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The Aryne aza-Diels–Alder Reaction: Flexible Syntheses of Isoquinolines

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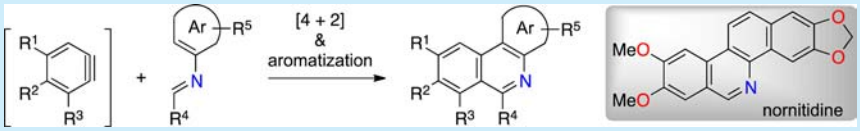
Supporting Information



ABSTRACT: Two cascade reactions have been developed for the time-efficient preparation of a variety of functionalized aromatic heterocyclic products exhibiting an isoquinoline core. The approach is based on the normal electron-demand [4 + 2] aza-Diels–Alder cycloaddition of electron-rich *N*-aryl imines with arynes. Using this strategy, an expeditious total synthesis of the naturally occurring benzo[*c*]phenanthridine alkaloid nornitidine was achieved.

Isoquinolines and their derivatives are important nitrogen-containing heterocycles generally endowed with biological properties, making them a privileged scaffold for applications in medicinal chemistry and pharmaceuticals.[1] Isoquinolines have also found applications in material sciences because of their interesting physicochemical properties.[1] Synthetic approaches to the isoquinolines (Figure 1) have largely relied on the

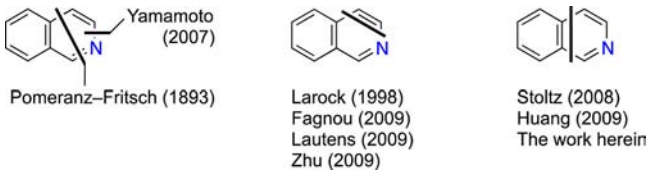


Figure 1. Retrosynthetic strategies for isoquinolines.

Pomeranz–Fritsch synthesis involving the assembly of benzaldehyde derivatives and aminoacetals.[2] These reactions typically require harsh acidic conditions, limiting their functional diversity tolerance. More recently, Yamamoto described an iodine-mediated electrophilic cyclization of elaborated 2-alkynyl benzyl azides for the synthesis of polysubstituted isoquinolines.[3] Besides other stepwise approaches using single bond-forming reactions, several metal-catalyzed multiple bond-forming transformations have been developed in recent years to prepare isoquinolines in a time-efficient manner.[4] Notably, the Larock group has established a general route to isoquinolines from benzylidene amines and alkynes based on a palladium-catalyzed cascade,[5] and the groups of Fagnou,[6a] Lautens,[6b] and Zhu[6c] have more recently used comparable approaches. All these approaches rely at some point on a carbon–nitrogen bond-forming event to assemble the desired bicyclic core. An alternative inticing but largely unexplored strategy to prepare isoquinolines would rely on the formation of two carbon–carbon bonds by a metal-free aza-Diels–Alder cycloaddition between 2-aza-dienes and arynes.[7,8] However, an obstacle to the development of this strategy is that benzyne is known to react with imines and 2-aza-dienes essentially by [2 + 2] cycloaddition reactions to provide the corresponding benzazetidines.[9] Moreover, the proposed aza-Diels–Alder reaction is a normal electron-demand cycloaddition of a 2-aza-diene, examples of which remain rare.[10,11] Circumventing these difficulties, the Stoltz group has reported an annulation reaction between secondary eneamides and arynes as a viable route to isoquinolines,[12a,b] and Huang has developed a pseudo four-component approach involving 2 equiv of benzynes via a *N*-allenyl aldimine intermediate generated in situ.[12c] The realization of aza-Diels–Alder cycloadditions between arynes and easily available 2-aza-dienes would open a direct and practical synthetic approach to functionalized isoquinolines. Herein, two distinct cascade reactions initiated by an aza-Diels–Alder cycloaddition between *N*-aryl imines and arynes are reported for the direct synthesis of a variety of functionalized heterocycles with an isoquinoline core.[13]

At the origin of this work, it was hypothesized that electron-rich *N*-aryl imines would be suitable candidates for aza-Diels–Alder cycloadditions with arynes affording 1,2-dihydroisoquinolines, the oxidation of which would provide a direct synthetic entry to isoquinolines (Scheme 1). In order to test that idea, the prototypical electron-rich *N*-pyrazolyl aldimine **2a** (1.5 equiv) and benzyne, generated in situ by fluoride-induced 1,2 elimination from the ortho-silylated phenyltriflate **1a**,[14] were allowed to react in THF (Scheme 2).[15] While **2a** was found to be almost unreactive at room temperature, a reaction performed at 70 °C allowed the isolation of the 1,2-dihydroisoquinoline **3a** (34%), a significant amount of the *N*-arylated over-reaction product **5a** (31%),[16] and 6% of the

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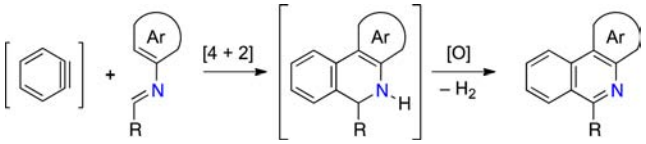
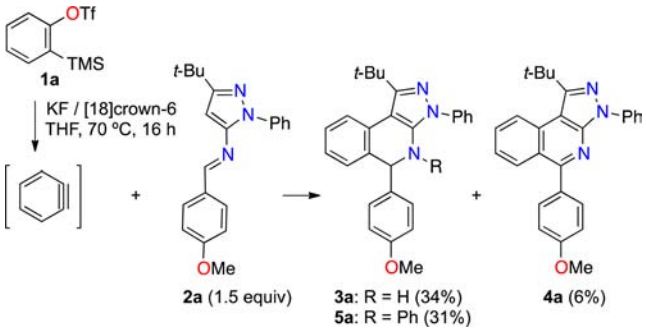
Scheme 1. Aryne aza-Diels–Alder Strategy toward Isoquinolines



Scheme 2. Aryne aza-Diels–Alder Reaction



ultimately targeted isoquinoline **4a**. Interestingly, no [2 + 2] adduct or its derivatives could be identified in the crude reaction mixture, which was considered possible.[9]

In order to rationalize the periselectivity ([2 + 2] vs [4 + 2]) of the cycloaddition of 2-aza-dienes with arynes, the reaction between benzyne and model *N*-aryl imines was examined theoretically by DFT calculations. In the case of *N*-phenyl benzylidene imine (Figure 2, top), and in agreement with previous experimental observations,[9] the [2 + 2] cycloaddition mode, a stepwise process, was found to be slightly kinetically favored (by ca. 2 kcal.mol^{-1}) and irreversible. In contrast, with a *N*-pyrazolyl benzylidene imine of type **2** (Figure 2, bottom), the [4 + 2] cycloaddition mode, a concerted asynchronous process, was found kinetically preferred (by ca. 6 kcal·mol^{-1}) and irreversible. In the corresponding transition state $\mathbf{TS_{GH}}$, the formation of the C–C bond between the pyrazolyl unit and benzyne was found slightly in advance to the formation of the C–C bond between the imine moiety and benzyne. From this study, it was concluded that the relative nucleophilicities of the nitrogen atom and the *N*-aryl moiety are essential factors that govern the periselectivity of the cycloaddition reactions between arynes and 2-aza-dienes.

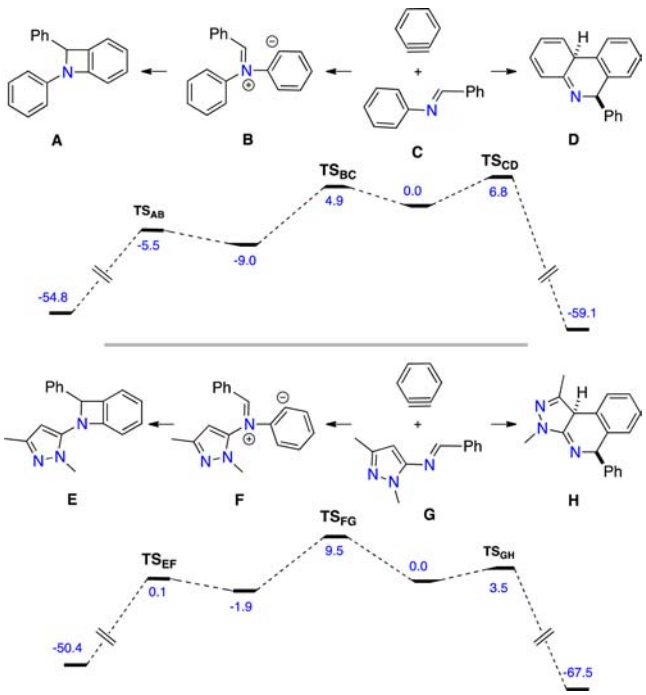
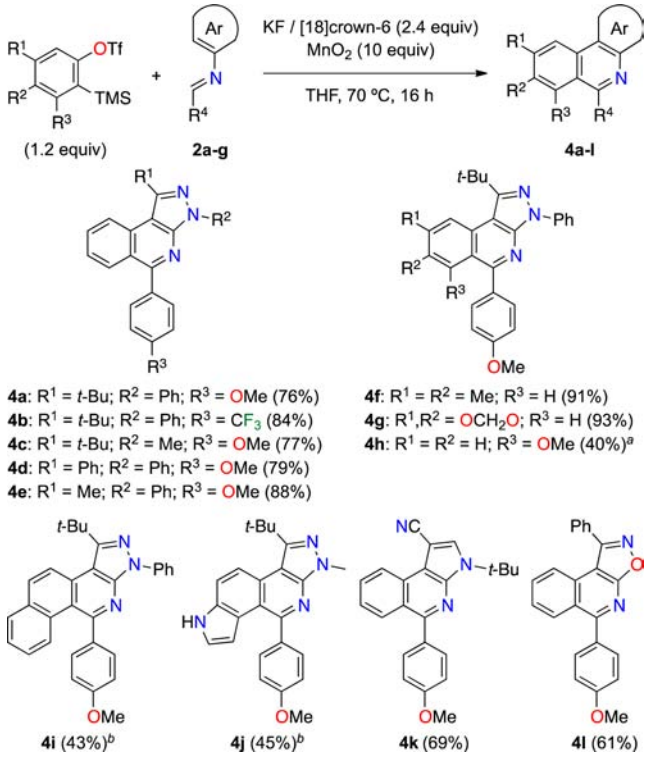


Figure 2. Mechanism and energy profile of the cycloaddition reactions between benzyne and *N*-aryl imines. The energy profiles were obtained by DFT calculations at the B3LYP/6-311++G** level of theory (free energies at 25 °C including ZPE corrections in kcal·mol^{-1} with the IEFPCM solvation model; see Supporting Information for details).

Before the aryne aza-Diels–Alder reaction could be of any synthetic utility to prepare isoquinolines, the issue of the undesired formation of the *N*-arylation over-reaction product **5a** had to be addressed. It was thus examined, if under oxidative conditions, a rapid in situ oxidation of intermediate **3a** could occur prior to the unwanted *N*-arylation over-reaction. In practice, several oxidizing agents were screened and the reaction conditions optimized (see Supporting Information). It was rapidly found that, in the presence of excess MnO_2, the isoquinoline **4a** could be obtained in good yield from the 2-aza-diene **2a** and benzyne (Scheme 3). The scope of the reaction was then examined with a variety of electron-enriched *N*-aryl imines and arynes under similar conditions. In each case the reaction was found productive, affording the isoquinoline products **4a–l** in good yields, and importantly, with good to

Scheme 3. Synthesis of Isoquinolines via the Oxidative Aryne aza-Diels–Alder Reaction



[a]With 20 equiv of MnO_2, regioisomer ratio >15:1. [b]The ^{1}H NMR analysis of the crude reaction mixture indicated the formation of the other possible regioisomer in minor proportion (ca. 6:1). The reported yield refers to the isolated 6:1 mixture of regioisomers.

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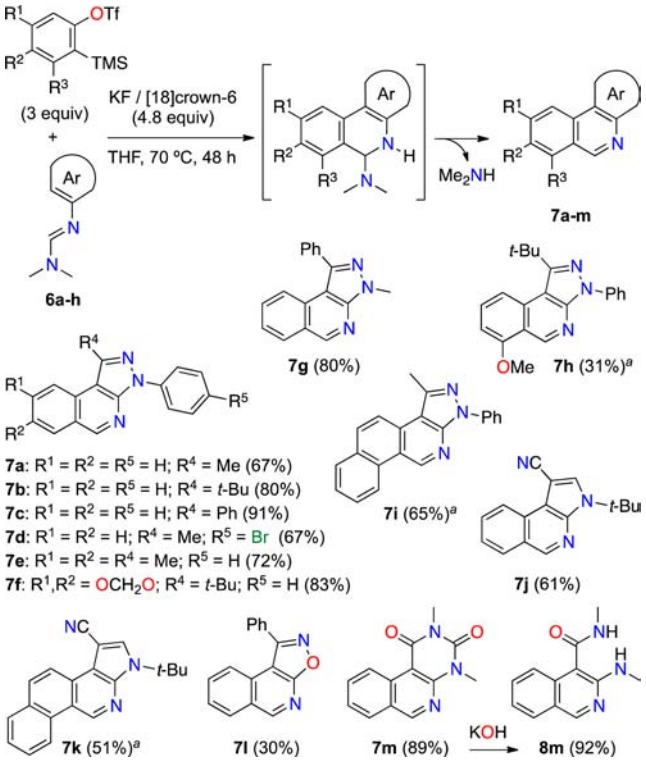
excellent regioselectivities with nonsymmetric arynes (in **4h**, **4i**, and **4j**; regioisomer ratios from 6:1 to >15:1). Notably, the reaction with the hetaryne[17] indol-4,5-yne regioselectively afforded the expected isoquinoline product **4j** bearing two fused *N*-containing heterocycles and a free N−H group. Finally, the scope of 2-aza-diene substrates was extended either to a *N*-pyrrolyl imine leading to product **4k** showing a 7-azaindole moiety or to a *N*-isoxazolyl imine delivering the product **4l**.

A second option to prepare isoquinolines via the aryne aza-Diels−Alder strategy would be the introduction of a sacrificial group, which would trigger the rapid eliminative aromatization of the intermediate cycloadduct. In line with this idea, a series of formimidamides **6a−h** bearing a potentially labile dimethylamino group were allowed to react with representative arynes (Scheme 4). Rewardingly, a series of diversely

Scheme 4. Synthesis of Isoquinolines via the Aryne aza-Diels−Alder Reaction

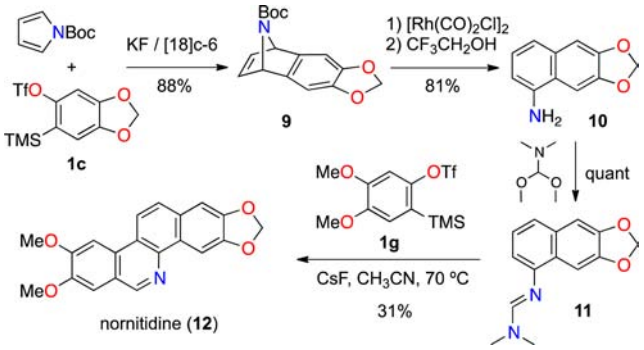


[a]The ^{1}H NMR analysis of the crude reaction mixture indicated the formation of the other possible regioisomer in minor proportion (8:1 for **7h**, 10:1 for **7i** and **7k**). The reported yield refers to the isolated pure major regioisomer.

substituted pyrazolo-, pyrrolo-, isoxazolo-, and pyrimido-isoquinolines **7a−m** could be prepared efficiently by this original cascade reaction, still with good regioselectivities with unsymmetrical arynes as in **7h**, **7i**, and **7k** (regioisomer ratios from 8:1 to 10:1).[18] The structures of products **7i** and **7j** have been secured by X-ray diffraction techniques,[19] and alkaline hydrolysis of the pyrimido-isoquinoline **7m** afforded the corresponding 3-amino-4-amido-isoquinoline **8m**.

The robustness of the aryne aza-Diels−Alder route to isoquinolines was evaluated in a concrete case, through the expeditious total synthesis of the naturally occurring benzo[*c*]-phenanthridine alkaloid nornitidine (**12**, Scheme 5).[20] The synthesis was initiated by a Diels−Alder cycloaddition between

Scheme 5. Total Synthesis of Nornitidine via Arynes



N-Boc-pyrrole and the functionalized benzyne derived from the *ortho*-silylated phenyltriflate **1c** to give the bridged compound **9**,[21a] which then underwent a rhodium-catalyzed ring opening reaction[21b] and a deprotection step[22] to afford the primary amine **10**. The required 2-aza-diene **11** was obtained quantitatively from the amine **10**. The pivotal benzyne aza-Diels−Alder reaction between **11** and the *o*-dimethoxy benzyne precursor **1g** directly afforded the target molecule **12** in 31% yield. Overall, the natural product **12** was obtained in five steps and 22% yield from *N*-Boc-pyrrole featuring two benzyne Diels−Alder cycloadditions. This original aryne-based synthesis of nornitidine (**12**) very favorably competes with existing routes. This synthesis also constitutes a formal total synthesis of nitidine, another benzo[*c*]phenanthridine alkaloid natural product with topoisomerase inhibition and potent antimalaria properties.[20]

In summary, two flexible cascade reactions have been developed to prepare diversely functionalized heteropolycyclic products with an isoquinoline core in a time-efficient manner. The approach relies on the normal electron-demand aza-Diels−Alder cycloaddition reactions between easily accessible electron-rich 2-aza-dienes and arynes, and a subsequent aromatization step. The substitution patterns available by the described approach are nicely complementary to the ones obtained by existing methods. It can be noted that heteropolycyclic compounds closely related to products **4** and **7** are of current high interest for their biological properties.[1d,23] The method was successfully applied to a concise total synthesis of the natural product nornitidine (**12**), a representative member of a class of naturally occurring biologically active benzo[*c*]phenanthridine alkaloids. The described aryne aza-Diels−Alder cycloaddition strategy is expected to become a useful tool for the synthesis of nitrogen-containing heterocyclic compounds and functional polyaromatic systems.

■ ASSOCIATED CONTENT

Supporting Information

Details of the computational study, CIFs for compounds **7i** and **7j**, detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01704.

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Notes

The authors declare no competing financial interest.

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