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Enabling the Use of Heterocyclic Arynes in Chemical Synthesis

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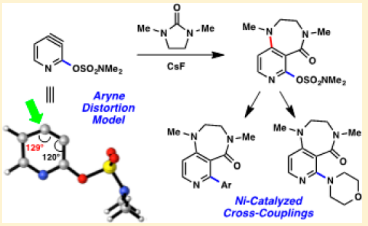
ABSTRACT: Heterocyclic arynes have long been targeted as potential tools for the synthesis of substituted heterocycles. Recent advances have led to an improved understanding of the factors that determine regioselectivity in reactions of these strained intermediates and, in turn, the aryne distortion model. This paper highlights the use of this predictive model to enable the use of heterocyclic arynes, such as indolynes and pyridynes, in chemical synthesis.



Arynes have long been recognized as powerful intermediates for the synthesis of substituted arenes.[1] Following the pioneering work of Roberts in 1953[2] that validated the triple bonded nature of *o*-benzyne (**1**), a wide variety of both carbocyclic (e.g., **2**–**4**) and heterocyclic (e.g., **5**–**9**) arynes[3] (hetarynes) were subsequently reported (Figure 1). Despite the initial promise in this area, the use of arynes, and especially hetarynes, in synthesis was largely tempered over the subsequent decades. However, the potential development of heterocyclic arynes offers a promising strategy for accessing functionalized heterocycles.

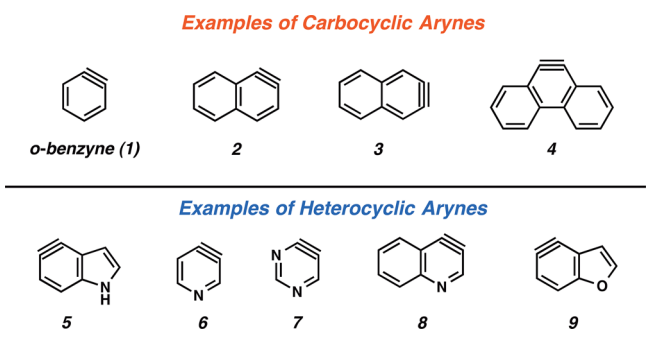


Figure 1. Carbocyclic arynes **1**–**4** and heterocyclic arynes **5**–**9**.

Two major hurdles have limited the synthetic utility of both arynes and hetarynes: methods for generation and regioselectivity in reactions of unsymmetrical arynes (Figure 2). Regarding aryne generation, early methods relied on the use of harsh conditions, such as strong bases needed to effect dehydrohalogenation of aryl halides (**10** → **13**) or strong oxidants in the case of aminotriazoles (**11** → **13**). Alternatively, the use of diazonium carboxylates as precursors (**12** → **13**) was potentially hazardous. With respect to unsymmetrical arynes, a major limitation is the formation of mixtures of regioisomeric products (**13** → **14** and **15**). Nonetheless, notable progress has been made toward resolving these problems. In 1983, Kobayashi reported that *o*-benzyne could be generated efficiently under mild conditions upon treatment of *o*-trimethylsilyl phenyltriflate (**16**) with a fluoride source.[4]

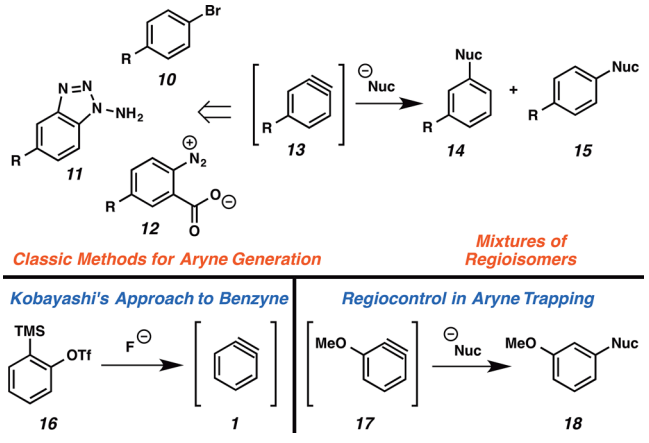


Figure 2. Aryne limitations, Kobayashi's mild method for aryne generation, and regiocontrolled trapping of methoxybenzyne.

Moreover, examples of unsymmetrical arynes that reacted with high degrees of regioselectivity, such as 3-methoxybenzyne (**17**), were disclosed.[1] Whereas the preference of **17** to give *meta*-substituted products (i.e., **18**) was rationalized using inductive effects, the ability to predict regioselectivity in reactions of more complex arynes, as well as heterocyclic arynes, had not been addressed.

■ ARYNE DISTORTION MODEL

With the aim of rendering heterocyclic arynes synthetically useful, our laboratory developed syntheses of indolynes,[5−7] the aryne derivatives of the medicinally privileged indole scaffold. In these studies, bench-stable silyltriflate precursors to indolynes were synthesized, which could then be used in a variety of trapping experiments to efficiently produce a series of uniquely substituted indole derivatives. Efforts in this area have been reviewed[8] and, importantly, led to the development of the aryne distortion model pioneered by Houk and co-workers.[9,10] DFT calculations show that unsymmetrical arynes are geo-

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metrically distorted in the ground state; in turn, this distortion leads to the observed regioselectivites in aryne trapping experiments.

An overview of the aryne distortion model is presented in Figure 3. In aryne **19**, where X is an electron-withdrawing

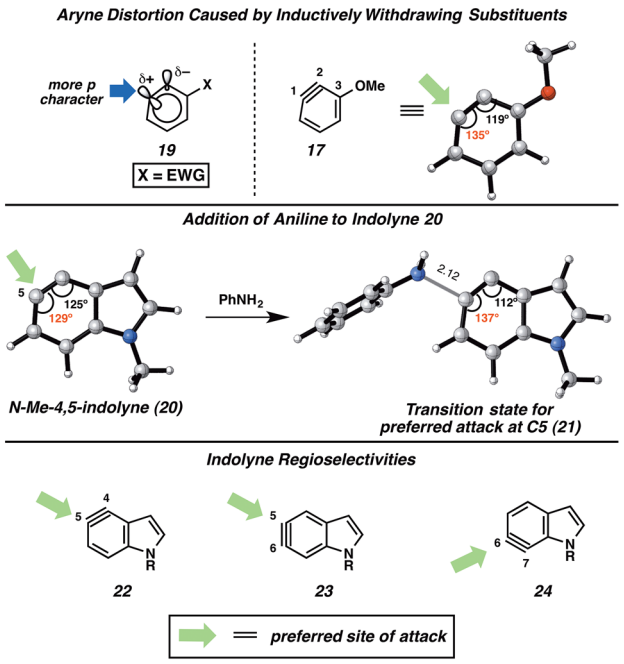

Figure 3. Summary of the aryne distortion model.

group (EWG), the triple bond is significantly distorted and polarized because of inductive effects. The aryne distortion is readily seen in the case of 3-methoxybenzyne (**17**), where DFT calculations show the internal angles are 135° at C1 and 119° at C2. Nucleophilic attack occurs on the carbon possessing higher p-character (or simply put, the terminus of the aryne with a larger internal angle). Similarly, in the case of 4,5-indolyne **20**, nucleophilic addition occurs at C5. The unsymmetrical distortion present in indolyne **20** arises as a response to the ring fusion, consistent with observations made by Suzuki and co-workers' study of ring fused carbocyclic arynes.[11] It should be emphasized that the favored transition state **21**, where attack occurs at C5, shows distortion that is reminiscent of the distortion present in the ground state of indolyne **20**. Consequently, this transition state has a lower distortion energy in comparison to the corresponding transition state for attack at C4.[9] Ultimately, it was determined that indolynes **22**–**24** react regioselectively in a manner consistent with computational studies and the aryne distortion model. Buszek and Cramer have also reported related indolyne computational studies, which led to similar conclusions.[12,6g]

PREDICTING HETARYNE REACTIVITY

The aryne distortion model allows chemists to overcome one of the previous limitations of heterocyclic arynes; namely, using the aryne distortion model, one can make reliable predictions regarding regioselectivity in hetaryne trapping experiments. To help further encourage the use of hetarynes in synthetic applications, the aryne distortion model was applied to more than 150 hetarynes that could be used to make highly substituted heterocycles of value to the pharmaceutical community.[13] For each of the hetarynes studied, geometry optimization calculations were performed using DFT (B3LYP/6-31G*).[14] The preferred site of attack is the terminus of the aryne with a larger internal angle, according to the aryne distortion model. Based on experimental results, angle differences of ≥4° typically lead to reactions that proceed with synthetically useful levels of regioselectivity, although variations are seen depending on the trapping agent employed. Select examples and some general trends are shown in Figure 4.

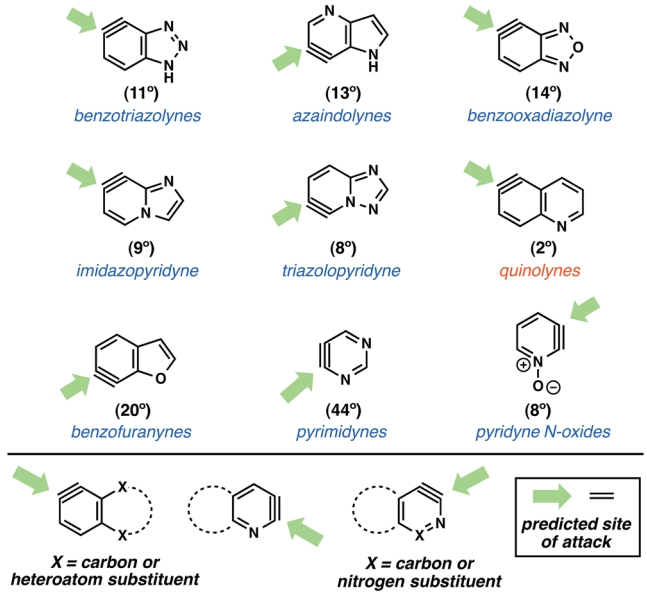

Figure 4. Preferred site of attack for selected hetarynes based on DFT calculations.

Many of the polyazine derivatives, such as benzotriazolynes, azaindolynes, benzooxadiazolynes, imidazopyridynes, and triazolopyridynes, are predicted to undergo highly selective reactions as a result of proximity to nitrogen or fusion to a 5-membered ring, whereas 6,6-fused systems in which the triple bond is not in the same ring as the heteroatom (e.g., quinolynes) are expected to display poorer selectivity. Although many of the hetarynes studied computationally have yet to be experimentally validated, species such as the 6,7-benzofuranyne,[15] the 4,5-pyrimidyne,[16] and the 2,3-pyridyne-*N*-oxide[17] are known to react in accord with predictions made by the aryne distortion model.

ENHANCING OR OVERTURNING INHERENT SELECTIVITY

In addition to being able to predict the preferred site of attack in heterocyclic aryne trapping experiments, it is possible to modulate selectivities using substituent effects. For example, indolyne **22** had been shown to undergo attack by nucleophiles with a preference for addition occurring at C5 (see Figure 3).[18] However, it was postulated that a 6-Br derivative of **22** would react with a switch in selectivity to favor attack at C4. Prior to synthesizing a suitable precursor and performing trapping experiments, geometry optimization of bromoindolyne **29** was undertaken using DFT calculations, which, in turn, suggested that attack at C4 would be favorable based on the aryne distortion model (Figure 5).[19] Indeed, treatment of indolyne precursor **25** with fluoride sources in the presence of various trapping agents led to C4-substituted indole products, with

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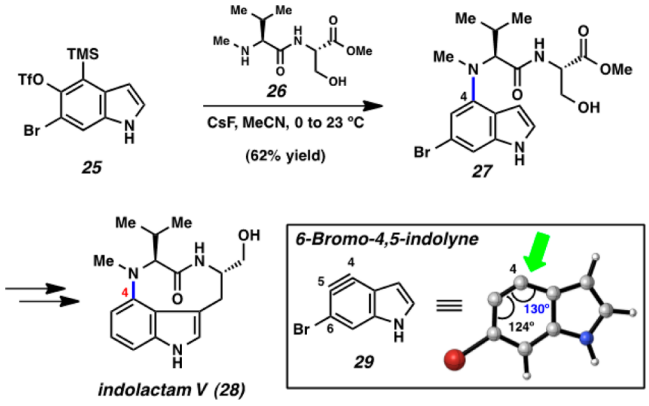

Figure 5. Overturning 4,5-indolyne regioselectivity and synthesis of indolactam V (**28**).

selectivities >10:1 for nucleophilic additions, and ~4:1 for formal cycloaddition reactions. Additionally, when peptide **26** was used to trap **29**, adduct **27** was obtained as a single regioisomer en route to a total synthesis of indolactam V (**28**).[20] This study not only served to probe the aryne distortion model but also provided a new approach toward C4-substituted indoles, which are commonly seen in natural products.

CONTROL OF 3,4-PYRIDYNE SELECTIVITIES

Having found that regioselectivity in indolyne trapping experiments could be modulated, we next studied the 3,4-pyridyne (**30**, Figure 6), which was first accessed in 1955.[21]

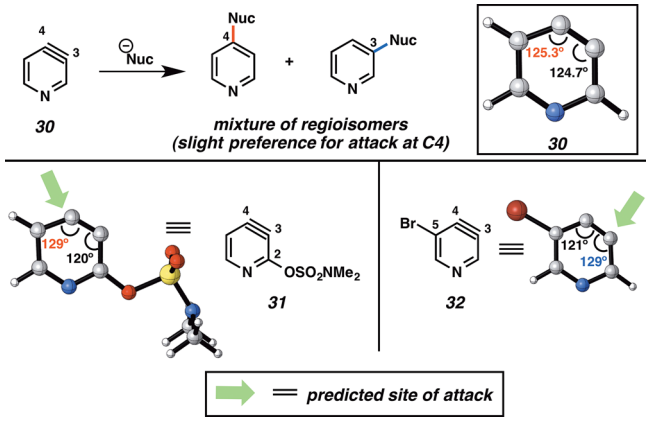

Figure 6. 3,4-Pyridyne (**30**) and substituted pyridynes **31** and **32**.

Notably, pyridyne **30** has been investigated extensively over the past few decades and is well known to react with poor regioselectivity.[22] The lack of regioselectivity can be explained by examining the energy-minimized structure of **30**, which exhibits little unsymmetrical distortion. Pioneering studies by Snieckus,[22j] Caubère,[22k] and Guitián[22d,e] have shown that substituent effects can modulate pyridyne regioselectivity; however, a general approach to controlling selectivity to favor attack at either C4 or C3 using directing groups, which in turn could be removed or employed as functional group handles, had not been disclosed.

In order to render the 3,4-pyridyne more generally useful, a variety of 2- and 5-substituted pyridynes were examined using DFT geometry optimization.[23] A number of substituted pyridynes displayed significant unsymmetrical aryne distortion. Inductively withdrawing halides and sulfamates were considered especially attractive, as they could likely be removed or used as a handle for functional group manipulation after a pyridyne trapping experiment. Also bearing in mind the potential ease of precursor synthesis, two substituted pyridynes were identified for experiments that would likely react with a complementary sense of regioselectivity. Whereas 2-sulfamoyl pyridyne **31** was expected to undergo preferential attack at C4, bromopyridyne **32** was predicted to react with attack occurring at C3.

After appropriate precursors to pyridynes **30**–**32** were synthesized, trapping experiments were performed. As seen in Figure 7, trapping with *N*-methylaniline confirmed the

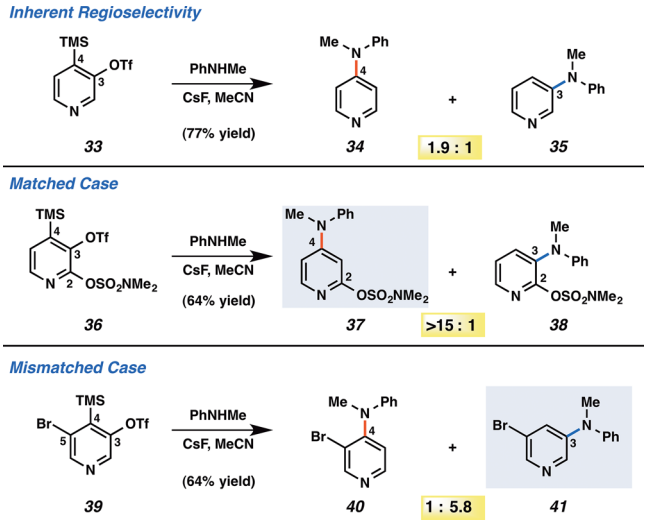

Figure 7. Trapping of pyridynes with *N*-methylaniline.

computational hypotheses regarding regioselectivities. Reaction of silyltriflate **33** gave the 4- and 3-substituted products **34** and **35**, respectively, with modest selectivity (i.e., 1.9:1 ratio). However, when sulfamoylated pyridyne precursor **36** was employed, selectivity improved to greater than 15:1 favoring attack at C4 (matched case). Finally, the use of bromopyridyne precursor **39** led to the desired switch in selectivity, as demonstrated by the preferred formation of C3-substituted product **41** over the C4-substituted adduct **40**, in a 5.8:1 ratio, respectively (mismatched case).

Analogous regioselectivity trends were observed when other trapping agents were employed, such as nitrone **42** (Figure 8). In the case of the parent pyridyne, reaction of silyltriflate **33** with **42** in the presence of CsF furnished **43** and **44**, with **43** being slightly preferred as expected (1.9:1 ratio, respectively). Selectivity improved considerably when silyltriflate **36** was employed, giving a 10.7:1 ratio of cycloadducts **45** and **46**, respectively (matched case). Finally, selectivity could be reversed by using pyridyne precursor **39**, as demonstrated by the formation of **47** and **48** in a 1:3.3 ratio, respectively (mismatched case). It should be noted that **48** forms as the major product, despite developing steric interactions between the Br and Ph substituents during the presumed transition state leading to **48**. In turn, this demonstrates that aryne distortion can override steric effects, which is similarly seen in reactions of silylarynes.[24]

One final example of pyridyne-trapping studies is highlighted in Figure 9, which involves utilizing 1,3-dimethyl-2-imidazolidinone (DMI) in a formal C–N bond insertion reaction. This

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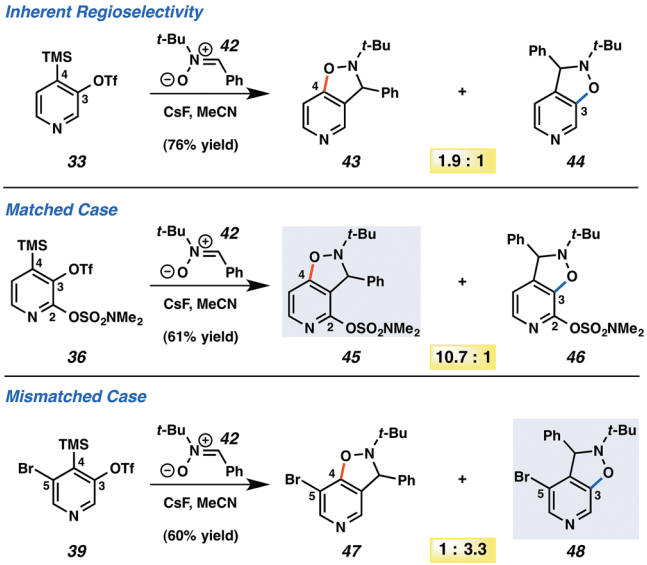

Figure 8. Results of pyridyne–nitrone cycloaddition experiments.

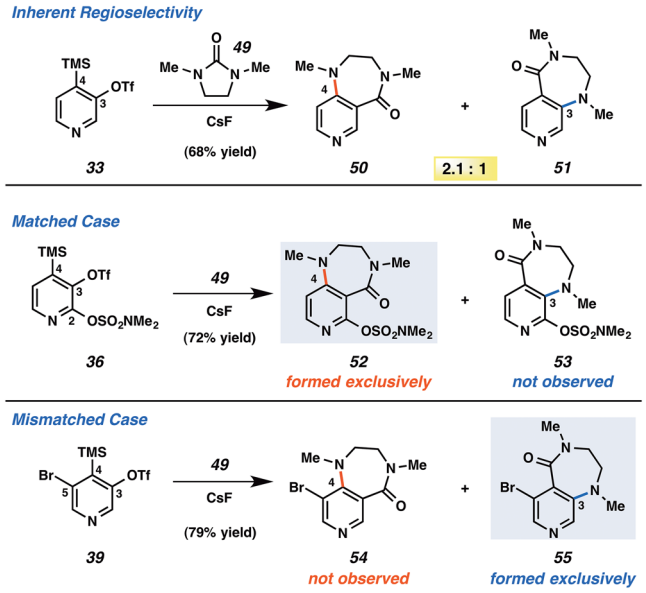

Figure 9. Trapping of pyridynes with dimethylurea **49**.

transformation, originally reported by Hiyama and co-workers on benzynes, is proposed to proceed via a stepwise addition/fragmentation process.[25] Whereas reaction of the parent silyltriflate **33** gave poor selectivity (i.e., 2.1 to 1 ratio of **50** to **51**), the use of the modified pyridyne precursors each gave rise to single isomers of products. Specifically, when sulfamate-containing substrate **36** was used, adduct **52** was formed exclusively and isomer **53** was not detected (matched case). Similarly, by employing bromopyridyne precursor **39**, **55** was obtained without the formation of isomer **54** (mismatched case). These results underscore the ability of the sulfamate and bromide substituents to govern aryne regioselectivity, while building a complex molecular scaffold. It should be noted that Saito and co-workers have seen similar results in reacting DMI and other related trapping agents (e.g., DMPU and cyclic carbamates) with substituted 2,3- and 3,4-pyridynes.[26]

MANIPULATING THE PYRIDYL BROMIDE OR SULFAMATE AFTER AN ARYNE TRAPPING EXPERIMENT

A key design element of the aforementioned pyridyne studies is that the bromide or sulfamate substituents could plausibly be removed following a pyridyne trapping experiment. To probe this notion, the cleavage of the bromide and sulfamate from DMI adducts **55** and **52**, respectively, was attempted (Figure 10). Whereas Pd-catalyzed hydrogenolysis could be used to

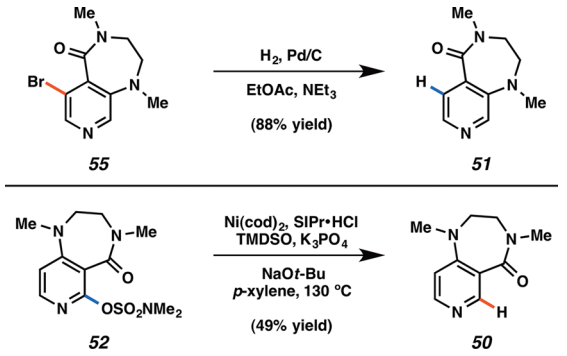

Figure 10. Reductive cleavage of pyridyl bromide and sulfamate.

remove the bromide of **55**, Ni-catalysis was utilized to cleave the sulfamate of **52**. Although Ni-catalyzed reductions of C–O bonds has been reported,[27] this is the first example involving the reductive cleavage of an aryl sulfamate.

As highlighted in Figure 11, the bromide and sulfamate substituents can also be used as functional group handles for

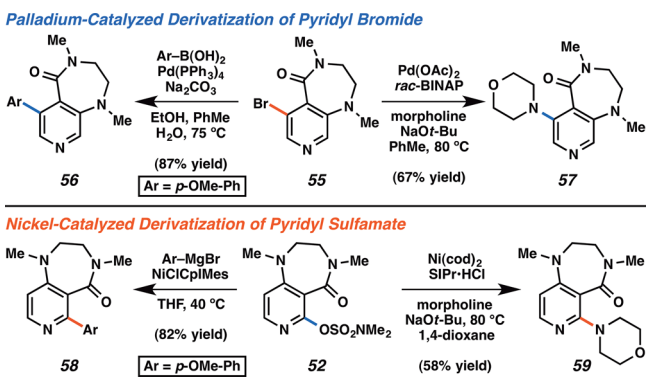

Figure 11. Functionalization of adducts **55** and **52** using transition-metal-catalyzed cross-couplings.

further manipulation. Bromide **55** was first elaborated using a Pd-catalyzed Suzuki–Miyaura coupling to afford **56**. In addition, a Pd-catalyzed amination of bromide **55** gave amine **57** in good yield. Given the recent interest in aryl sulfamates as alternative oxygen-based electrophiles for Ni-catalyzed cross-coupling reactions,[28] the analogous transformations using sulfamate **52** were also pursued. It was found that Ni-catalyzed Kumada–Corriu[29] coupling of sulfamate **52** gave cross-coupled product **58**, whereas amination[30] of sulfamate **52** provided adduct **59**. These transformations highlight a key advantage of utilizing the bromide and sulfamate functional groups as directing groups for aryne reactions; namely, in addition to governing aryne distortion and regioselectivities for the generation of unique scaffolds, the bromide and sulfamate

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substituents can be used for further derivatization en route to novel, multifunctionalized pyridine derivatives.

CONCLUSIONS

In recent years, there has been a dramatic renaissance in the field of aryne chemistry. Spawned by improved and mild methods for aryne generation, synthetic chemists have developed an array of aryne-trapping reactions that allow for the efficient assembly of functionalized arenes. These efforts have been complemented by new studies of heterocyclic arynes and the development of the aryne distortion model. As summarized herein, regioselectivities of aryne and hetaryne trapping experiments can now be predicted using simple and reliable computational methods. Moreover, trapping experiments of indolynes and pyridynes allow for the efficient assembly of an array of unique heterocyclic scaffolds.

Several further developments in the field of heterocyclic arynes and the aryne distortion model[31] can be expected in the future. First, we anticipate that there will be a growing use of indolynes and pyridynes for the assembly of intricate and unusual heterocyclic scaffolds. Several indolyne and pyridyne silyltriflate precursors are now commercially available,[32] which should help to enable their widespread use. Although not the focus of this review, it should be noted that indolynes and pyridynes have already shown use in the synthesis of natural products, such as the welwitindolinones,[33] indolactam V,[20] *cis*-trikentrin A,[6c] ellipticine,[22e] and macrostomine.[22f] Along with the increased use of indolynes and pyridynes, we expect there to be exploratory studies involving other heterocyclic arynes that have not yet been exploited synthetically. Given that many heterocyclic arynes are predicted to react with notable regioselectivities according to the aryne distortion model, we anticipate that access to new hetarynes will provide a fertile area of research.

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Notes

The authors declare no competing financial interest.

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Adam Goetz is currently a fifth year graduate student in Professor Neil K. Garg's laboratory at the University of California, Los Angeles. His graduate studies are focused on understanding and controlling selectivity in the reactions of heterocyclic arynes.

Neil Garg is a Professor of Chemistry at the University of California, Los Angeles. His laboratory develops novel synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.

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