers was observed when employing an *o*-methyl aryne intermediate (**Figure 1a**).²¹ In contrast, when using the electronically activated methoxy substrate, only one regioisomer was observed. A number of elegant computational models have been developed to probe the origins of selectivity for aryne reactions.^{22–28} For example, Garg and Houk have developed the aryne distortion model which states that the “nucleophile attacks the alkyne terminus that is more distorted toward linearity” (**Figure 1b**).²² This distortion can be induced by electronically-activating functional groups ortho to one of the positions on the triple bond.^{29,30} Other studies have further corroborated this electronic influence on aryne regioselectivity (**Figure 1b**).^{31–37} This effect has been leveraged in the synthesis of substituted 3,4-pyridines. Addition of functional groups in both positions ortho to the triple bond allowed for both enhanced and reversed selectivity compared to the parent unsubstituted 3,4-pyridine.^{29,38} In all of these examples, regioselectivity is substrate controlled.

To our knowledge, there are no studies reported to date that attempt to systematically control the regioselectivity in metal-catalyzed aryne reactions. Furthermore, selectivity-establishing strategies employed in metal-free aryne reactions do not translate. For example in a report by Hosoya and coworkers, a metal-bound *o*-methoxy aryne (generated from an *o*-borylaryl triflate precursor) shows no selectivity upon exposure to the coupling partners (**Figure 1c**) despite complete inherent regioselectivity of the *o*-methoxy aryne in a metal-free aryne reaction (**Figure 1a**).³⁹ This is corroborated by other groups as well.^{40–53} Sporadic reports using, for example,

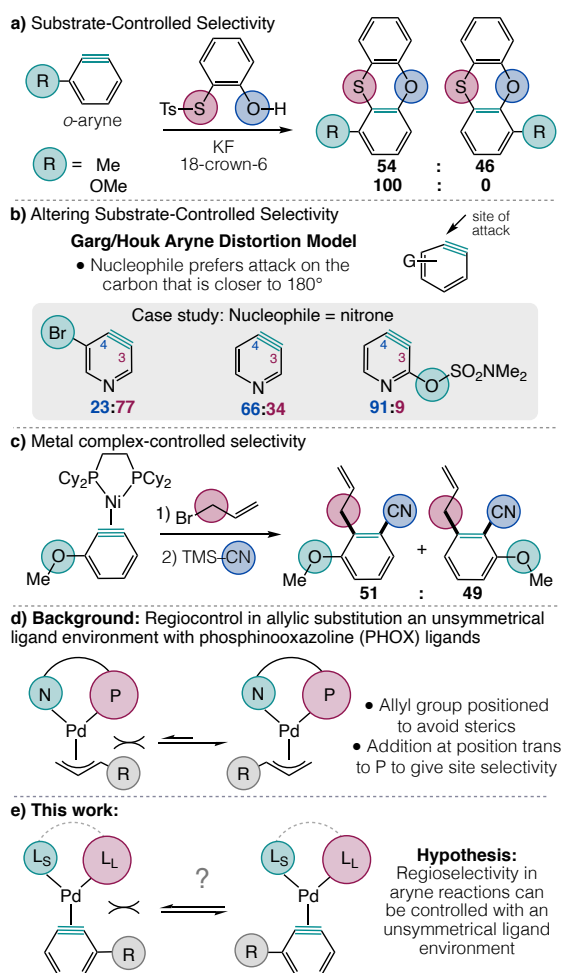


Figure 1. Inherent and induced regioselectivity in a,b) metal-free arynes and c) metal-bound aryne, d,e) ligand impact on regioselectivity incidental directing groups results in a handful of examples where selectivity is reported but this phenomenon is not systematically studied or leveraged.^{54–58}

Inspired by reports in the allylic substitution literature, we hypothesized that selectivity could be controlled by a metal catalyst with an unsymmetrical ligand environment such as those induced by phosphinooxazoline (PHOX) ligands (**Figure 1d**).^{59–63} If an unsymmetrical ligand environment could be created, then selectivity could potentially be induced in aryne reactions as well (**Figure 1e**). Herein we report, to the best of our knowledge, the first systematic study of ligand effects of regioselectivity of a metal-catalyzed aryne reaction. These results confirm that substrate steric control can be magnified by catalyst control to increase regioselectivity in metal-catalyzed aryne reactions.

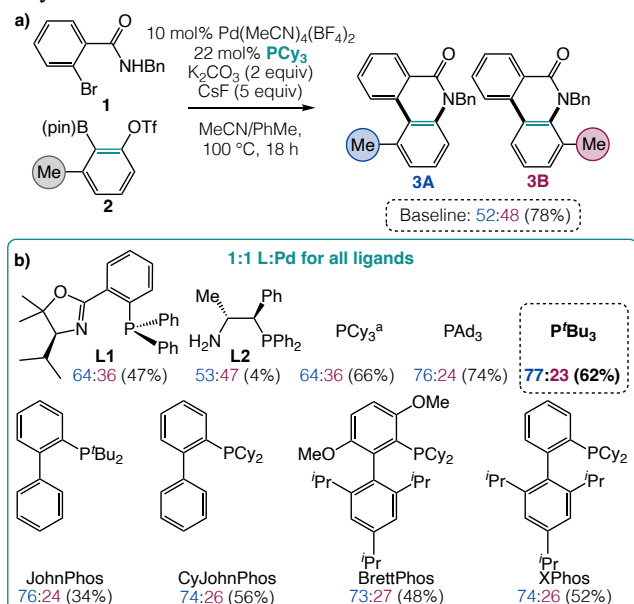


Figure 2. a) Establishing baseline regioselectivity in a symmetrical ligand environment; b) Screening bidentate, alkyl phosphines, and Buchwald biaryl phosphines in a 1:1 molar ratio with Pd to induce regioselectivity. Yields determined as a mixture of **3A** + **3B** by ¹H NMR spectroscopy with mesitylene as an internal standard. ^aAs PCy₃PdG3

We chose a Pd-catalyzed system originally studied by Larock and coworkers for the generation of phenanthridinones to use as a model reaction because Pd has predictable reactivity and well-studied ligand effects (**Figure 2**).⁶⁴ Additionally, substituted phenanthridinones have found use as PARP inhibitors, thus are impactful targets to study.⁶⁵ We initiated this investigation by using an *o*-methyl aryne as our initial substrate for optimization as it would be very challenging to induce selectivity with such a small steric profile. *o*-Borylaryl triflates were chosen as the aryne precursor due to the recent success of these precursors in generating discrete metal-bound arynes in stoichiometric studies (**Figure 1c**).³⁹ The formation of the aryne at the metal center through oxidative addition followed up by intramolecular transmetalation avoids side reactions such as dimerization and trimerization that traditional Kobayashi *o*-silylaryl triflate precursors suffer from.

To commence our studies, we established baseline selectivity and reactivity. Since tricyclohexylphosphine (PCy₃) is known to ligate Pd twice, this ligand system will herein serve as our model symmetrical ligand environment. As expected, very low levels of regioselectivity (A:B = 52:48) were established with the *o*-methyl aryne; however, we were pleased to see that catalytic turnover was achieved using *o*-borylaryl triflates (**Figure 2a**). Next, ligands were screened in a 1:1 molar ratio

with Pd by using an 11 mol % ligand loading (**Figure 2b**). Beginning with P,N-bidentate ligands, a modest, yet promising increase in regioselectivity was observed using a PHOX ligand, **L1**, (64:36) but the yield decreased to 47%. Using another P,N-bidentate ligand, **L2**, the yield plummeted to 4%. Through further studies, bidentate ligands were ultimately deemed detrimental to the overall yield. This is likely due to their rigidity and lessened lability. We hypothesized that an unsymmetrical ligand environment such as that imposed by the different P versus N donors in the PHOX ligand could also be established using monodentate phosphine ligands in a 1:1 molar ratio with Pd. The N-donor on the benzamide substrate **1** or coordinating MeCN would serve as the other donor ligand, creating a "pseudo-PHOX" P,N-ligand environment (**Figure 1e**, L_S = N, L_L = P). We tested this hypothesis by utilizing a PCy₃ Pd G3 Buchwald precatalyst as the Pd source, effectively lowering the loading of PCy₃ to 1:1 compared to Pd. This did, in fact, increase the regioselectivity a modest amount (64:36) compared to our baseline (52:48). We hypothesized that by increasing the cone angle of the ligand, selectivity could be further enhanced. Tris(1-adamantyl)phosphine (PA₃) and tritert-butylphosphine (P^tBu₃) were utilized.^{66,67} We saw enhanced regioselectivity with the greatest impact using P^tBu₃ (77:23). Finally, a selection of Buchwald biaryl ligands (JohnPhos, CyJohnPhos, BrettPhos, and XPhos) were screened due to their bulky nature and tunability. As expected, these also led to enhanced regioselectivities with regioisomeric ratios ranging from 73:27 to 76:24. However, yields were somewhat diminished compared to that of P^tBu₃, perhaps due to their pseudo-bidentate nature. Due to P^tBu₃ providing the best combination of regioisomeric ratio and yield, this system was carried forward. It should be noted that both **3A** and **3B** are

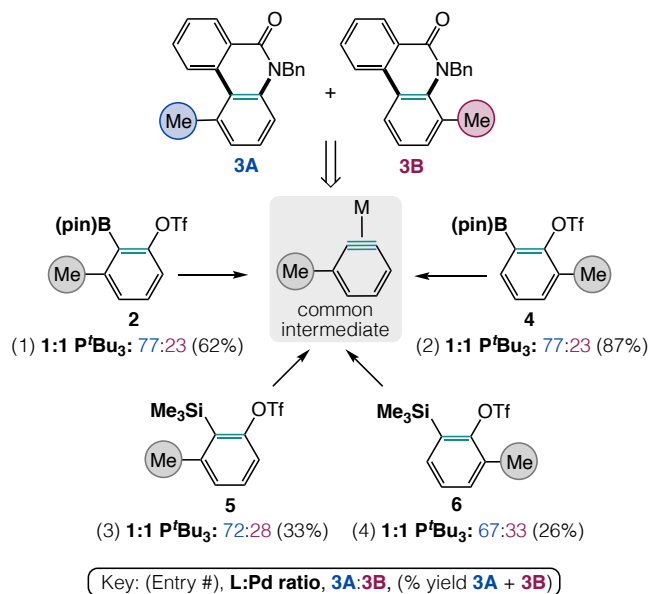
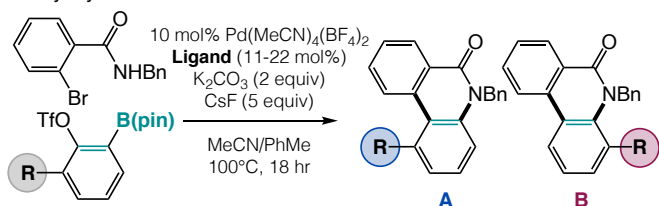


Figure 3. Evidence for common metal-bound aryne intermediate. Yields determined by ¹H NMR spectroscopy with mesitylene as an internal standard.

a) *o*-Borylaryl Triflate Reaction Scheme



b) Ligand = Symmetric PCy₃ (L: Pd = 2:1)

Entry	R	Charton Value (ν)	yield (%) ^a	rr (A:B)	Log([B]/[A])
1	Me	0.52	83%	51:49	-0.03
2	Et	0.56	86%	43:57	0.10
3	ⁱ Pr	0.76	81%	34:66	0.27
4	^t Bu	1.24	37%	18:82	0.67

c) Ligand = Unsymmetric P^tBu₃ (L: Pd = 1:1)

Entry	R	Charton Value (ν)	yield (%) ^a	rr (A:B)	Log([B]/[A])
1	Me	0.52	87% (78%)	77:23	-0.51
2	Et	0.56	82% (73%)	73:27	-0.43
3	ⁱ Pr	0.76	91% (75%)	57:43	-0.10
4	^t Bu	1.24	60% (59%)	9:91	1.00

d) *o*-Borylaryl Triflate Charton Plot

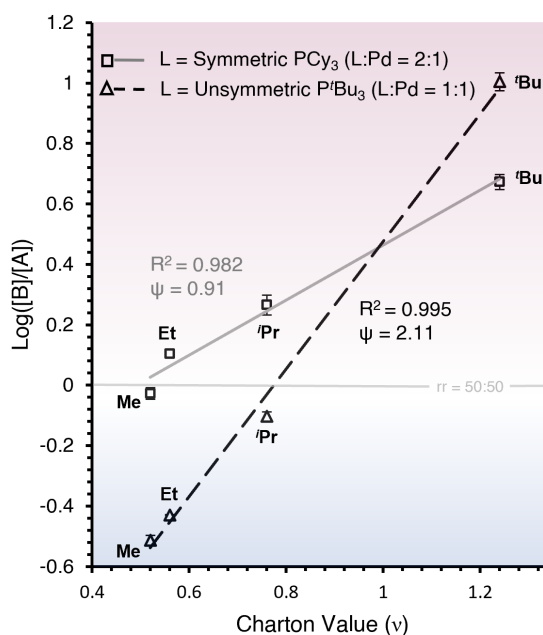


Figure 4. a) General reaction scheme with *o*-borylaryl triflates; b) Symmetrical ligand environment; c) Unsymmetric ligand environment; d) Charton analysis; ^aYields determined by ¹H NMR spectroscopy with mesitylene as an internal standard as an average of 3 runs; isolated yields in parentheses

separable by chromatography for characterization, but yields are reported as the combined yield of both regioisomers.

Having achieved catalytic turnover and regioselectivity, we next wanted to support the presence of a metal-bound aryne intermediate. The *o*-borylaryl triflate substrates have the potential to undergo iterative Suzuki-Miyaura aryl-aryl cross-coupling followed by aryl-N Buchwald-Hartwig amidation. Thinking retrosynthetically, if an aryne intermediate was occurring, there are two possible isomers of the *o*-borylaryl triflate precursor (**2** and **4**) that would lead to the same *o*-methyl metal-bound aryne intermediate. If the iterative cross-coupling processes were occurring, the major regioisomer using **2** and **4** would generate opposite regioisomeric products upon annulation. Additionally, if both the regioisomers of the well-established Kobayashi aryne precursors (**5** and **6**) give the same major isomer upon annulation as both **2** and **4** this provides further support for an aryne intermediate. When using the optimized conditions with each of the *o*-borylaryl triflates **2** and **4** and Kobayashi precursors **5** and **6** the same regioisomer is favored to a similar magnitude in all cases (**Figure 3** entries 1-4); however, a lower yield is observed for both Kobayashi precursors perhaps due to off catalytic cycle formation resulting in side reactions away from the metal center. This is likely due to their difference in mechanism of aryne formation. Overall, this set of results supports a common aryne intermediate and strongly suggests against an iterative Suzuki-Miyaura/Buchwald-Hartwig cross-coupling pathway. A single example exists for these *o*-borylaryl triflates being used in catalysis, presumably through an aryne intermediate, but this is the first time that *o*-borylaryl triflates have been conclusively demonstrated as aryne intermediates in catalysis.⁶⁸

Next, we wanted to systematically probe the interplay of sterics on the aryne intermediate with the impact of the ligand. Our studies were inspired by recent reports correlating steric encumbrance to enantioselectivity in asymmetric catalysis via

the use of Charton (ν) plots.⁶⁹⁻⁷³ Charton plots are linear free energy relationships that can be used to establish quantitative structure-selectivity relationships using values derived from Van der Waals radii to gauge steric influence of a key substituent on selectivity.^{69,74} Thus, a series of substrates with increasing steric demand (R = Me, Et, ⁱPr, ^tBu) in the *o*-position to the aryne was screened (**Figure 4a**). To gain further insight on whether the ligand was still influencing the regioselectivity with this series, both the symmetrical and unsymmetrical ligand environments were studied (**Figure 4b/c**).

Interestingly, with both ligand systems, we observed a trend towards regioisomer B as steric demand on the aryne was increased. By plotting the log of the regioisomeric ratio (B:A) as a function of the Charton value, ν , (derived from Van der Waals radii) we observe highly linear relationships for both P^tBu₃ and PCy₃ ($R^2 = 0.995$ and 0.982 , respectively). The observed linear relationships indicate regioselectivity does depend on sterics of the aryne substituent. The sensitivity value (ψ), obtained from the slope of the Charton plot, indicates how influenced the system is by steric effects. The observed sensitivity value for P^tBu₃ ($\psi = 2.11$) is significantly larger in magnitude than that of the symmetric PCy₃ system ($\psi = 0.91$). This suggests the regioselectivity not only depends on the steric contribution from the aryne itself, but it also is impacted by the ligand environment; thus indicating the synergistic effects of the ligand and substrate. Overall, this observation is a direct example of catalyst control and is the most definitive evidence that catalysts can be used to intentionally control the regioselectivity of aryne reactions.

The highly linear relationship observed in **Figure 4d** implies a similar transition state is maintained between all substrates, further supporting that a metal-bound aryne intermediate is operative. We hypothesize the Curtin-Hammett Principle may explain the regioselectivity observed in our system. Since rotation about the metal-aryne bond is likely possible, two

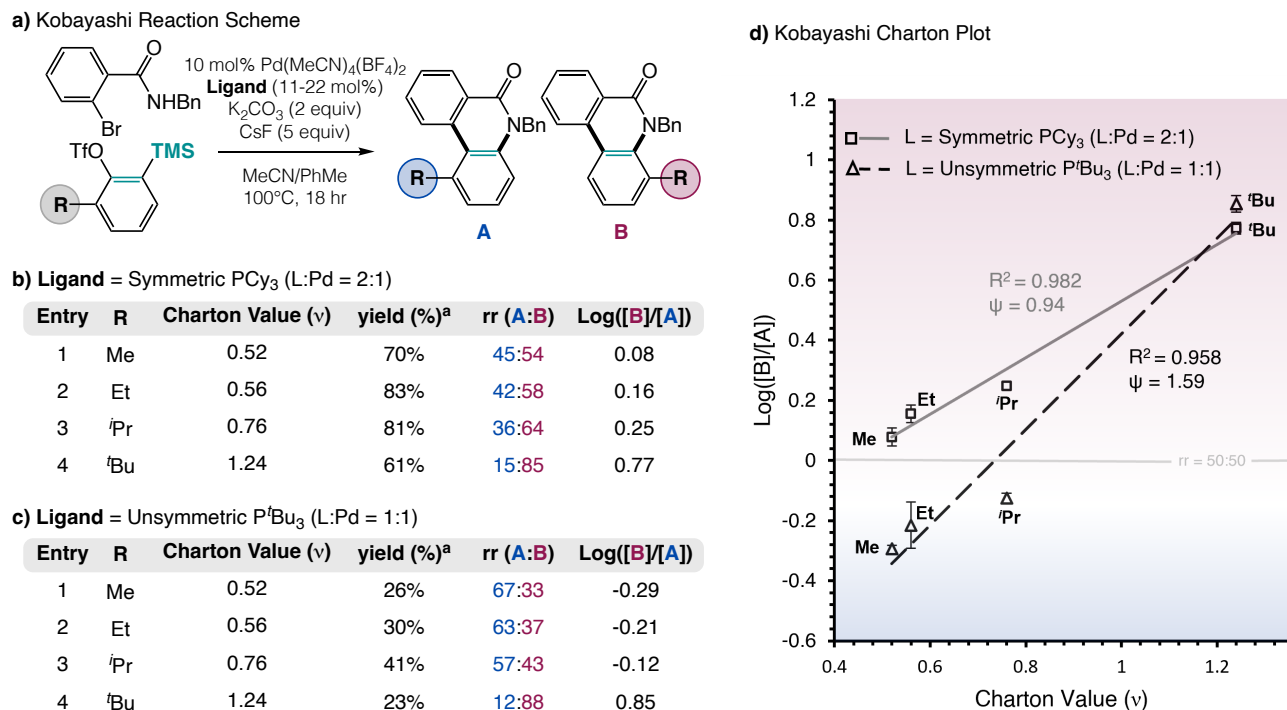


Figure 5. a) General reaction scheme with *o*-silylaryl triflates; b) Symmetrical ligand environment; c) Unsymmetric ligand environment; d) Charton analysis; ^aYields determined by ¹H NMR spectroscopy with mesitylene as an internal standard as an average of 3 runs

conformers of the metal-bound aryne can exist and interconvert. Thus, the regioisomeric ratio of products will depend both on the difference in energy between the two aryne conformers and the energy barriers from each of the aryne conformers to their respective products. Increasing the steric interaction between ligand and aryne is bound to have both stabilizing and destabilizing effects on the two aryne conformers as well as other intermediates and transition states throughout the reaction process. Overall, the steric effects of the aryne and ligand can work synergistically to provide an enhanced regioisomeric ratio as when R = Me or ^tBu; however, it is also possible these factors may oppose one another to give reversed selectivity as when R = Et or ⁱPr.

Due to potential differences in the mechanism of aryne formation and metalation, we also examined Kobayashi precursors by Charton analysis. While the *o*-borylaryl triflate precursors are recognized to form solely at the metal center, Kobayashi precursors can form through an elimination pathway independently of the metal center. To study this effect on regioselectivity, we screened the same *ortho*-substituent series (R = Me, Et, ⁱPr, ^tBu) using Kobayashi precursors (**Figure 5a**). Interestingly in both ligand systems (**Figure 5b-c**), we observed the same trend with an increase in preference for regioisomer B when steric demand was increased. Again with Charton analysis, a linear correlation is observed for both the symmetric PCy₃ ($R^2 = 0.982$) and the unsymmetric P^tBu₃ ligand environment ($R^2 = 0.958$) (**Figure 5d**). In the symmetric ligand environment, a comparable sensitivity value is observed between Kobayashi precursors and *o*-borylaryl triflates. However, we observe disparate sensitivity values in the unsymmetric ligand environment with P^tBu₃ for the Kobayashi precursors ($\psi = 1.59$) compared to the *o*-borylaryl triflate precursors ($\psi = 2.11$). This may be a consequence of their differing mechanisms of aryne metalation which is also supported by the decreased yields compared to the *o*-borylaryl triflates (**Figure 4c vs. 5c**). Overall, this suggests that both

mechanism of aryne formation as well as the steric interactions at the metal center contribute to regioselectivity.

Since the degree of catalyst control appears to be dependent on the mechanism of aryne formation, we sought to explore whether altering oxidative addition rates of the benzamide coupling partner would lead to changes in regioselectivity and/or yield.⁷⁵ We approached this study by varying the halide on the benzamide coupling partner which competitively undergoes oxidative addition with the *o*-borylaryl triflate aryne precursor (**Figure 6**). When the benzamide halide is less susceptible to oxidative addition as with chloride **1-Cl**, regioselectivity is comparable to that of the **Br** (**1**) using both regioisomers of the *o*-methyl aryne precursor (**2** and **4**). This is likely due to the oxidative addition of the aryl triflate before

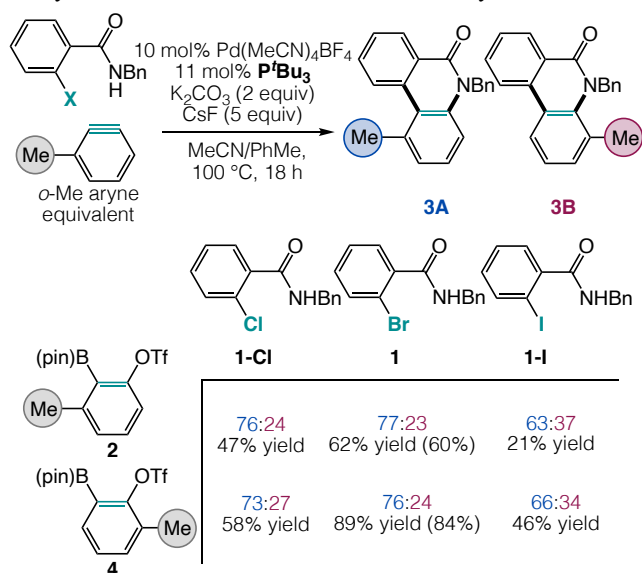


Figure 6. Influence of *o*-halobenzamide identity. Yields determined by ¹H NMR spectroscopy with a mesitylene as an internal standard, isolated yields in parentheses

either **1** or **1-Cl**. Unsurprisingly, the overall yield decreases when using **1-Cl**. This decrease in yield is presumably due to the slower rate of aryl chlorides to undergo oxidative addition compared to aryl bromides. In contrast, when oxidative addition of the aryl halide outcompetes that of the aryne precursor as in the iodide example using **1-I**, regioselectivity and yield suffers. This result is likely due to **1-I** undergoing oxidative addition prior to the *o*-borylaryl triflate and either sequestering the Pd catalyst or changing the mechanism of the reaction. Therefore, it is critical that the aryne precursor react before the benzamide coupling partner.

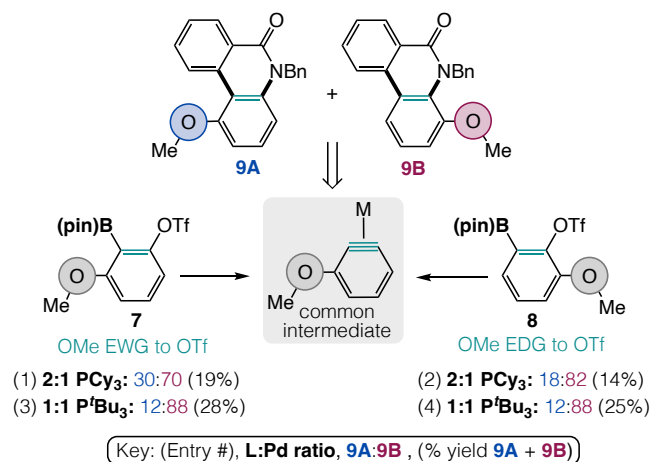


Figure 7. Influence of electronics on aryne regioselectivity

Knowing that the rates of oxidative addition impact the yields and regioselectivities of the products, we next turned to evaluating the electronics of the aryne. *o*-Methoxy benzyne is the ideal substrate to study as the two precursors **7** and **8** represent a methoxy group in the *meta* and *ortho* positions to the triflate, respectively. This renders **7** as electron withdrawing to triflate and **8** as electron donating (**Figure 7**). Baseline selectivity and reactivity in a symmetric environment was again established using PCy₃ in a 2:1 molar ratio with Pd (Entries 1 and 2). Both isomers of the *o*-borylaryl triflate precursor **7** and **8** gave comparable yields of regioisomers (19% and 14%, respectively) and were selective for product regioisomer **9B**, though to significantly different degrees (**9A:9B** = 30:70 and 18:82, respectively). The particular placement of the inductively withdrawing methoxy substituent could have an impact on a number of elementary steps throughout the reaction process including the rate of oxidative addition, which we have shown in **Figure 6** to be crucial to both regioselectivity as well as yield. This could explain the difference in selectivity between the **7** and **8** precursors in the symmetric ligand system despite sharing a common metal-bound aryne intermediate.

When the ligand system was replaced with a 1:1 molar ratio of P^tBu₃ and Pd, both **7** and **8** became more selective for regioisomer **9B** in a 12:88 regioisomeric ratio of **9A:9B** and with comparable yields (Entries 3 and 4). Interestingly, when the logs of these regioisomeric ratios are plotted on the corresponding Charton plot against the Charton value of methoxy ($\nu = 0.36$) there is no correlation with the previous linear trends observed for alkyl substituents (See **Figure S3**).⁷⁶ This indicates that sterics are not the only factor governing regioselectivity in metal-mediated reactions of electronically influenced arynes. It is clear that the introduction of electronically biased substituents to the aryne increases the

complexity of the system exponentially, and thus requires an independent investigation which is currently underway.

This report represents, to the best of our knowledge, the first example of a study that evaluates the impact of ligand environments on selectivity of metal-catalyzed aryne reactions. Through this study we have also shown *o*-borylaryl triflates to be competent aryne precursors for use in transition metal catalysis. Charton analysis shows greater ligand-aryne steric interaction amplifies baseline regioselectivity. However, interesting differences are observed as a consequence of the aryne precursor employed, presumably due to differences in the aryne-binding mechanism. Further studies involving electronic perturbations to key oxidative addition steps throughout the reaction sequence reveal that electronics also play an important role in the regioselectivity of the reaction. This exciting finding is being followed up to demonstrate the applicability of this manifold to other metal-catalyzed aryne reactions as well as to determine the regioselectivity determining step.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental (PDF)

AUTHOR INFORMATION

Corresponding Author

*Courtney C. Roberts ccr0b@umn.edu

Author Contributions

‡These authors contributed equally.

Funding Sources

The University of Minnesota is acknowledged for startup funds. We also acknowledge the NIH R35GM146957 for funds.

ACKNOWLEDGMENT

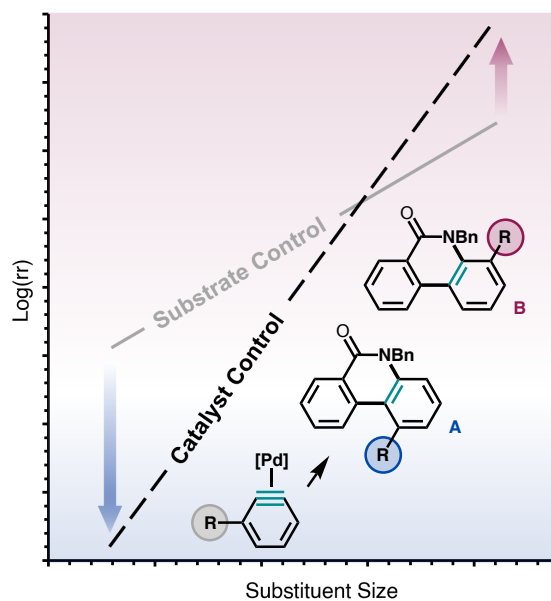
REFERENCES

- (1) Tadross, P. M.; Stoltz, B. M. A Comprehensive History of Arynes in Natural Product Total Synthesis. *Chem. Rev.* **2012**, *112* (6), 3550–3577. <https://doi.org/10.1021/cr200478h>.
- (2) Anthony, S. M.; Wonilowicz, L. G.; McVeigh, M. S.; Garg, N. K. Leveraging Fleeting Strained Intermediates to Access Complex Scaffolds. *JACS Au* **2021**, *1* (7), 897–912. <https://doi.org/10.1021/jacsau.1c00214>.
- (3) Lin, J. B.; Shah, T. K.; Goetz, A. E.; Garg, N. K.; Houk, K. N. Conjugated Trimeric Scaffolds Accessible from Indolyne Cyclotrimerizations: Synthesis, Structures, and Electronic Properties. *J. Am. Chem. Soc.* **2017**, *139* (30), 10447–10455. <https://doi.org/10.1021/jacs.7b05317>.
- (4) Spence, K. A.; Chari, J. V.; Niro, M. D.; Susick, R. B.; Ukwitegetse, N.; Djurovich, P. I.; Thompson, M. E.; Garg, N. K. π -Extension of Heterocycles via a Pd-Catalyzed Heterocyclic Aryne Annulation: π -Extended Donors for TADF Emitters. *Chem. Sci.* **2022**, *13* (20), 5884–5892. <https://doi.org/10.1039/D2SC01788A>.
- (5) Chari, J. V.; Spence, K. A.; Susick, R. B.; Garg, N. K. A Platform for On-the-Complex Annulation Reactions with Transient Aryne Intermediates. *Nat Commun* **2021**, *12* (1), 3706. <https://doi.org/10.1038/s41467-021-23970-8>.

- (6) Shi, J.; Li, L.; Li, Y. O-Silylaryl Triflates: A Journey of Kobayashi Aryne Precursors. *Chem. Rev.* **2021**, *121* (7), 3892–4044. <https://doi.org/10.1021/acs.chemrev.0c01011>.
- (7) García-López, J.-A.; Greaney, M. F. Synthesis of Biaryls Using Aryne Intermediates. *Chem. Soc. Rev.* **2016**, *45* (24), 6766–6798. <https://doi.org/10.1039/C6CS00220J>.
- (8) Berthelot-Bréhier, A.; Panossian, A.; Colobert, F.; Leroux, F. R. Atroposelective Synthesis of Axially Chiral P,S-Ligands Based on Arynes. *Org. Chem. Front.* **2015**, *2* (6), 634–644. <https://doi.org/10.1039/C5QO00067J>.
- (9) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. Benzyne Click Chemistry: Synthesis of Benzotriazoles from Benzyne and Azides. *Org. Lett.* **2008**, *10* (12), 2409–2412. <https://doi.org/10.1021/ol800675u>.
- (10) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. Use of Benzyne for the Synthesis of Heterocycles. *Org. Biomol. Chem.* **2012**, *11* (2), 191–218. <https://doi.org/10.1039/C2OB26673C>.
- (11) Bhattacharjee, S.; Guin, A.; Gaykar, R. N.; Biju, A. T. Thiophenols as Protic Nucleophilic Triggers in Aryne Three-Component Coupling. *Org. Lett.* **2020**, *22* (22), 9097–9101. <https://doi.org/10.1021/acs.orglett.0c03494>.
- (12) Seo, J. H.; Ko, H. M. Transition-Metal-Free Synthesis of Aromatic Amines via the Reaction of Benzyne with Isocyanates. *Tetrahedron Letters* **2018**, *59* (7), 671–674. <https://doi.org/10.1016/j.tetlet.2018.01.022>.
- (13) Gupta, E.; Kant, R.; Mohanan, K. Decarboxylative Arylation Employing Arynes: A Metal-Free Pathway to Arylfluoroamides. *Org. Lett.* **2017**, *19* (21), 6016–6019. <https://doi.org/10.1021/acs.orglett.7b03072>.
- (14) Kaicharla, T.; Thangaraj, M.; Biju, A. T. Practical Synthesis of Phthalimides and Benzamides by a Multicomponent Reaction Involving Arynes, Isocyanides, and CO₂/H₂O. *Org. Lett.* **2014**, *16* (6), 1728–1731. <https://doi.org/10.1021/ol500403x>.
- (15) Varlamov, A. V.; Guranova, N. I.; Listratova, A. V.; Borisova, T. N.; Khrustalev, V. N.; Titov, A. A.; Voskressensky, L. G. Transformations of 10-Substituted Tetrahydrobenzo[b][1,6]Naphthyridines through Interaction with Dehydrobenzene. *Chem Heterocycl Comp* **2014**, *50* (2), 264–270. <https://doi.org/10.1007/s10593-014-1470-y>.
- (16) Tambar, U. K.; Stoltz, B. M. The Direct Acyl-Alkylation of Arynes. *J. Am. Chem. Soc.* **2005**, *127* (15), 5340–5341. <https://doi.org/10.1021/ja050859m>.
- (17) Jin, T.; Yamamoto, Y. An Efficient, Facile, and General Synthesis of 1H-Indazoles by 1,3-Dipolar Cycloaddition of Arynes with Diazomethane Derivatives. *Angewandte Chemie International Edition* **2007**, *46* (18), 3323–3325. <https://doi.org/10.1002/anie.200700101>.
- (18) May, C.; Moody, C. J. A Concise Synthesis of the Antitumour Alkaloid Ellipticine. *J. Chem. Soc., Chem. Commun.* **1984**, No. 14, 926–927. <https://doi.org/10.1039/C39840000926>.
- (19) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. Synthesis and Diels-Alder Reactions of 1,3-Dimethyl-4-(Phenylsulfonyl)-4H-Furo[3,4-b]Indole. A New Annulation Strategy for the Construction of Ellipticine and Isoellipticine. *J. Org. Chem.* **1984**, *49* (23), 4518–4523. <https://doi.org/10.1021/jo00197a039>.
- (20) Seo, J. H.; Ko, H. M. Transition-Metal-Free Synthesis of Aromatic Amines via the Reaction of Benzyne with Isocyanates. *Tetrahedron Letters* **2018**, *59* (7), 671–674. <https://doi.org/10.1016/j.tetlet.2018.01.022>.
- (21) Kanemoto, K.; Sakata, Y.; Hosoya, T.; Yoshida, S. Synthesis of Phenoxathiins and Phenothiazines by Aryne Reactions with Thiosulfonates. *Chem. Lett.* **2020**, *49* (5), 593–596. <https://doi.org/10.1246/cl.200132>.
- (22) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* **2014**, *136* (44), 15798–15805. <https://doi.org/10.1021/ja5099935>.
- (23) Goetz, A. E.; Bronner, S. M.; Cisneros, J. D.; Melamed, J. M.; Paton, R. S.; Houk, K. N.; Garg, N. K. An Efficient Computational Model to Predict the Synthetic Utility of Heterocyclic Arynes. *Angew. Chem. Int. Ed.* **2012**, *51* (11), 2758–2762. <https://doi.org/10.1002/anie.201108863>.
- (24) Picazo, E.; Houk, K. N.; Garg, N. K. Computational Predictions of Substituted Benzyne and Indolyne Regioselectivities. *Tetrahedron Letters* **2015**, *56* (23), 3511–3514. <https://doi.org/10.1016/j.tetlet.2015.01.022>.
- (25) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. Indolyne and Aryne Distortions and Nucleophilic Regioselectivities. *J. Am. Chem. Soc.* **2010**, *132* (4), 1267–1269. <https://doi.org/10.1021/ja9098643>.
- (26) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. Steric Effects Compete with Aryne Distortion To Control Regioselectivities of Nucleophilic Additions to 3-Silylarynes. *J. Am. Chem. Soc.* **2012**, *134* (34), 13966–13969. <https://doi.org/10.1021/ja306723r>.
- (27) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. Indolyne Experimental and Computational Studies: Synthetic Applications and Origins of Selectivities of Nucleophilic Additions. *Journal of the American Chemical Society* **2010**, *132* (50), 17933–17944. <https://doi.org/10.1021/ja1086485>.
- (28) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. Experimental and Theoretical Investigations into the Unusual Regioselectivity of 4,5-, 5,6-, and 6,7-Indole Aryne Cycloadditions. *Org. Lett.* **2010**, *12* (1), 96–99. <https://doi.org/10.1021/ol902415s>.
- (29) Goetz, A. E.; Garg, N. K. Enabling the Use of Heterocyclic Arynes in Chemical Synthesis. *J. Org. Chem.* **2014**, *79* (3), 846–851. <https://doi.org/10.1021/jo402723e>.
- (30) Bronner, S. M.; Goetz, A. E.; Garg, N. K. Overturning Indolyne Regioselectivities and Synthesis of Indolactam V. *J. Am. Chem. Soc.* **2011**, *133* (11), 3832–3835. <https://doi.org/10.1021/ja200437g>.
- (31) Liu, Z.; Larock, R. C. Facile N-Arylation of Amines and Sulfonamides and O-Arylation of Phenols and Arenecarboxylic Acids. *J. Org. Chem.* **2006**, *71* (8), 3198–3209. <https://doi.org/10.1021/jo0602221>.
- (32) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. Regioselective Reactions of Highly Substituted Arynes. *Org. Lett.* **2010**, *12* (6), 1224–1227. <https://doi.org/10.1021/ol1000796>.
- (33) Liu, Z.; Larock, R. C. Facile N-Arylation of Amines and Sulfonamides. *Org. Lett.* **2003**, *5* (24), 4673–4675. <https://doi.org/10.1021/ol0358612>.
- (34) Yoshida, H.; Sugiura, S.; Kunai, A. Facile Synthesis of N-Alkyl-N'-Arylimidazolium Salts via Addition of Imidazoles to Arynes. *Org. Lett.* **2002**, *4* (16), 2767–2769. <https://doi.org/10.1021/ol0262845>.
- (35) Takagi, A.; Ikawa, T.; Kurita, Y.; Saito, K.; Azechi, K.; Egi, M.; Itoh, Y.; Tokiwa, H.; Kita, Y.; Akai, S. Generation of 3-Borylbenzyne, Their Regioselective Diels-Alder Reactions, and Theoretical Analysis. *Tetrahedron* **2013**, *69* (21), 4338–4352. <https://doi.org/10.1016/j.tet.2013.03.016>.

- (36) Takagi, A.; Ikawa, T.; Saito, K.; Masuda, S.; Ito, T.; Akai, S. Ortho-Selective Nucleophilic Addition of Amines to 3-Borylbenzynes: Synthesis of Multisubstituted Anilines by the Triple Role of the Boryl Group. *Org. Biomol. Chem.* **2013**, *11* (46), 8145–8150. <https://doi.org/10.1039/C3OB41787E>.
- (37) Anthony, S. M.; Tona, V.; Zou, Y.; Morrill, L. A.; Billingsley, J. M.; Lim, M.; Tang, Y.; Houk, K. N.; Garg, N. K. Total Synthesis of (–)-Strictosidine and Interception of Aryne Natural Product Derivatives “Strictosidyne” and “Strictosamidyne.” *J. Am. Chem. Soc.* **2021**, *143* (19), 7471–7479. <https://doi.org/10.1021/jacs.1c02004>.
- (38) Goetz, A. E.; Garg, N. K. Regioselective Reactions of 3,4-Pyridines Enabled by the Aryne Distortion Model. *Nature Chem* **2013**, *5* (1), 54–60. <https://doi.org/10.1038/nchem.1504>.
- (39) Sumida, Y.; Sumida, T.; Hashizume, D.; Hosoya, T. Preparation of Aryne–Nickel Complexes from Ortho-Borylaryl Triflates. *Org. Lett.* **2016**, *18* (21), 5600–5603. <https://doi.org/10.1021/acs.orglett.6b02831>.
- (40) Jeganmohan, M.; Bhuvanewari, S.; Cheng, C.-H. A Cooperative Copper- and Palladium-Catalyzed Three-Component Coupling of Benzynes, Allylic Epoxides, and Terminal Alkynes. *Angewandte Chemie International Edition* **2009**, *48* (2), 391–394. <https://doi.org/10.1002/anie.200804873>.
- (41) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. Biaryl Synthesis via Palladium-Catalyzed Aryne Multicomponent Coupling. *Org. Lett.* **2007**, *9* (26), 5589–5592. <https://doi.org/10.1021/ol702584t>.
- (42) Bhuvanewari, S.; Jeganmohan, M.; Cheng, C.-H. Carbocyclization of Aromatic Iodides, Bicyclic Alkenes, and Benzynes Involving a Palladium-Catalyzed C–H Bond Activation as a Key Step. *Org. Lett.* **2006**, *8* (24), 5581–5584. <https://doi.org/10.1021/ol0622918>.
- (43) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. Catalytic Carbonylation Reactions of Benzyne Derivatives. *J. Am. Chem. Soc.* **2001**, *123* (50), 12686–12687. <https://doi.org/10.1021/ja011923c>.
- (44) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. Highly Efficient Route to O-Allylbiaryls via Palladium-Catalyzed Three-Component Coupling of Benzynes, Allylic Halides, and Aryl Organometallic Reagents. *Org. Lett.* **2005**, *7* (14), 2921–2924. <https://doi.org/10.1021/ol050859r>.
- (45) Li, R.-J.; Pi, S.-F.; Liang, Y.; Wang, Z.-Q.; Song, R.-J.; Chen, G.-X.; Li, J.-H. Palladium-Catalyzed Annulations of Arynes with 2-(2-Iodophenoxy)-1-Substituted Ethanones. *Chem. Commun.* **2009**, *46* (43), 8183–8185. <https://doi.org/10.1039/C9CC02720K>.
- (46) Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. Palladium-Catalyzed Decarboxylative Coupling of Allylic Alkynoates with Arynes. *Org. Lett.* **2009**, *11* (11), 2309–2312. <https://doi.org/10.1021/ol900643r>.
- (47) Yoshida, H.; Honda, Y.; Shirakawa, E.; Hiyama, T. Palladium–Iminophosphine-Catalysed Carbostannylation of Arynes: Synthesis of Ortho-Substituted Arylstannanes. *Chem. Commun.* **2001**, *0* (18), 1880–1881. <https://doi.org/10.1039/B103745P>.
- (48) Tang, C.-Y.; Wu, X.-Y.; Sha, F.; Zhang, F.; Li, H. Pd-Catalyzed Assembly of Phenanthridines from Aryl Ketone O-Acetyloximes and Arynes through C–H Bond Activation. *Tetrahedron Letters* **2014**, *55* (5), 1036–1039. <https://doi.org/10.1016/j.tetlet.2013.12.075>.
- (49) Jeganmohan, M.; Cheng, C.-H. Substituted 1-Allyl-2-Allylbenzenes via Palladium-Catalyzed Allylation of Benzyne Derivatives. *Synthesis* **2005**, *2005* (10), 1693–1697. <https://doi.org/10.1055/s-2005-869966>.
- (50) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. Three-Component Coupling of Benzyne: Domino Intermolecular Carbopalladation. *J. Am. Chem. Soc.* **2006**, *128* (23), 7426–7427. <https://doi.org/10.1021/ja0615526>.
- (51) *Facile and Efficient Synthesis of Hydrophenanthren-1(2H)-ones and Naphtho[2,1-c]furan-3(1H)-ones by a Palladium-Catalyzed Aryne Annulation Strategy - Huang - 2010 - Advanced Synthesis & Catalysis - Wiley Online Library*. <https://onlinelibrary-wiley-com.ezp3.lib.umn.edu/doi/full/10.1002/adsc.200900703> (accessed 2022-06-20).
- (52) Lin, Y.; Wu, L.; Huang, X. Palladium-Catalyzed [3+2] Cycloaddition Reaction of (Diarylmethylene)Cyclopropa[b]Naphthalenes with Arynes: An Efficient Synthesis of 11-(Diarylmethylene)-11H-Benzo[b]Fluorenes. *European Journal of Organic Chemistry* **2011**, *2011* (16), 2993–3000. <https://doi.org/10.1002/ejoc.201100035>.
- (53) Peng, X.; Wang, W.; Jiang, C.; Sun, D.; Xu, Z.; Tung, C.-H. Strain-Promoted Oxidative Annulation of Arynes and Cyclooctynes with Benzamides: Palladium-Catalyzed C–H/N–H Activation for the Synthesis of N-Heterocycles. *Org. Lett.* **2014**, *16* (20), 5354–5357. <https://doi.org/10.1021/ol5025426>.
- (54) Zhang, X.; Larock, R. C. Palladium-Catalyzed Annulation of Arynes by 2-Halobenzaldehydes: Synthesis of Fluoren-9-Ones. *Org. Lett.* **2005**, *7* (18), 3973–3976. <https://doi.org/10.1021/ol0514597>.
- (55) Zhao, J.; Li, H.; Li, P.; Wang, L. Annulation of Benzamides with Arynes Using Palladium with Photoredox Dual Catalysis. *J. Org. Chem.* **2019**, *84* (14), 9007–9016. <https://doi.org/10.1021/acs.joc.9b00893>.
- (56) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. Palladium-Catalyzed Controlled Carbopalladation of Benzyne. *J. Am. Chem. Soc.* **2000**, *122* (30), 7280–7286. <https://doi.org/10.1021/ja001205a>.
- (57) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. Efficient Palladium-Catalyzed Cyclotrimerization of Arynes: Synthesis of Triphenylenes. *Angewandte Chemie International Edition* **1998**, *37* (19), 2659–2661. [https://doi.org/10.1002/\(SICI\)1521-3773\(19981016\)37:19<2659::AID-ANIE2659>3.0.CO;2-4](https://doi.org/10.1002/(SICI)1521-3773(19981016)37:19<2659::AID-ANIE2659>3.0.CO;2-4).
- (58) Wei, Z.; Wen, L.; Zhu, K.; Wang, Q.; Zhao, Y.; Hu, J. Regioselective Aromatic Perfluoro-Tert-Butylation Using Perfluoro-Tert-Butyl Phenyl Sulfone and Arynes. *J. Am. Chem. Soc.* **2022**. <https://doi.org/10.1021/jacs.2c10479>.
- (59) Helmchen, G.; Pfaltz, A. Phosphinooxazolines A New Class of Versatile, Modular P,N - Ligands for Asymmetric Catalysis. *Accounts of Chemical Research* **2000**, *33* (6), 336–345. <https://doi.org/10.1021/ar9900865>.
- (60) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. A Facile and Modular Synthesis of Phosphinooxazoline Ligands. *Org. Lett.* **2007**, *9* (13), 2529–2531. <https://doi.org/10.1021/ol070884s>.
- (61) Behenna, D. C.; Stoltz, B. M. The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc.* **2004**, *126* (46), 15044–15045. <https://doi.org/10.1021/ja044812x>.
- (62) Margalef, J.; Biosca, M.; de la Cruz Sánchez, P.; Faiges, J.; Pàmies, O.; Diéguez, M. Evolution in Heterodonor P–N, P–S and P–O Chiral Ligands for Preparing Efficient Catalysts for Asymmetric Catalysis. From Design to Applications. *Coordination Chemistry Reviews* **2021**, *446*, 214120. <https://doi.org/10.1016/j.ccr.2021.214120>.
- (63) Connon, R.; Roche, B.; Rokade, B. V.; Guiry, P. J. Further Developments and Applications of Oxazoline-Containing Ligands in Asymmetric Catalysis. *Chem. Rev.* **2021**, *121*

- (11), 6373–6521.
<https://doi.org/10.1021/acs.chemrev.0c00844>.
- (64) Lu, C.; Dubrovskiy, A. V.; Larock, R. C. Palladium-Catalyzed Annulation of Arynes by o-Halobenzamides: Synthesis of Phenanthridinones. *J. Org. Chem.* **2012**, *77* (19), 8648–8656. <https://doi.org/10.1021/jo3016192>.
- (65) Aleti, R. R.; Festa, A. A.; Voskressensky, L. G.; Van der Eycken, E. V. Synthetic Strategies in the Preparation of Phenanthridinones. *Molecules* **2021**, *26* (18), 5560. <https://doi.org/10.3390/molecules26185560>.
- (66) Carrow, B. P.; Chen, L. Tri(1-Adamantyl)Phosphine: Exceptional Catalytic Effects Enabled by the Synergy of Chemical Stability, Donicity, and Polarizability. *Synlett* **2017**, *28* (3), 280–288. <https://doi.org/10.1055/s-0036-1588128>.
- (67) Chen, L.; Ren, P.; Carrow, B. P. Tri(1-Adamantyl)Phosphine: Expanding the Boundary of Electron-Releasing Character Available to Organophosphorus Compounds. *J. Am. Chem. Soc.* **2016**, *138* (20), 6392–6395. <https://doi.org/10.1021/jacs.6b03215>.
- (68) García-López, J.-A.; Greaney, M. F. Use of 2-Bromophenylboronic Esters as Benzyne Precursors in the Pd-Catalyzed Synthesis of Triphenylenes. *Org. Lett.* **2014**, *16* (9), 2338–2341. <https://doi.org/10.1021/ol5006246>.
- (69) Sigman, M. S.; Miller, J. J. Examination of the Role of Taft-Type Steric Parameters in Asymmetric Catalysis. *J. Org. Chem.* **2009**, *74* (20), 7633–7643. <https://doi.org/10.1021/jo901698t>.
- (70) Zahrt, A. F.; Athavale, S. V.; Denmark, S. E. Quantitative Structure–Selectivity Relationships in Enantioselective Catalysis: Past, Present, and Future. *Chem. Rev.* **2020**, *120* (3), 1620–1689. <https://doi.org/10.1021/acs.chemrev.9b00425>.
- (71) Guan, Y.; Buivydas, T. A.; Lalis, R. F.; Attard, J. W.; Ali, R.; Stern, C.; Hadad, C. M.; Mattson, A. E. Robust, Enantioselective Construction of Challenging, Biologically Relevant Tertiary Ether Stereocenters. *ACS Catal.* **2021**, *11* (10), 6325–6333. <https://doi.org/10.1021/acscatal.1c01095>.
- (72) Saint-Denis, T. G.; Lam, N. Y. S.; Chekshin, N.; Richardson, P. F.; Chen, J. S.; Elleraas, J.; Hesp, K. D.; Schmitt, D. C.; Lian, Y.; Huh, C. W.; Yu, J.-Q. Mechanistic Study of Enantioselective Pd-Catalyzed C(Sp³)-H Activation of Thioethers Involving Two Distinct Stereomodels. *ACS Catal.* **2021**, *11* (15), 9738–9753. <https://doi.org/10.1021/acscatal.1c02808>.
- (73) Mantilli, L.; Gérard, D.; Torche, S.; Besnard, C.; Mazet, C. Improved Catalysts for the Iridium-Catalyzed Asymmetric Isomerization of Primary Allylic Alcohols Based on Charton Analysis. *Chemistry – A European Journal* **2010**, *16* (42), 12736–12745. <https://doi.org/10.1002/chem.201001311>.
- (74) Charton, M. Steric Effects. I. Esterification and Acid-Catalyzed Hydrolysis of Esters. *J. Am. Chem. Soc.* **1975**, *97* (6), 1552–1556. <https://doi.org/10.1021/ja00839a047>.
- (75) Reeves, E. K.; Entz, E. D.; Neufeldt, S. R. Chemodivergence between Electrophiles in Cross-Coupling Reactions. *Chemistry* **2021**, *27* (20), 6161–6177. <https://doi.org/10.1002/chem.202004437>.
- (76) Akhani, R. K.; Moore, M. I.; Pribyl, J. G.; Wiskur, S. L. Linear Free-Energy Relationship and Rate Study on a Silylation-Based Kinetic Resolution: Mechanistic Insights. *J. Org. Chem.* **2014**, *79* (6), 2384–2396. <https://doi.org/10.1021/jo402569h>.



- Regioselectivity via unsymmetrical ligand environment •
- Use of Charton analysis to determine the role of sterics •
- Use of *o*-Borylaryl triflate aryne precursors in catalysis •
- Evidence of a metal-bound aryne intermediate •

