Indolynes as Electrophilic Indole Surrogates:
Fundamental Reactivity, Regioselectivity, and Synthetic Applications

The indole heterocycle is observed in an astonishing number of medicinal agents and natural products. Currently, over 60 drugs contain the indole moiety and another 150 indole-containing compounds are undergoing clinical trials. Given the value of indoles, the discovery of new methods that allow for their functionalization is critical. Although numerous methods for accessing C2- and C3-substituted products from indole building blocks have been discovered, access to C4–C7-substituted indoles remains a significant challenge.

Our approach to this issue contrasts with the usual paradigm of indole reactivity. The indole heterocycle is typically exploited for its nucleophilic character (1→2, Figure 1). Conversely, we reasoned that substitution of the benzenoid ring may proceed by rendering the indole susceptible to attack by nucleophiles (1→3). To this end, we sought to prepare indolynes, or aryne derivatives of indoles (4–6).

Indolyne species were first looked into in the 1960’s with modest success, but were unexplored for several decades. In 2007, both the Buszek group and our group independently re-examined the synthetic utility of the indolyne methodology. Buszek and coworkers demonstrated that C3-substituted indolynes may be generated from dihaloindoles upon treatment with butyllithium reagents, and used in a variety of Diel–Alder reactions. Despite these advances, my thesis research delves into previously unexplored areas in the chemistry of indolynes: (a) the use of indolynes as electrophilic indole surrogates, (b) sources of regioselectivity for nucleophilic attack on indolynes and other unsymmetrical arynes, and (c) methods to overturn the inherent regioselectivity of unsymmetrical arynes.

Figure 1
1. Generation and Reactivity of Indolynes$^{4,5,6}$

Following extensive experimentation, we determined that indolynes 4–6 could be accessed from silyl triflates 7–9 using the general Kobayashi$^7$ approach. In turn, synthetic routes to indolyne precursors 7–9, with varying N1-substituents, were developed using hydroxyindole starting materials. Presented in Scheme 1 is our rapid, high yielding synthesis of our initial target, 4,5-indolyne precursor 14. To confirm that silyl triflate 14 would function as a suitable precursor to the targeted 4,5-indolyne, 14 was treated with TBAF in the presence of furan (15) to yield Diels–Alder adduct 16. The reactivity of indolyne intermediates was further explored by performing experiments involving indolynes and nucleophilic trapping reagents. A sampling of the numerous nucleophiles that undergo smooth reaction with the indolyne intermediate is shown in Scheme 2. Indolyne precursor 14 could also be used in a variety of formal cycloaddition processes to access unique 4,5-disubstituted indole derivatives (e.g., 18–20).
Our strategy for preparing silyl triflates from hydroxyindole precursors proved amenable to the synthesis of 5,6- and 6,7-indolyne precursors, and allowed us to vary the N1-substituent. Thus, we readily gained access to indolyne precursors 7–9 (Figure 2). Trapping indolyne intermediates with nucleophilic agents provided access to several novel substituted indoles (e.g., 22–29).

2. **Origin of Regioselectivity of Nucleophilic Additions to Indolynes**

Of note, our studies demonstrated that nucleophilic additions to indolynes can occur with significant regioselectivity. In collaboration with the Houk group at UCLA, we have shown that distortion energies control regioselectivities and have produced a simple, predictive model for nucleophilic additions to indolynes and other unsymmetrical arynes. Our predictive model advocates a comparison of the internal angles at the aryne termini of the geometry-optimized aryne. The B3LYP/6-31G(d)-optimized structures, obtained from Gaussian, of indolynes 30–32 are shown in Figure 3. In each case, the preferred site of nucleophilic attack is the flatter (i.e., larger internal angle), more electropositive carbon. Furthermore, the degree of regioselectivity was found to correlate to the magnitude of the internal angle difference.

To test our model, we sought to control the regioselectivity of nucleophilic additions to indolynes. We postulated that a bromide substituent at C3 would increase the regioselective preference for nucleophilic attack at C5 of the 4,5-indolyne. To support this hypothesis, geometry optimization of 3-bromo-4,5-indolyne 33 and desbromo-indolyne 30 was performed (Figure 3). The internal angles at C5 and C4 of 33 were found to be 131° and 124°, respectively. This finding suggests that bromoindolyne 33 should display a greater preference for nucleophilic attack at C5 compared to 30 (for comparison, desbromo derivative 30 possesses internal angles of 129° and 125°). Alternatively, we hypothesized that a bromide substituent at C6 would reverse regioselectivity.
of the 4,5-indolyne to favor nucleophilic attack at C4. Our energy-minimized structure of 34 validates this hypothesis, as C4 now possesses the larger internal angle. As shown in Scheme 3, both hypotheses were validated experimentally.

3. Application of the Indolyne Methodology to Total Synthesis

To test our indolyne methodology in a complex setting, we undertook a total synthesis of indolactam V (40), a C4-substituted indole that is both a tumor promoter and a stem cell differentiator. As shown in Scheme 4, treatment of silyl triflate 35 with peptide 36 in the presence of CsF furnished C4-aminated product 37 in 62% yield. Subsequent debromination and dehydration readily provided unsaturated ester 38. ZrCl₄-mediated cyclization gave the desired tricycle 39, after which C9 epimerization and reduction furnished indolactam V (40).
4. Regioselectivity: Distortion vs. Steric Factors

Our aryne distortion model does not take steric factors into consideration. As a means to further probe the model, we examined the influence of inductively donating silyl substituents on aryne regioselectivities. C2 of the geometry optimized 3-triethylsilylbenzyne structure, obtained using DFT methods (B3LYP/6-31G*), is severely distorted (41, Figure 4). Following the aryne distortion model, nucleophilic addition at C2 is favored electronically; however meta substitution should be preferred based on steric considerations. Silylaryne 41, obtained upon treating 42 with a fluoride source, was trapped with a variety of nucleophiles and cycloaddition partners (Scheme 5). The preference for initial attack was found to vary as a function of the trapping agent. Ortho-substituted products were formed when the nucleophile possessed minimal steric hindrance (e.g., benzylamine) as a result of aryne distortion. However, when bulky nucleophiles (e.g., aniline) were used, meta substitution predominated. In the case of 3-t-butylbenzyne (43), which does not possess considerable aryne distortion, nucleophilic addition gives meta-substituted products. These studies suggest that aryne distortion can play an important role in governing regioselectivity in reactions of unsymmetrical arynes.

5. Application of Distortion Model to Other Heterocyclic Arynes

More recently, in collaboration with the Houk laboratory, we have developed an efficient computational approach for evaluating the synthetic potential of heterocyclic arynes. We have found that rapid calculations of arene dehydrogenation energies can effectively predict the likelihood that a given hetaryne can be generated. Additionally, we have used our aryne angle distortion model to predict the degree of regioselectivity that can be expected in a reaction between a given hetaryne and nucleophilic trapping agent. This analysis was applied to
over 150 heterocyclic arynes. Comparisons between calculations and experimental data were used to validate the utility of this predictive tool.

In conclusion, our studies elucidate the factors that govern the regioselectivity of nucleophilic addition to unsymmetrical arynes, a subject that once confounded synthetic chemists. By allowing these reactions to proceed with predictable regioselectivity, it is expected that the classic field of heterocyclic arynes will realize more practical application in the modern field of synthetic chemistry. Current research efforts in the Garg lab are focused on continuing to probe the aryne distortion model in complex molecule synthesis.

References:


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