Superseding Substrate Control with Catalyst Control to Increase 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 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 91:9 r.r.). We also report the reversal of regioselectivity between ligand environments. These investigations demonstrate that catalyst control can supersede substrate control in metal-catalyzed aryne reactions.

Arynes are highly reactive intermediates which have enabled the synthesis of natural products, ligands, and conjugated materials.[1–10] One challenge is the use of unsymmetrically substituted arynes as multiple regioisomeric products are possible.[6,11–20] As stated by Li and coworkers in a recent review on arynes, "Regioselectivity is a fundamental issue in aryne chemistry…the diminished reaction efficiency attributed by the formation of an unwanted regioisomer in an aryne transformation will severely damage its synthetic application."[6] To illustrate this limitation, in a report by Yoshida and coworkers for the synthesis of phenoxathiins, a 54:46 ratio of regioisomers was observed when using a Kobayashi precursor to generate an *o*-methyl aryne (**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 free 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-pyridyne.[29,38]

While regioselectivity-enhancing strategies have been explored with free arynes, to our knowledge, there are no studies reported to date that attempt to influence the regioselectivity in metal-catalyzed aryne reactions. This is likely in part because using unsymmetrical aryne precursors often results in 50:50 regioisomeric ratios (r.r.) when metals are present.[39–52] For example in a report by Hosoya and coworkers, a metal-bound *o*-methoxy aryne shows no selectivity upon exposure to the coupling partners (**Figure 1c**) despite complete inherent
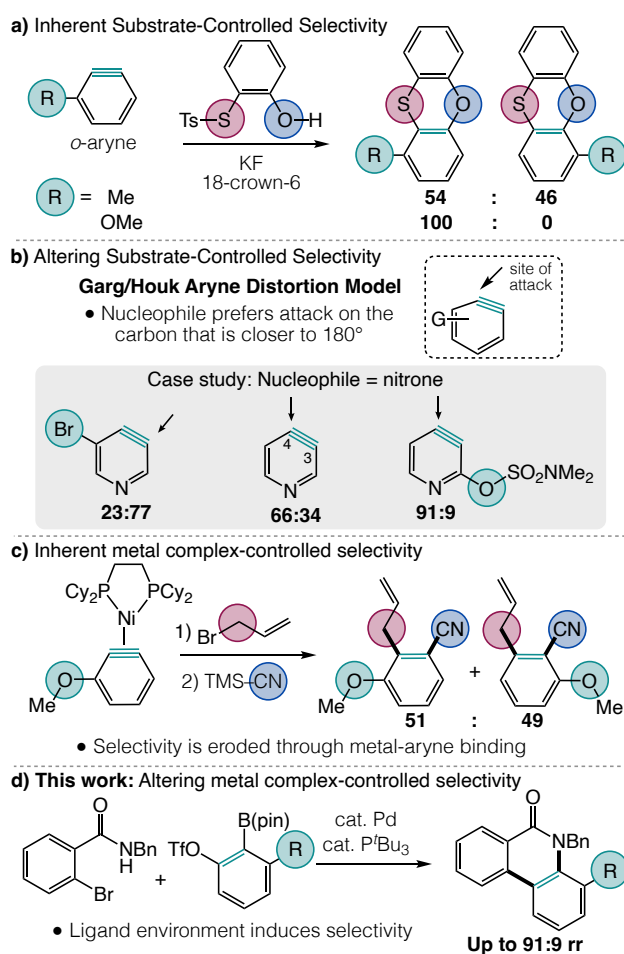

Figure 1. Inherent and induced regioselectivity in a,b) free arynes and c,d) metal-bound arynes

regioselectivity of the *o*-methoxy aryne in a free aryne reaction (**Figure 1a**).[53] Sporadic reports using, for example, incidental

directing groups results in a handful of examples where modest selectivity is reported but this phenomenon is not explored or leveraged.[54–56]

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.[57–61] If a C_1 symmetric ligand environment could be created, then selectivity could potentially be induced in aryne reactions as well. Herein we report a Pd-catalyzed annulation reaction with up to 91:9 r.r. being achieved through use of an unsymmetrical ligand environment. We also report reversal of selectivity in some systems when different ligands are used. These results confirm that substrate control can be replaced by catalyst control in increase regioselectivity in metal-catalyzed aryne reactions.
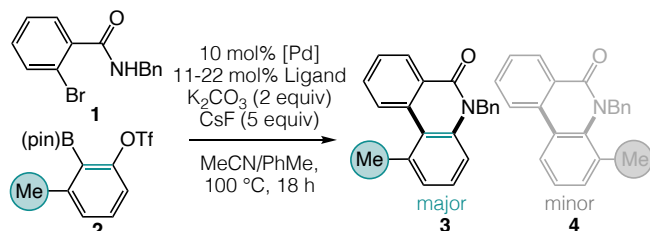
Entry	Pd Source	Ligand (ratio L:Pd)	Yield (%)[a]	r.r.
1	Pd(PPh₃)₄	PCy₃ (2:1)	21	50:50
2	Pd(dba)₂	PCy₃ (2:1)	74	57:43
3	Pd(OAc)₂	PCy₃ (2:1)	59	43:57
4	Pd(MeCN)₄(BF₄)₂	PCy₃ (2:1)	76	53:47
5	Pd(MeCN)₄(BF₄)₂	L1 (1:1)	47	64:36
6	Pd(MeCN)₄(BF₄)₂	L2 (1:1)	4	53:47
7	Pd(MeCN)₄(BF₄)₂	PCy₃ (1:1)	66	59:41
8	Pd(MeCN)₄(BF₄)₂	PAd₃ (1:1)	74	76:24
9	Pd(MeCN)₄(BF₄)₂	PᵗBu₃ (1:1)	62 (60)	**77:23**
10	Pd(MeCN)₄(BF₄)₂	P(o-tolyl)₃ (1:1)	62	73:27

[a] Yields determined by ¹H NMR spectroscopy with an internal standard. Isolated yields in parentheses.
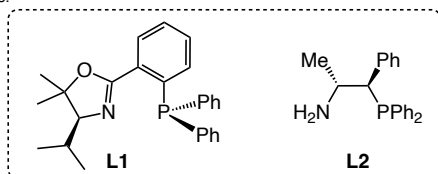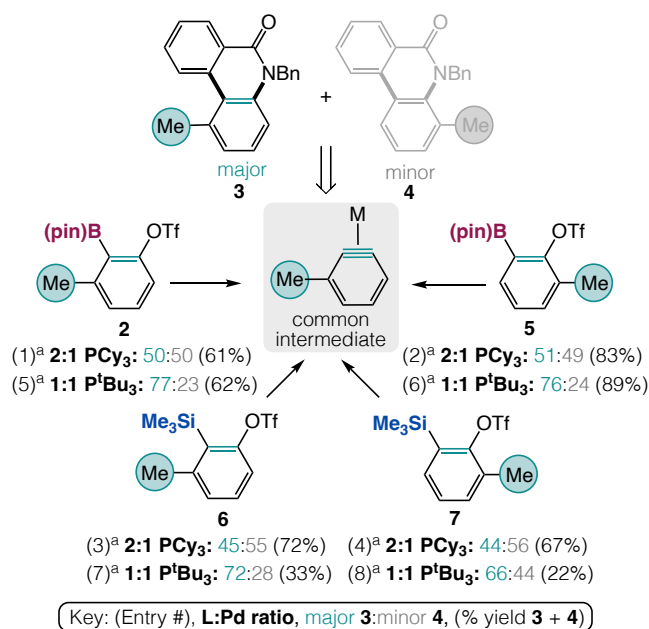

Figure 2. Optimization of Pd-catalyzed aryne annulations with borylaryl triflate aryne precursors

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.[62] Additionally, substituted phenanthridinones have found use as PARP inhibitors, thus are impactful targets to study.[63] 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. To generate this aryne, ortho substituted borylaryl triflates were used as aryne precursor due to the recent success of these precursors in generating discrete metal-bound arynes in stoichiometric studies.[53] Yields and selectivity of these relatively unknown aryne precursors are compared to current state-of-the-art Kobayashi silyl triflates as well. It should be noted that Kobayashi precursors can undergo off cycle

dimerizations and trimerizations that can diminish yields which was also observed in our system.[6]

We needed to optimize yields using borylaryl triflate aryne precursors rather than the originally used Kobayashi precursors. Additionally, in Larock's original publication no examples of unsymmetrically substituted arynes were reported and thus we needed to establish a baseline selectivity. A variety of Pd catalysts were screened using a 2:1 PCy₃:Pd molar ratio (**Figure 2** entries 1-4). Since PCy₃ (tricyclohexylphosphine) is known to ligate Pd twice, this ligand system will herein serve as our model symmetrical ligand environment to establish baseline selectivity and reactivity. As expected, very low levels of regioselectivity, ranging from 50:50 to 57:43 at the highest, were established with the o-methyl aryne in a symmetrical ligand environment; however, we were pleased to see that catalytic turnover was achieved using borylaryl triflates. Pd(MeCN)₄(BF₄)₂ (entry 4) was selected due to the best yield (76%) and reproducibility using this catalyst. This catalyst was carried forward and tested with P,N-bidentate ligands **L1** and **L2** which are known to impart regio- and enantioselectivity in allylic substitution reactions through the difference in the P versus N donor atoms on the ligand (**Figure 2** entries 5 & 6).[57,60] A modest, yet promising increase in regioselectivity was observed using **L1** (64:36) but the yield decreased to 47%. Using **L2**, the yield plummeted to 4%. Bidentate ligands were ultimately deemed detrimental to the overall yield when using borylaryl triflates, 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 **L1** 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 solvent would serve as the other donor ligand, creating a "pseudo-PHOX" ligand environment. We tested this hypothesis by lowering the loading of PCy₃ to 1:1 compared to Pd (entry 7). This did, in fact, increase the regioselectivity a minimal amount (59:41) compared to using PCy₃ in a 2:1 molar ratio with Pd. We hypothesized that by increasing the cone angle of the ligand, selectivity could be further enhanced. In entries 8 and 9 respectively, tris(1-adamantyl)phosphine (PAd₃) and tri-tert-butylphosphine (PᵗBu₃) were utilized. [64,65] We saw enhanced regioselectivity with the greatest impact using PᵗBu₃ (77:23). Finally, tri-o-tolylphosphine (P(o-tolyl)₃) was screened due to its exceptionally large cone angle (entry 10). Surprisingly, a decrease in r.r. (73:27) was observed from the prior entry, potentially due to the lessened electron donation of P(o-tolyl)₃ versus PᵗBu₃. Due to PᵗBu₃ providing the best regioisomeric ratio, this system was carried forward. It should be noted that both regioisomers of all substituted phenanthridinone products are separable by column chromatography for characterization but yields are reported as the combined yield of both regioisomers.

Figure 3. Evidence for a common metal-bound aryne intermediate

Key labels (Figure 3):
- major **3** + minor **4**
- **2**: (pin)B, OTf, Me — (1)[a] **2:1 PCy₃**: 50:50 (61%); (5)[a] **1:1 P^tBu₃**: 77:23 (62%)
- **5**: (pin)B, OTf, Me — (2)[a] **2:1 PCy₃**: 51:49 (83%); (6)[a] **1:1 P^tBu₃**: 76:24 (89%)
- common intermediate (M, Me)
- **6**: Me₃Si, OTf, Me — (3)[a] **2:1 PCy₃**: 45:55 (72%); (7)[a] **1:1 P^tBu₃**: 72:28 (33%)
- **7**: Me₃Si, OTf, Me — (4)[a] **2:1 PCy₃**: 44:56 (67%); (8)[a] **1:1 P^tBu₃**: 66:44 (22%)

Key: (Entry #), **L:Pd ratio**, major **3**:minor **4**, (% yield **3** + **4**)

[a]Conditions: 1 equiv. **1**, 1.5 equiv. **2**, **5**, **6**, or **7**, 10 mol% Pd(MeCN)₄BF₄, 11–22 mol% Ligand, K₂CO₃ (2 equiv), CsF (5 equiv), MeCN/PhMe, 100 °C, 18 h; ¹H NMR yields

Having achieved catalytic turnover and regioselectivity, we next wanted to support the presence of a metal-bound aryne intermediate. The borylaryl triflate substrates could undergo iterative Suzuki-Miyaura cross-coupling and Buchwald-Hartwig amidation reactions to yield the major product that is observed in **Figure 3**. Thinking retrosynthetically, if an aryne intermediate was occurring, there are two possible isomers of the borylaryl triflates (**2** and **5**) 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 **5** would generate opposite regioisomeric products upon annulation. Additionally, if both the regioisomers of the well-established Kobayashi aryne precursors (**6** and **7**) give the same major isomer upon annulation as both **2** and **5** this provides further support for an aryne intermediate. Using all four precursors and a molar ratio of 2:1 PCy₃:Pd , nearly 50:50 ratios of the product regioisomers are observed as the baseline selectivity (**Figure 3** entries 1-4). Alternatively, when using 1 equivalent of P^tBu₃ relative to Pd with each of the *o*-borylaryl triflates **2** and **5** and Kobayashi precursors **6** and **7** the same regioisomer is favored to a similar magnitude in all cases (**Figure 3** entries 5-8). This set of results indicates a common aryne intermediate and rules out an iterative Suzuki-Miyura/Buchwald-Hartwig cross-coupling pathway. A single example exists for these 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.[66]

As oxidative addition of both the aryne precursor, as well as the *o*-halobenzamide are expected to occur over the reaction progression, we sought to study the contrast between the *o*-borylaryl triflates (**2** and **5**) and various halides of the benzamide starting material **1** (**Figure 4**).[67] When the aryl halide is less susceptible to oxidative addition as with chloride **1-Cl**, regioselectivity is comparable to that of the Br **1** using both
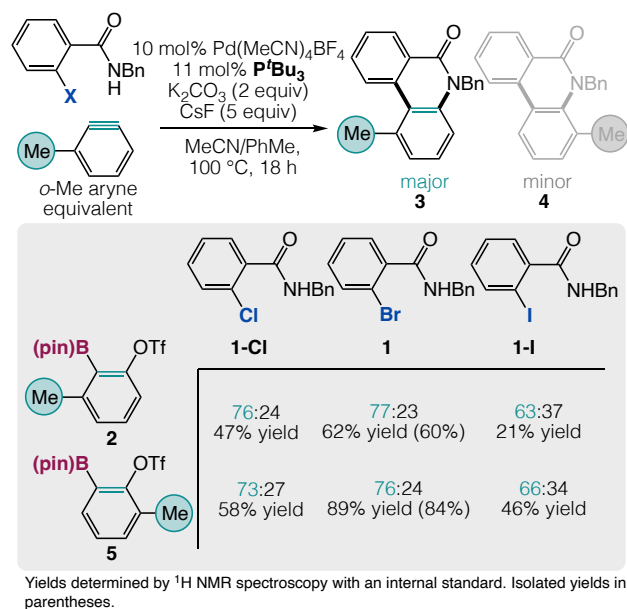

Figure 4. Influence of *o*-halobenzamide identity

Table (Figure 4):

	Cl (1-Cl)	Br (1)	I (1-I)
(pin)B OTf Me **2**	76:24 47% yield	77:23 62% yield (60%)	63:37 21% yield
(pin)B OTf Me **5**	73:27 58% yield	76:24 89% yield (84%)	66:34 46% yield

Yields determined by ¹H NMR spectroscopy with an internal standard. Isolated yields in parentheses.

regioisomers of starting material, but overall yield decreases. This is presumably due to the lessened ability 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 the **1-I** undergoing oxidative addition prior to the borylaryl triflate and either sequestering the Pd catalyst or changing the mechanism. The aryl bromide **1**, which has a similar oxidative addition rate to an aryl triflate bridges the gap with the highest regioselectivity as well as the highest yields. The trend holds well for both regioisomers of the borylaryl triflate (**2** and **5**), further supporting the role of an aryne intermediate as the observed regioisomeric ratio of products are consistent.
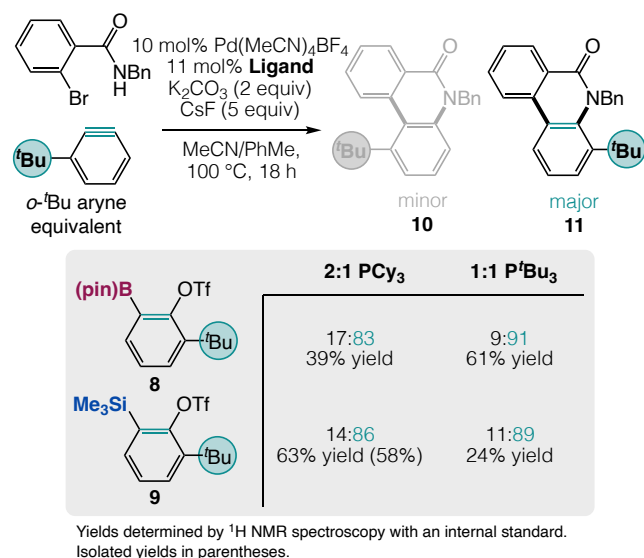

Figure 5. Impact of *t*Bu substituent on regioselectivity

Table (Figure 5):

	2:1 PCy₃	1:1 P^tBu₃
(pin)B OTf *t*Bu **8**	17:83 39% yield	9:91 61% yield
Me₃Si OTf *t*Bu **9**	14:86 63% yield (58%)	11:89 24% yield

Yields determined by ¹H NMR spectroscopy with an internal standard. Isolated yields in parentheses.

After establishing selectivity with the challenging *o*-methyl aryne, we sought to study the effect of larger substituents, beginning with the *o*-tert-butyl aryne in order to see the range of

regioselectivities that would be achieved with this manifold (**Figure 5**). As with the methylated substrate, we utilized both borylaryl triflate **8** and Kobayashi aryne precursor **9** in this study. The baseline selectivity of these precursors was again established using the model symmetrical ligand environment with 2:1 PCy$_3$:Pd. Unlike the *o*-methyl aryne, the *o-tert*-butyl aryne undergoes a regioselective annulation even in the presence of this symmetrical ligand environment when using both borylaryl triflate or Kobayashi aryne precursors 17:83 and 14:86 respectively of products **10** and **11** (**Figure 5**). This is likely due to the large steric profile of the ^{t}Bu substituent. Interestingly, the opposite regioisomer is observed as the major product compared to the *o*-methyl aryne (see **S9**). We were pleased to see that the inherent selectivity was amplified with application of P^{t}Bu$_3$ as the ligand (9:91 and 11:89), further supporting our hypothesis that the catalyst can still enhance selectivity.

Yields determined by ^{1}H NMR spectroscopy with an internal standard. Isolated yields in parentheses.
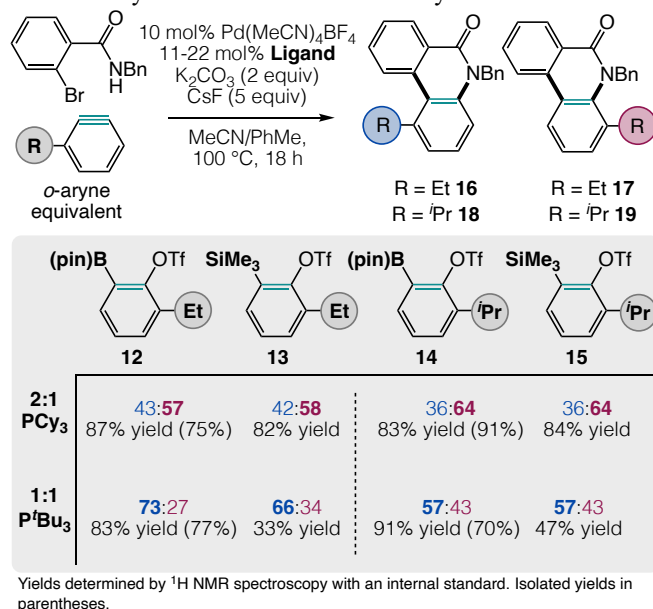
Figure 6. Change in regioisomer based on ligand identity

We next studied *o*-ethyl aryne precursors **12** and **13** and *o*-isopropyl aryne precursors **14** and **15** to investigate the intermediate steric effects and to further study the switch in the major regioisomer. (**Figure 6**). Similarly to the *o-tert*-butyl substrate these arynes had some inherent selectivity even in a symmetrical ligand environment with 2:1 PCy$_3$:Pd molar ratio, although to a lesser extent. The maximum selectivity for the *o*-ethyl substituted aryne was 42:58 for ethyl substituted products **16**:**17,** and 36:64 for *o*-isopropyl substituted **18**:**19**. Surprisingly, when subjected to P^{t}Bu$_3$ ligand the regioselectivity was not enhanced (as in the *o-tert*-butyl and *o*-methyl examples), but was rather reversed to favor the opposite regioisomer than is observed with 2:1 PCy$_3$:Pd. This is an interesting catalyst-controlled complement to Garg's use of substrate control with *o*-bromides to reverse the inherent selectivity of 3,4-pyridynes (**Figure 1b**).[38] Regioisomeric ratios using the *o*-ethyl substituted aryne precursors **12** and **13** generated up to a 73:27 ratio of **16**:**17**. This change in regioisomer with a change of ligand is the most definitive evidence that a catalysts can be used to control the regioselectivity of aryne reactions. This phenomenon is being further explored in our group.

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. We have demonstrated that by using bulky phosphines, selectivity can be induced in up to synthetically useful 9:91 r.r. While some regioisomeric ratios are modest, this represents the beginning of this field of superseding substrate control with catalyst control in aryne reactions. 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.

Supporting Information

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

Experimental (PDF)

AUTHOR INFORMATION

Corresponding Author

*Courtney C. Roberts ccrob@umn.edu

Author Contributions

‡These authors contributed equally.

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 Benzynes 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 Benzynes 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 Benzynes with Isocyanates. *Tetrahedron Lett.* **2018**, *59* (7), 671–674. https://doi.org/10.1016/j.tetlet.2018.01.022.

(13)   Gupta, E.; Kant, R.; Mohanan, K. Decarbethoxylative 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. Compd.* **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. *Angew. Chem. Int. Ed.* **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 Benzynes with Isocyanates. *Tetrahedron Lett.* **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 Lett.* **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 Regioselectivites. *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. *J. Am. Chem. Soc.* **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-Borylbenzynes, 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-Pyridynes Enabled by the Aryne Distortion Model. *Nat. Chem.* **2013**, *5* (1), 54–60. https://doi.org/10.1038/nchem.1504.

(39) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. A Cooperative Copper- and Palladium-Catalyzed Three-Component Coupling of Benzynes, Allylic Epoxides, and Terminal Alkynes. *Angew. Chem. Int. Ed.* **2009**, *48* (2), 391–394. https://doi.org/10.1002/anie.200804873.

(40) 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.

(41) Bhuvaneswari, 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.

(42) 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.

(43) 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.

(44) 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/C0CC02720K.

(45) 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.

(46) 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.

(47) 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 Lett.* **2014**, *55* (5), 1036–1039. https://doi.org/10.1016/j.tetlet.2013.12.075.

(48) Jeganmohan, M.; Cheng, C.-H. Substituted 1-Allyl-2-Allenylbenzenes via Palladium-Catalyzed Allylallenylation of Benzyne Derivatives. *Synthesis* **2005**, *2005* (10), 1693–1697. https://doi.org/10.1055/s-2005-869966.

(49) 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.

(50) *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).

(51) 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. *Eur. J. Org. Chem.* **2011**, *2011* (16), 2993–3000. https://doi.org/10.1002/ejoc.201100035.

(52) 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.

(53) 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.

(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) Helmchen, G.; Pfaltz, A. PhosphinooxazolinesA New Class of Versatile, Modular P,N - Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33* (6), 336–345. https://doi.org/10.1021/ar9900865.

(58) 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.

(59) 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.

(60) 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. *Coord. Chem. Rev.* **2021**, *446*, 214120. https://doi.org/10.1016/j.ccr.2021.214120.

(61) 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.

(62) 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.

(63) 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.

(64) 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.

(65) 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.

(66) 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.

(67) Reeves, E. K.; Entz, E. D.; Neufeldt, S. R. Chemodivergence between Electrophiles in Cross-Coupling Reactions. *Chem. Weinh. Bergstr. Ger.* **2021**, *27* (20), 6161–6177. https://doi.org/10.1002/chem.202004437.

SYNOPSIS TOC (Word Style "SN_Synopsis_TOC"). If you are submitting your paper to a journal that requires a synopsis graphic and/or synopsis paragraph, see the Instructions for Authors on the journal's homepage for a description of what needs to be provided and for the size requirements of the artwork.

To format double-column figures, schemes, charts, and tables, use the following instructions:

Place the insertion point where you want to change the number of columns
From the **Insert** menu, choose **Break**
Under **Sections**, choose **Continuous**
Make sure the insertion point is in the new section. From the **Format** menu, choose **Columns**
In the **Number of Columns** box, type **1**
Choose the **OK** button

Now your page is set up so that figures, schemes, charts, and tables can span two columns. These must appear at the top of the page. Be sure to add another section break after the table and change it back to two columns with a spacing of 0.33 in.

Table 1. Example of a Double-Column Table

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.

Insert Table of Contents artwork here