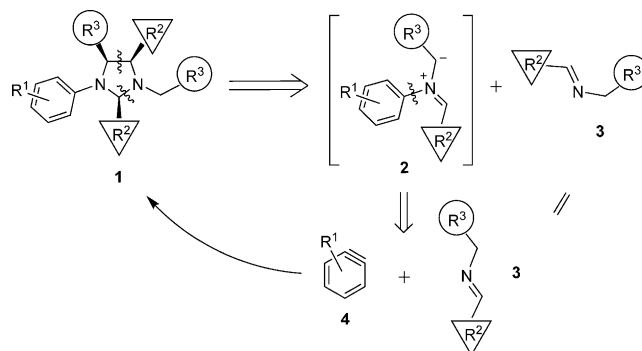


Aryne-Induced Novel Tandem 1,2-Addition/(3+2) Cycloaddition to Generate Imidazolidines and Pyrrolidines**

Sharada P. Swain, Yi-Chun Shih, Shwu-Chen Tsay, Joby Jacob, Chun-Cheng Lin, Kuo Chu Hwang, Jia-Cherng Horng, and Jih Ru Hwu*

Abstract: A new “single-flask” method was developed for the synthesis of imidazolidines and pyrrolidines with high stereo-selectivity. First, a Schiff base was arylated with an aryne. Second, an intramolecular proton transfer took place from the methylene position to the anionic aryne ring. Third, the resultant ylide reacted with a second equivalent of the same Schiff base in situ or an electron-deficient alkene through a (3+2) cycloaddition. These sequential tandem 1,2-addition/(3+2) cycloaddition reactions led to the desired heterocycles in 63–88 % yields.

Arynes are highly reactive species that can be derived from an aromatic ring by removal of two *ortho* substituents.^[1,2] These species are commonly generated at low temperatures and used in situ.^[2,3] Examples of their recent applications in organic syntheses include the intramolecular aryne–ene reaction,^[4] the intermolecular sp^2 C–H bond arylation,^[5] and the insertion of arynes into a $C_{sp}-O_{sp^3}$ σ bond.^[6] More than 75 natural products have been synthesized with arynes to generate the key synthetic intermediates.^[7] The present authors’ research group utilized benzyne to induce the olefination of β -amino alcohols and produce alkenes with high stereospecificity.^[8] Furthermore, a deoxygenative olefination reaction that involves benzyne has been successfully applied as the key step in the syntheses of deoxy- and iminosugars.^[9] To continue the study of aryne-induced reactions, we developed a new method for synthesizing imidazolidines **1** by the 1,3-dipolar cycloaddition (Huisgen



Scheme 1. “Two-step” design with a “single-flask” procedure: $(4 + 3) + 3 \rightarrow 1$.

cycloaddition)^[10,11] between azomethine ylides **2** and Schiff bases **3**.

The intriguing aspect of this synthetic strategy as shown in Scheme 1 is that the azomethine ylides **2** are generated in situ from arynes **4** and Schiff bases **3**. Then the intermediates **2** react with a second equivalent of the Schiff base **3** already present in the reaction flask to produce targets **1** through a (3+2) cycloaddition pathway. The overall reaction involves a “two-step” design and a “single-flask” procedure for the synthesis of imidazolidines.^[12,13] This novel strategy with effectiveness and efficiency could also be extended to the synthesis of pyrrolidines by replacement of the second equivalent of the Schiff bases with various electron-deficient alkenes.

1,3-Cycloaddition reactions provide a powerful tool for the synthesis of cyclic compounds.^[12] Reactions between 1,3-dipoles and molecules that have a double or triple bond often give heterocycles in high yields.^[14,15] As popular 1,3-dipoles, azomethine ylides are often generated by a thermal 1,2-prototropy shift in iminoesters or by the base-assisted formation of metallodipoles. Various methods have been developed for their preparation from aldehydes, ketones, imines, aziridines, heterocycles, etc.^[16] However, metallodipoles are the most frequently used species because simple and mild conditions are needed.^[15] With these two advantages, the strategy in Scheme 1 involves the use of an aryne that serves as both an electrophile and a proton acceptor for a Schiff base during the generation of an azomethine ylide. Accordingly, the metallodipole intermediate^[15] is no longer required.

Imidazolidines were selected as the synthetic targets in this study owing to their significant biological activities. For example, Perillo and co-workers^[17] found that some imidazolidines function as anti-*Trypanosoma cruzi* agents through interfering with the biosynthesis of polyamines in a parasite.

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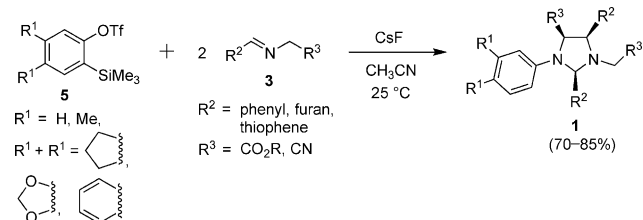
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201503319>.

They exhibit high and selective activity against the proliferative stages of the parasite with IC_{50} values in the low micromolar range. Sigma (σ) receptors are unique mammalian proteins. The two subtypes, σ_1 and σ_2 , are extensively distributed throughout the central nervous system. Kassiou and co-workers^[18] reported that certain imidazolidines show σ_1 affinities on a nanomolar scale ($K_i = 6.45\text{--}53.5\text{ nM}$) and relatively low levels of subtype selectivity ($\sigma_2/\sigma_1 = 58\text{--}237$). Additionally, Sharma and Khan^[19] found that tetrahydroimidazoles possess promising anti-inflammatory and analgesic activities.

Various methods have been developed for the synthesis of imidazolidines.^[20,21] Nenajdenko et al.^[22] disclosed the unexpected finding that the reaction of β -halogeno- β -polyfluoromethylstyrenes with N,N -binucleophiles leads to imidazolidines through fragmentation. Xiao and co-workers^[23] successfully induced the intramolecular cyclization of diamines by visible light to yield highly substituted imidazolidines. Katritzky et al.^[24] found that condensations of N -substituted ethanediamines with formaldehyde (2 equiv) and benzotriazole (1 equiv) produce 1,3-disubstituted imidazolidines in high yields. Hiemstra and co-workers^[25] conducted the oxidative cyclization of formaldehyde amins to form imidazolidines.

Herein, we report the development of a new 1,3-dipolar reaction as shown in Scheme 2. This reaction was induced by arynes **4**, which were generated from α -silylaryl triflates **5** and CsF. It can convert two equivalents of Schiff bases **3** to imidazolidines **1** with high yields and excellent diastereoselectivity under mild conditions. Furthermore, the same type of the “single-flask” reaction was found to be feasible for the replacement of the second equivalent of the Schiff base with an electron-deficient alkene. Accordingly, various pyrrolidines with multiple substitutes were generated with success through this novel tandem 1,2-addition/(3+2) cycloaddition.

For investigation on the feasibility of the new aryne-induced reactions,^[8] (trimethylsilyl)aryl triflates **5** (1.0 equiv) were treated with cesium fluoride (3.0 equiv) and Schiff bases **3** (2.2 equiv) in acetonitrile at 25 °C. After 10–12 h of stirring, normal workup, and purification by column chromatography, the desired imidazolidines **1** were obtained with a purity of >98.1% by HPLC. Various aryl triflates **5a–e** and Schiff bases **3a–h** as listed in Table 1 were utilized to elucidate the characteristics of the new reaction. The benzene nuclei of silylaryl triflates **5** therein were dimethyl-substituted or fused with a cyclopentene, 1,3-dioxole, and benzo ring (i.e., **5a–e**). In the Schiff bases **3**,^[26,27] the aryl terminal (R^2) was attached to a methyl, methoxy, fluoro, or bromo group. It could also be



Scheme 2. A new aryne-induced 1,3-dipolar cycloaddition reaction for the synthesis of imidazolidines **1** from α -silylphenyl triflates **5** and Schiff bases **3**.

Table 1: Reactants **3** and **5**, imidazolidine products **1**, as well as the yields of isolated products of the newly developed “single-flask” reaction.

Silylaryl triflate	Reactants Schiff base	Product Imidazolidine	Yield [%]
5a	3a	1a	85
5b	3a	1b	82
5c	3a	1c	85
5d	3a	1d	80
5e	3a	1e	82
5a	3b	1f	78
5a	3c	1g	82
5a	3d	1h	81
5a	3e	1i	82

Table 1: (Continued)

	Reactants	Product	Yield
Silylaryl triflate	Schiff base	Imidazolidine	[%]
5a			71
5a			80
5a			70 ^[a]

[a] Its epimer was isolated in 6% yield.

a furanyl or a thiophenyl group. The alkyl terminal (R^3) was attached to an electron-withdrawing group, such as an alkoxycarbonyl or a cyano group. All of these reactions gave good yields of 70–85%. The optimized conditions, including various combinations of reagents, equivalents, reaction time, and temperature, are described in detail in the Supporting Information.

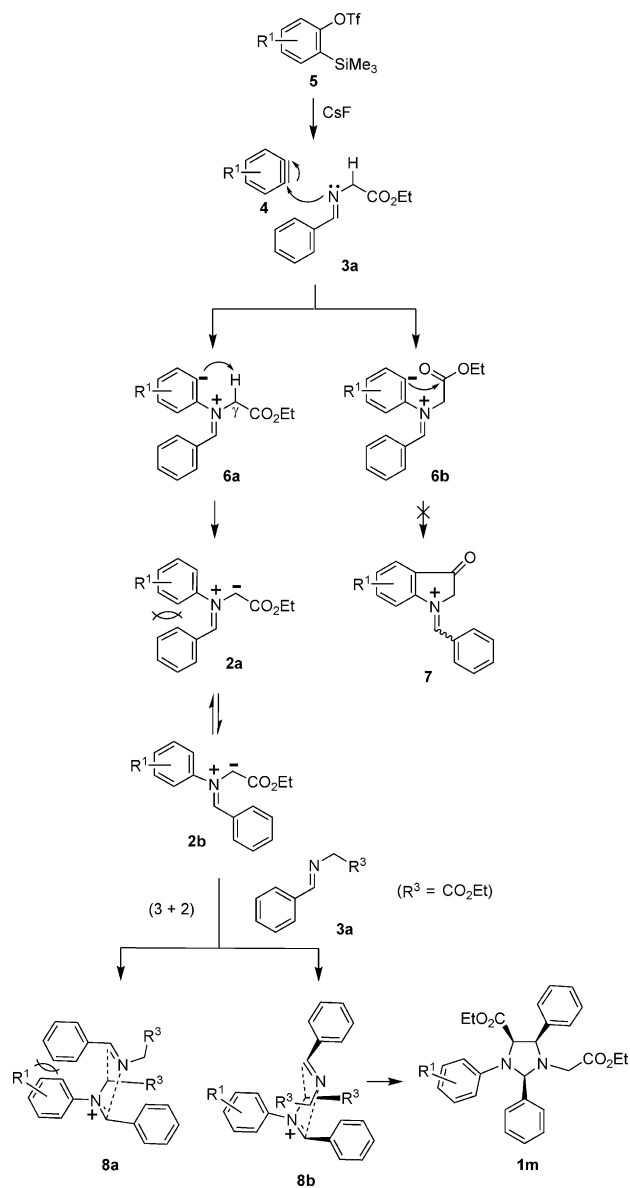
The key to the success of the aryne-induced 1,3-cycloaddition was the generation of required arynes under mild conditions by the fluoride displacement of the trimethylsilyl group in triflates **5**. The use of CsF was crucial and this should not be replaced by $n\text{Bu}_4\text{NF}$. Attempts to perform the same reaction to generate arynes by use of other methods^[28] that involve various strong bases or higher temperatures have failed. Such methods included eliminations from aryl halides with NaNH_2 , from 1,2-dibromobenzene with $n\text{BuLi}$, from 1,2-bromofluorobenzene with magnesium metal, and from arene-diazonium-2-carboxylates with heat. Additionally, symmetric aryne **5** was used as shown in Table 1 to prevent the formation of regioisomeric mixtures.

The structures of all new imidazolidines were identified on the basis of their spectroscopic characteristics. For example, the exact mass of compound **1g** was measured as 491.2183 for $(M+H)^+$, which is very close to its theoretical value of 491.2182 ($\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_6+H$)⁺. Its ^1H NMR spectrum included a doublet with $J=8.4$ Hz at 4.48 ppm for the MeO_2CCHN proton and a doublet with the same coupling constant at 5.01 ppm for the PhCHN proton on the ring. Two singlets appeared at 3.79 and 3.78 ppm for the two methoxy groups in separate benzene rings. A characteristic singlet associated with the NCHN proton resonated at 5.41 ppm. The ^{13}C NMR spectrum of **1g** showed a peak at 79.46 ppm for the hemiaminal carbon (NCN). A DEPT-90 was also used to detect the methine (NCN) carbon, which was observed as a positive signal.^[29] Meanwhile, the ^{13}C NMR spectrum exhibited two peaks in the downfield region at 172.23 and 170.76 ppm, corresponding to the two $-\text{CO}_2-$ carbons. Its IR

spectrum showed a strong absorption band at 1743 cm^{-1} , which was associated with the stretching vibration of $\text{C}=\text{O}$ in the alkoxycarbonyl groups.

The imidazolidine products possessed three stereogenic centers, so up to four possible enantiomeric pairs of stereoisomers could be formed. For a conclusive verification of their stereo-configuration, the molecular framework of compound **1g** was obtained by single-crystal X-ray diffraction analysis (Figure 1). Its monoclinic crystals (m.p 168–169°C, dichloromethane) possessed the space group $P2_1$ with $a=10.628(2)\text{ Å}$, $b=18.617(4)\text{ Å}$, $c=12.955(3)\text{ Å}$, $\alpha=90^\circ$, $\beta=105.512(7)^\circ$, and $\gamma=90^\circ$. Its X-ray data reveal that all of the three substituents, comprising one COOMe and two $p\text{-(MeO)Ph}$ groups, that were attached to the three non-epimerizable carbons of the heterocyclic five-membered ring were in *cis* orientation.

When a Schiff base with an alkoxycarbonyl group at its α position was used as the starting material, the imidazolidine



Scheme 3. A plausible mechanism for the “single-flask” synthesis of imidazolidines by aryne-induced cycloaddition reaction.

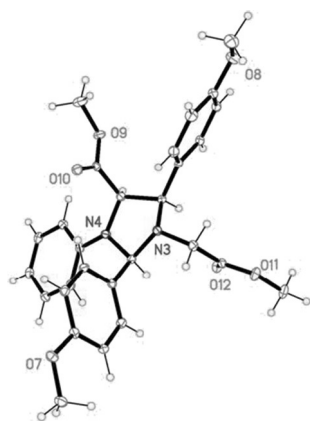


Figure 1. ORTEP diagram of compound **1g** as determined by X-ray analysis.

with *cis* configuration was generated as the exclusive product (**1a–k**). When a Schiff base with a cyano group (e.g., **3h**) was used, the imidazolidine **1l** was produced as the major product in 70 % yield along with its C5 epimer as the by-product in 6 % yield. The ratio of the amount of these *endo/exo* products was 11.7:1. The diversity in diastereoselectivity may arise from the steric effect of these two groups. Schiff bases with a small cyano group may form two conformational isomers of an azomethine ylide; the major form is U-shaped and the minor form is S-shaped.^[14] Both forms would react with the second equivalent of the same Schiff base in situ.

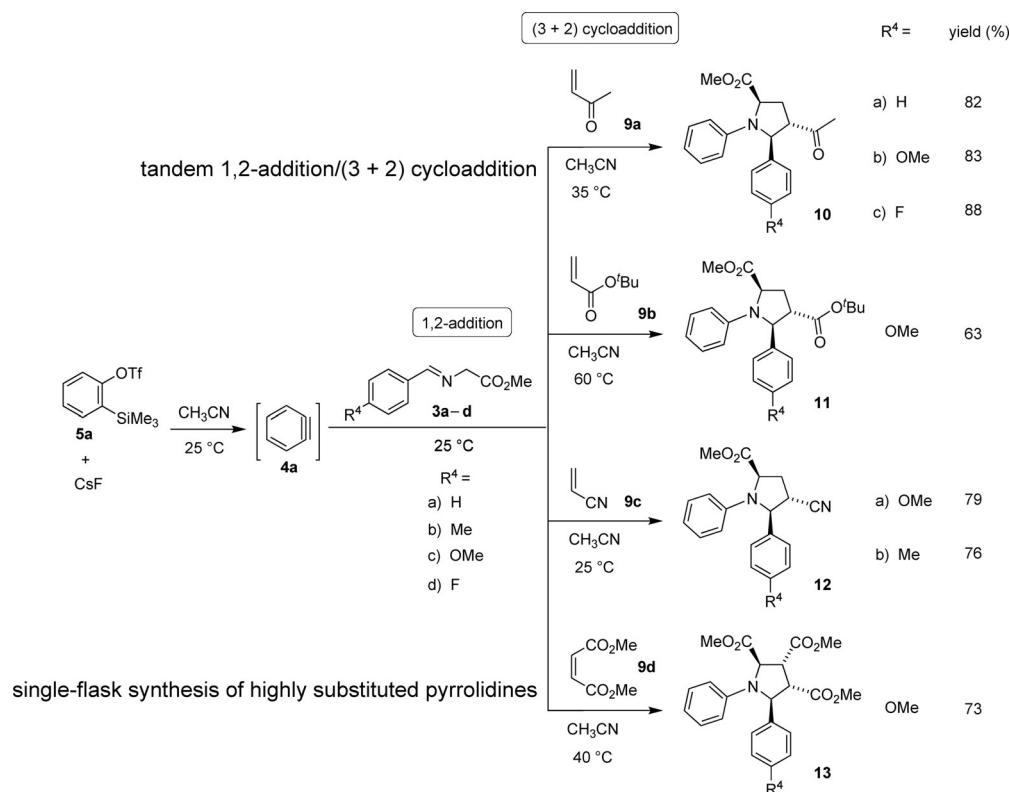
Arynes often undergo [4+2] cyclization reactions with furan^[7,30] and thiophene.^[31,32] Such cycloaddition in this study did not compete with the desired (3+2) cycloaddition as shown in Scheme 2. The isolation of products **1j** and **1k** in good yields (Table 1) manifests the wide applicability of this novel reaction that was initiated by arynes.

Scheme 3 presents a plausible mechanism by which arynes **4** can function as “initiators” of heterocyclic ring formation. After they are generated by the 1,2-elimination of silylphenyl triflates **5** with CsF,^[33] arynes **4** first act as electrophiles^[2,34] to react with the Schiff bases **3a**. Then the nucleophilic aryl carbanionic center in the resultant betaines **6a** abstracts an acidic proton at the γ position^[35] to form ylides **2a**. In this reaction, no by-products were detected resulting from the indoxyl intermediates

7. Thus an intramolecular cyclization between the carbanionic center of **6b** and the ethoxycarbonyl group nearby^[36] (i.e., **6b**→**7**) did not take place. Steric congestion between the two phenyl groups in ylides **2a** with the *cis* configuration caused their isomerization to the *trans* isomers **2b**.^[37] Then a regio-selective^[10] (3+2) cycloaddition takes place between azomethine ylides **2b** and the second equivalent of Schiff bases **3a** in situ. The transition state **8b** is believed to be more thermodynamically stable than **8a** because of steric congestion existing in the latter. The remarkably high degree of *endo* stereocontrol and excellent diastereofacial discrimination^[16,20,38] of the transition state **8b** cause the imidazolidines **1m** to be generated as the exclusive products.

The new single-flask reactions shown in Scheme 2 were successfully extended to examples with dipolarophiles that were different from the Schiff bases. As depicted in Scheme 4, various electron-deficient alkenes including methyl vinyl ketone (**9a**), *tert*-butyl acrylate (**9b**), acrylonitrile (**9c**), and dimethyl maleate (**9d**), were allowed to react with the azomethine ylides that were generated from the Schiff bases **3a–d** and benzyne (**4a**). Performance of these sequential tandem 1,2-addition followed by (3+2) cycloaddition reactions in acetonitrile at 25–60 °C led to the desired pyrrolidines **10–13** in 63–88 % yields. Stereo-configuration of these multi-substituted adducts was determined with the aid of NMR spectroscopy and X-ray crystallography.

The new tandem reactions shown in Schemes 2 and 4 exhibit four advantages: 1) The starting materials—arynes, Schiff bases with various substituents, and electron-deficient alkenes—are readily available. 2) Imidazolidines and pyrro-



Scheme 4. Benzyne-induced 1,2-addition followed by 1,3-dipolar cycloaddition for the synthesis of pyrrolidines from α -silylphenyl triflates **5a**, Schiff bases **3**, and electron-deficient alkenes **9**.

lidines are frequently generated in a highly stereoselective manner with all substituents attached to the carbon atoms. 3) The reaction generates the products in good yields under mild conditions. 4) The entire process is a “single-flask” reaction that can be easily conducted; isolation of intermediates is unnecessary.

In conclusion, a new and efficient method was developed for the direct synthesis of various imidazolidines from two equivalents of Schiff bases and one equivalent of 2-(trimethylsilyl)aryl triflates. It involves an aryne-induced ylide formation, which proceeded through an addition followed by proton transfer. Subsequent (3+2) cycloaddition with the same Schiff base produced imidazolidines in situ under mild conditions in good to excellent yields. Furthermore, the scope of this unprecedented reaction was broadened to the synthesis of highly substituted pyrrolidines in a single flask. It involved tandem 1,2-addition to an aryne, formation of azomethine ylide from a Schiff base, and a (3+2) cycloaddition to an alkene. The appealing antiviral activities of heterocyclic products against emerging and neglected viral infections will be reported in due course.

Keywords: 1,3-dipolar cycloaddition · arynes · azomethine ylides · imidazolidines · pyrrolidines

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