Organic Syntheses

Discussion Addendum for:

The Direct Acyl-Alkylation of Arynes. Preparation of Methyl 2-(2-acetylphenyl)acetate

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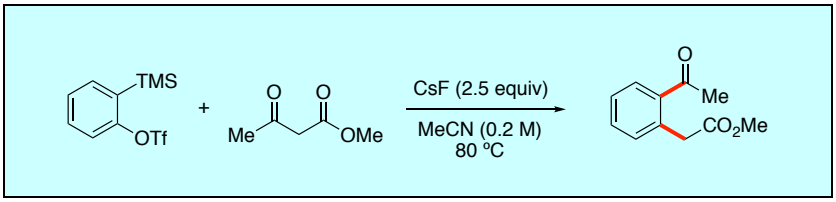
Original Article: Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. Org. Synth. **2009**, *86*, *161–171.*



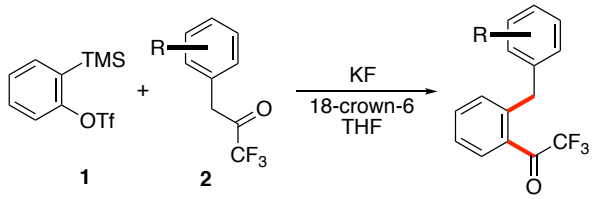
For the past 50 years, benzynes and related arynes have been a major subject of study among physical organic chemists due to their unusual electronic and structural properties. However, the utility of these strained intermediates in the domain of chemical synthesis has only relatively recently undergone a vibrant expansion. The direct insertion of aryne and heteroaryne moieties into carbon–carbon and carbon–heteroatom σ bonds presents an intriguing and unique strategy for the rapid functionalization of aryl and heteroaryl systems. Following our 2009 *Organic Syntheses* article on the acyl-alkylation of arynes with β -ketoesters,[2] there have been numerous reports of related transformations involving these highly reactive intermediates. This discussion addendum is intended to document advances made in the field of (hetero)arynes since our initial disclosure. Topics covered will be divided as follows: recent methods for the acyl-functionalization of arynes, syntheses of related strained systems, applications in heterocycle synthesis, miscellaneous transformations, and strategic uses in natural product synthesis. A supplemental review on aryne insertions into σ bonds is available.[3]

DOI: 10.15227/orgsyn.096.0080

Applications of arynes in transition metal catalysis will not be discussed in detail, however there are thorough reviews on the subject.[4,5]

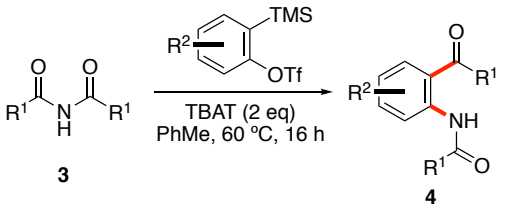
Acyl-functionalization of Arynes

Yoshida reported an analogous acyl-alkylation method to ours, but using trifluoromethyl ketones (**2**, Scheme 1).[6] The trifluoromethyl group is required because it enhances the acidity of the α-keto C–H bonds. The authors note that the presence of bulky R groups on the aryl system of **2** results in competitive *O*-addition of the enolate intermediate.



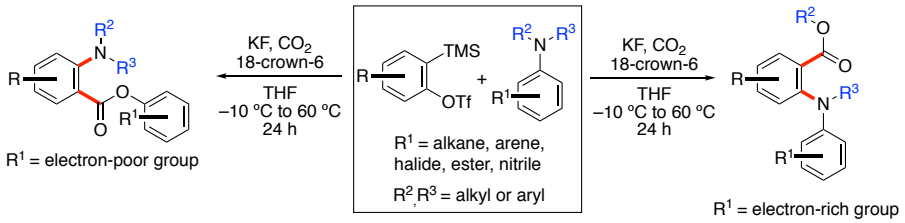
Scheme 1. Aryne insertion into benzyl trifluoromethyl ketones

Our lab has discovered a related insertion of arynes into various symmetrical imides **3** to afford acyl-aminated arenes **4** (Scheme 2).[7] The difunctionalized products can be derivatized to quinolones and indoles. Christmann and coworkers later applied the principles of flow chemistry to this acyl-amination protocol with unsymmetrical imides, achieving the total synthesis of several natural products.[8]



Scheme 2. Aryne insertion into imides

The Biju group disclosed an amino-carboxylation of arynes using aniline derivatives (Scheme 3).[9] This method offers a divergent approach for the synthesis of differentially substituted acyl-aminated arenes depending on the electronics of the aniline ring.



Scheme 3. Tunable acyl-amination of arynes with anilines

Arynes in Heterocycle Synthesis

Perhaps the greatest recent synthetic advances in aryne chemistry are dedicated to the one-step construction of heterocycles (Figure 1). Larock provides an excellent review on the subject.[10] The Larock group has also disclosed numerous aryne annulation approaches for the synthesis of dihydrobenzisoxazoles (**5**),[11] indazoles (**6**),[12,13] and pyrido[1,2-*a*]indoles (**7** and **8**).[14] Shioji and coworkers disclosed the preparation of xanthones (**9**), xanthenes, and xanthols using arynes.[15] Our lab has reported the divergent synthesis of iminoindenones and iminoisobenzofurans (**10**) via a three-component procedure.[16] We have also disclosed the one-pot preparation of 3-hydroxyisoquinolines (**11**) through an acyl-alkylation/condensation approach.[17] Additionally, we reported the formation of *N*-phenyl acridone (**12**) by means of a C–N insertion of β-lactam.[18] The Studer lab disclosed the rapid synthesis of *N*-substituted carbazoles (**13**) by reacting arynes with nitrosoarenes.[19] Greaney and coworkers prepared phenoxathiin-dioxides (**14**) via a thia-Fries/cyclization process.[20] The Kobayashi group reported the formation of isocoumarins (**15**) via a Pd-catalyzed three-component reaction between arynes, alkynes, and carbon dioxide.[21] Isocoumarins can also be prepared under transition-metal-free conditions.[22] Biju presented methods for the synthesis of oxaphosphacycles (**16**),[23] phthalimides (**17**),[24] and indoles (**18**).[25] The Greaney lab has also synthesized indoles from arynes by means of a Fischer indole-type reaction.[26] The Miyabe group reported the synthesis of benzofurans (**19**).[27] They have also discovered the cycloaddition between arynes and DMF to afford 4-aminobenzopyrans such as **20**.[28] The Li group prepared benzothiazoles (**21**) by means of a relay aryne sequence.[29] Lastly, Su and coworkers prepared 2-arylated benzoxazoles (**22**) by means of a domino aryne reaction.[30]

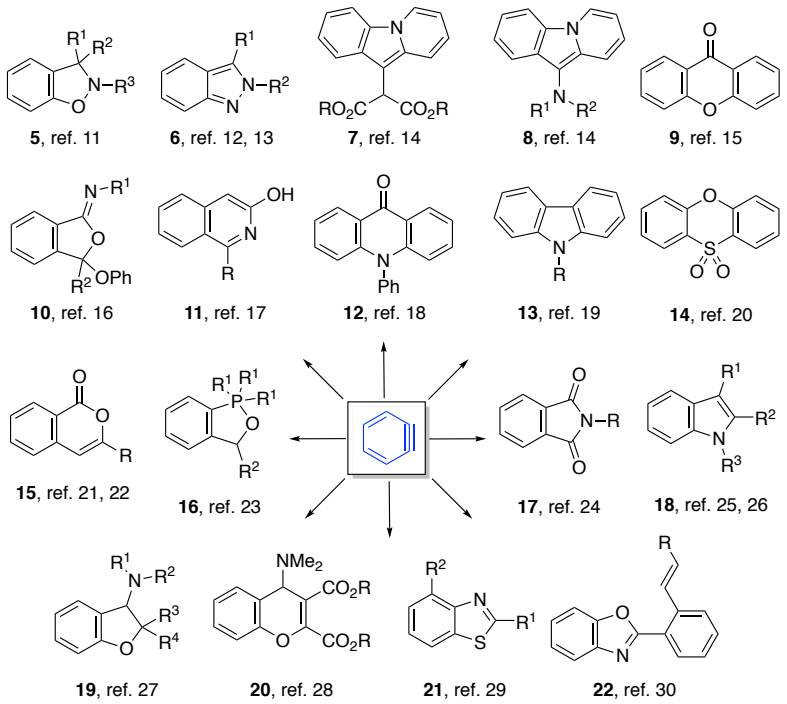


Figure 1. Various heterocycles recently assembled by aryne annulation methods

Methods for the Synthesis Heteroarynes and Other Strained Intermediates

In 2010, our lab reported the formation of highly substituted aryne precursors and their potential synthetic applications in the construction of complex molecules (Figure 2).[31] The marked carbons denote the preferred site of selective nucleophilic attack following aryne formation.

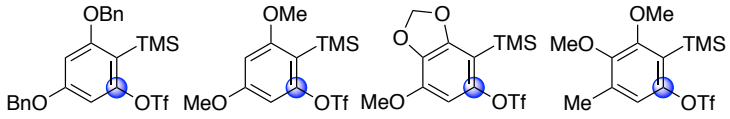


Figure 2. Synthesizable highly substituted aryne precursors

The laboratory of Garg has investigated various insertion strategies with heteroarynes and other strained ring systems. Because many of these reactions result in unsymmetrical products, they have computationally derived a model for predicting the regioselectivity during the insertion step based on angle distortion.[32,33] This model has been exploited for the regioselective insertion of indolynes,[34] pyridynes,[35,36] piperidynes,[37] as well as various oxacyclic alkynes (Figure 3).[38] Contemporaneously, the Danheiser lab reported the first preparation and diverse applications of *N*-tosylpiperidynes.[39] It is worthwhile to note that the preferred site of nucleophilic attack may be either enhanced or overturned depending on the substitution pattern on the heteroaryl ring. The chemistry of pyrimidynes has also been investigated, but there have been no reports of their successful formation.[40]

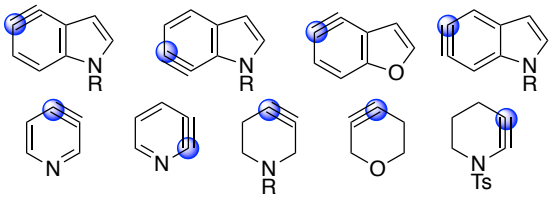
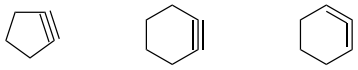


Figure 3. Strained heterocycles studied recently by the Garg and Danheiser labs

Similar insertion strategies have been achieved with strained non-aromatic carbocycles such as cyclopentyne (**23**, Figure 4),[41] cyclohexyne (**24**), and cyclic allene **25**.[42]



23 **24** **25**

Figure 4. Strained non-aromatic ring systems

The Hoye group has vigorously studied the generation of arynes via an unusual hexadehydro-Diels–Alder reaction (HDDA, Figure 5).[43,44] Areas of study in the field are numerous, including Lewis-acid-promoted C–H insertion,[45] domino reactions,[46,47] photochemistry,[48,49] mechanistic studies,[50,51] multicomponent reactions,[52] and natural product diversification.[53] The regioselectivity for the ensuing insertion process is influenced by both the choice of nucleophile and the substituents on the aryne system.[54] The Lee

group has demonstrated that these HDDA adducts can also participate in ene reactions.[55]

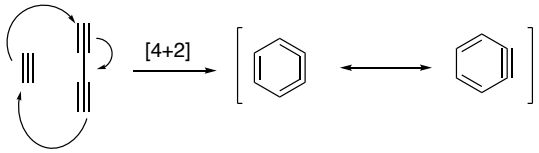
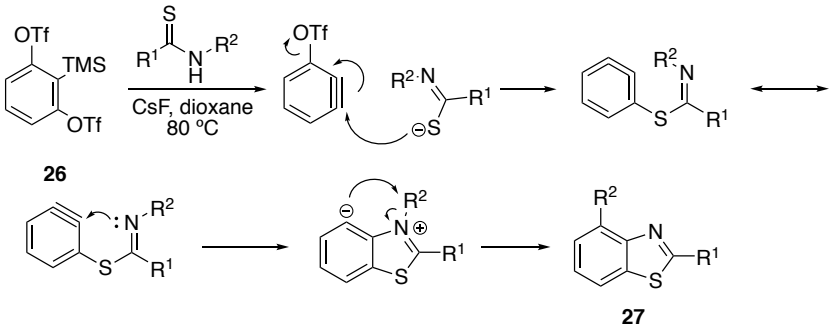


Figure 5. A hexadehydro-Diels–Alder affords an aryne

The advent of silylaryl-1,3-ditriflates such as **26** has given rise to aryne relay chemistry (Scheme 4). Li and coworkers demonstrated the utility of these substrates as a means to generate trifunctionalized systems with thioamides, furnishing benzothiazoles (**27**).[29] A plausible mechanism for this process is shown below. They have also achieved similar relay chemistry with sulfoxides[56] and sulfonamides.[57,58,59] In 2016, Yoshida reported an advancement of this concept.[60] The Li group discovered that these latent 1,2-benzdiynes can also participate in ene reactions.[61]



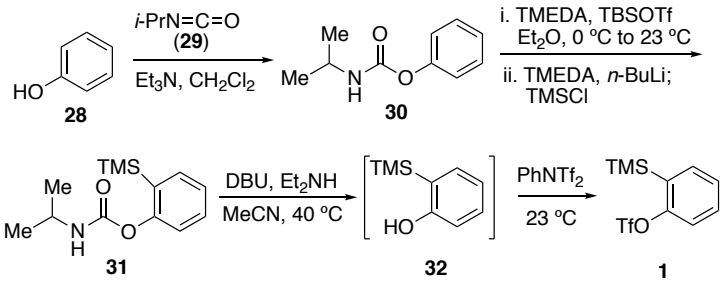
Scheme 4. One-pot elaboration of 1,2-benzdiyne precursor 26 to benzothiazole 27

Miscellaneous Transformations

Many recent methods involving arynes are not readily classifiable in the above sections. This section provides a brief survey of such transformations. The Greaney group has discovered a means of difunctionalizing arynes with thioureas to afford thioaryl amidines.[62] They also pioneered other heterofunctionalization strategies via three-component coupling[63] and Truce–Smiles rearrangement.[64] The Biju group has found many novel

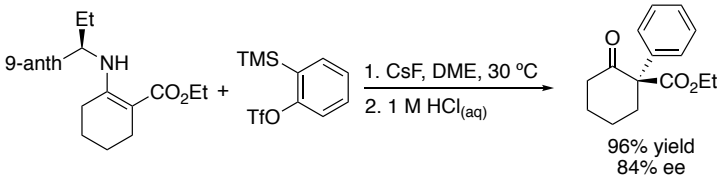
applications of arynes, including their ability to induce 2,3-Stevens rearrangements in allylthioethers.[65,66] They have also identified arynes as latent aryl anion equivalents.[67] The Studer lab has reported the formation of *ortho*-sulfinylaryl vinyl ethers,[68] biphenyls,[69] trialkylstannyl arylphosphanes,[70] and sulfonium ylides[71] by means of aryne insertion chemistry. The Lautens group has actively explored the applications of the intramolecular aryne–ene reactions.[72,73]

Despite a resurgent interest in the study of benzyne, there remain relatively few methods for the preparation of the trimethylsilylaryl triflate precursor (**1**, Scheme 5).[74] In 2009, the Garg lab reported a facile synthesis of precursor **1** in three steps starting from phenol (**28**).[75] Thus, **28** was treated with isopropyl isocyanate (**29**) to afford carbamate **30**. Following *N*-silylation, a directed *ortho*-lithiation and subsequent trapping with TMSCl provides silylarene **31** upon acidic workup**.** The carbamate functionality of **31** is next cleaved by aminolysis to form transient phenol derivative **32**, which is converted to silylaryl triflate **1** by reaction with *N*-phenyl triflimide.



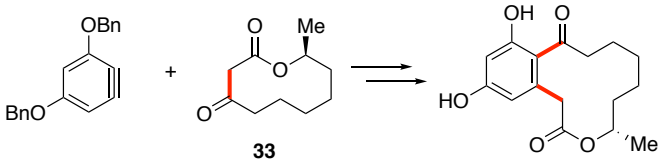
Scheme 5. Garg's 3-step synthesis of benzyne precursor 1

There has been one report harnessing arynes and cyclic alkynes for the asymmetric construction of all-carbon quaternary centers (Scheme 6).[76] Chiral enamine auxiliaries bearing 9-anthryl substituents were found to confer the highest levels of stereoinduction.



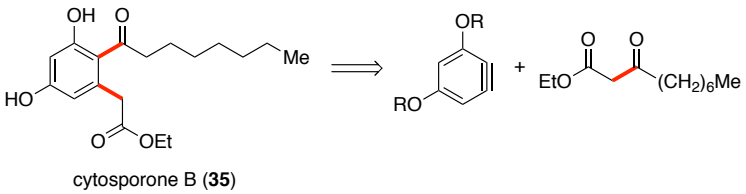
Scheme 6. Asymmetric formation of quaternary centers with arynes

In recent years, arynes have enjoyed a privileged role in total synthesis. For more information, we recommend consulting two reviews[77,78]and the references therein. In 2010, our lab performed an enantioselective synthesis of (–)-curvularin (**34**, Scheme 7) and (–)-diplodialide C via aryne acyl-alkylation.[79] The requisite macrocycle **33** was constructed by means of a ring-closing metathesis.



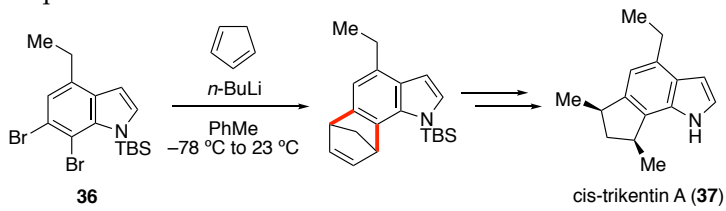
Scheme 7. Concise synthesis of 34 enabled by aryne acyl-alkylation

Similarly, Yoshida and coworkers presented an expedient approach to the synthesis of cytosporone B (**35,** Scheme 8), relying on an acyl-alkylation disconnection.[80]



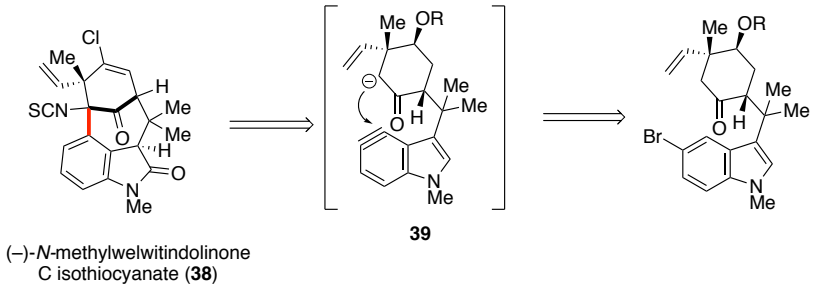
Scheme 8. Retrosynthetic analysis of 35 leads to an aryne insertion

The Buszek group reported the total synthesis of cis-trikentin A (**37**, Scheme 9) using an indolyne cycloaddition.[81] In this case, the indolyne intermediate is generated from dibromide **36** via lithium-halogen exchange and subsequent elimination.



Scheme 9. Facile synthesis of 37 via an indolyne cycloaddition

Likewise, the Garg lab reported a synthesis of various *N*-methylwelwitindolinones such as **38**[82] by means of an indolyne cyclization (Scheme 10).[83,84,85,86,87] Here, indolyne formation is triggered by base-induced halide elimination. The authors note minor issues of competing *O*-addition of the enolate in intermediate **39**.

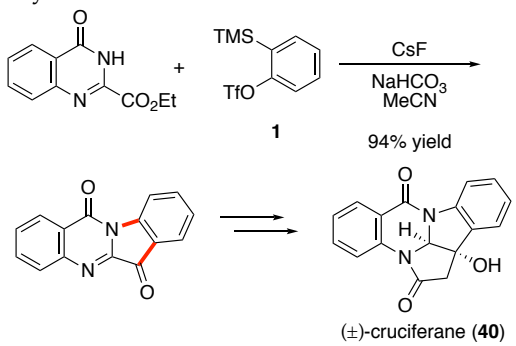


(–)-*N*-methylwelwitindolinone C isothiocyanate (**38**)

39

Scheme 10. Garg's retrosynthetic analysis of 38 reveals an indolyne annulation

Argade and coworkers disclosed the total synthesis of (±)-cruciferane (**40**, Scheme 11) using aryne chemistry.[88] Notably, the crucial aryne insertion step occurs in excellent yield.

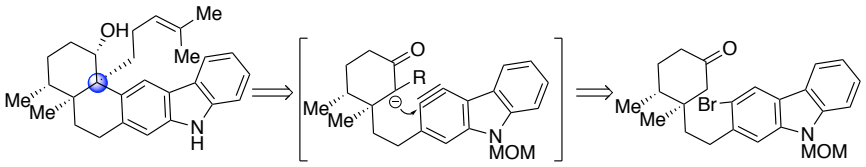


1

(±)-cruciferane (**40**)

Scheme 11. Expedient total synthesis of 40 by aryne cyclization

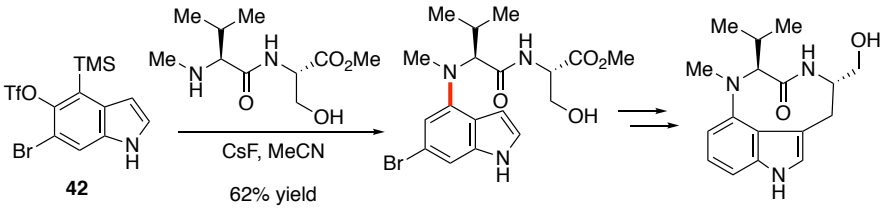
The Garg lab has incorporated carbazolyne chemistry in the total syntheses of tubingensin A[89] (**41**, Scheme 12) and tubingensin B.[90] The labeled quaternary stereocenter in **41** is formed in good yield and with exquisite diastereoselectivity due to the rigid conformational constraints on the system.



tubingensin A (**41**)

Scheme 12. Retrosynthesis of tubingensin A (41) by carbazolyne annulation

Garg has also synthesized indolactam-containing natural products such as indolactam V (**43**, Scheme 13).[91] The strategically placed bromide substituent in **42** is essential for overturning the inherent regioselectivity associated with the key C–N bond-forming step.



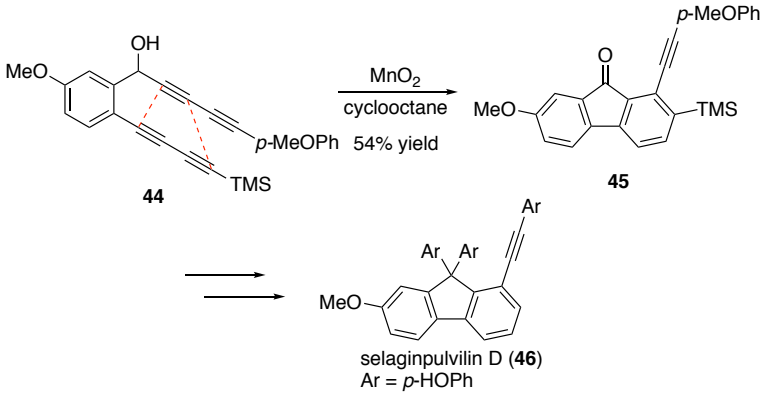
42

(7 steps, 62% yield)

indolactam V (**43**)

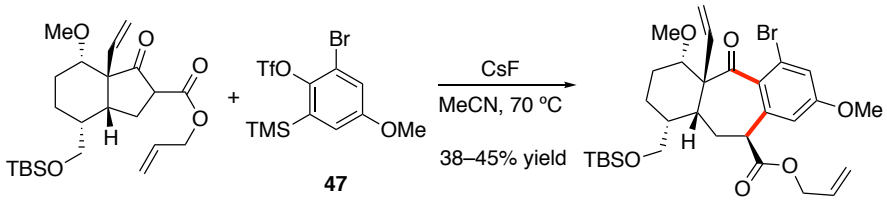
Scheme 13. Synthesis of indolactam V (43) by indolyne amination

The Lee group leveraged HDDA chemistry for the rapid total synthesis of selaginpulvilin D (**46**, Scheme 14).[92] It is interesting to note that despite occurring under formally oxidizing conditions, the benzyne intermediate arising from an intramolecular HDDA of tetrayne **44** undergoes *in situ* transfer hydrogenation by the action of cyclooctane to afford fluorenone **45**.



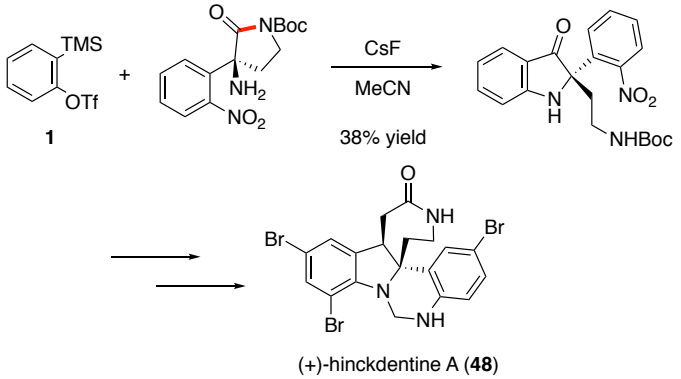
Scheme 14. Lee's total synthesis of 46 hinges on an elegant oxidation/intramolecular HDDA/hydrogenation sequence

In 2018, the Sarpong lab reported the acyl-alkylation of benzyne derivative **47** to access the seven-membered carbocyclic core of the diterpenoid alkaloid cossonidine (Scheme 15).[93] Once again, a bromide substituent is necessary in order to ensure proper regioselectivity.



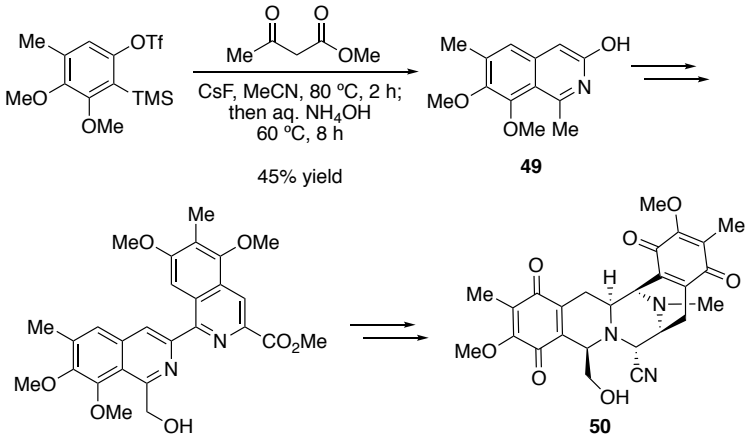
Scheme 15. Sarpong's acyl-alkylation approach to the central seven-membered ring of cossonidine

Zhu and coworkers disclosed a novel heteroannulation of arynes using α-amino imides.[94] This method was employed for the total synthesis of (+)-hinckdentine A (**48**, Scheme 16).



Scheme 16. Zhu harnessed a novel acyl-amination strategy for the total synthesis of 48

Recently, our lab reported the non-biomimetic total syntheses of (–)-jorunnamycin A (**50**, Scheme 17) and (–)-jorumycin in 15 and 16 steps, respectively.[95] Amid this route, one of the necessary isoquinoline monomers was prepared using aryne chemistry. In this instance, the acyl-alkylation product is subjected to *in situ* condensation with ammonium hydroxide to afford densely functionalized isoquinoline **49**.[17] Remarkably, four of the five carbon-based stereocenters present in **50** are set in one step via an iridium-catalyzed asymmetric hydrogenation. Unlike previous approaches to these bis-tetrahydroisoquinoline natural products, this route is amenable to the synthesis of a diverse array of nonnatural analogs, because the aryne chemistry is independent of classical Pictet-Spengler approaches that have been employed in the syntheses of these alkaloids.



Scheme 17. Formation of isoquinoline monomer 49 en route to (–)-jorunnamycin A (50) and (–)-jorumycin

Concluding Remarks

Clearly the field of aryne chemistry has experienced rapid growth over the last decade. In addition to the discovery of various methods strategically related to our initial acyl-alkylation disclosure, there have been many other impressive applications in the context of methods and total synthesis. Based on these recent developments, it is evident that these curious and highly reactive intermediates will continue to inspire chemists to discover new and synthetically useful reactions for the foreseeable future.

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