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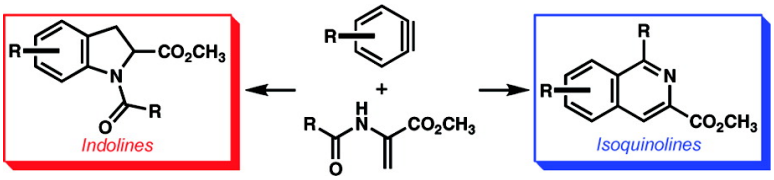

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Orthogonal Synthesis of Indolines and Isoquinolines via Aryne Annulation

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Aryne cycloaddition reactions have a long history dating back to early reports of Diels−Alder reactions[1] and [2+2] cyclodimerizations.[2,3] Additionally, aryne cyclizations have proved to be an exceptional method for gaining metal-free access to heterocyclic molecules.[4,5] On the basis of our recent success in the area of benzyne C−C insertion reactions,[6] we sought to develop a series of aryne annulations using readily available *N*-acyl dehydroamino esters. Herein, we report two orthogonal addition reactions that directly produce either indolines or isoquinolines by reaction of arynes with differentially substituted enamines (Scheme 1). Given the prevalence of these heterocycles within countless bioactive molecules, this methodology will provide new avenues toward substances relevant to the advancement of human medicine.

Our initial investigations focused on implementing *N*-carbamoyl dehydroalanine esters in the annulation reactions. These substrates, when reacted with silyl aryl triflates[7] in the presence of fluoride sources, produced an indoline adduct arising from a formal [3+2] cycloaddition (Table 1).[8,9] Optimization of standard reaction parameters identified $Bu_4NPh_3SiF_2$ (TBAT) and THF as the best fluoride source and solvent, respectively.

Importantly, the reaction produces a range of substituted indolines (entries 1−3) by reaction of *O*-*t*-Bu carbamate substrates with symmetrical and nonsymmetrical aryne precursors.[10,11] Moreover, a dehydrophenylalanine derivative proved competent under the reaction conditions, affording the corresponding 1,2,3-trisubstituted indoline as a single isolated diastereomer (entry 4). Interestingly, an unexpected cis stereochemical relationship is observed, which suggests that protonation occurs from the less-hindered face of the adduct enolate, anti to the bulky β-substituent. Although the formation of these products suffers generally from modest yields, our reaction provides a rapid and straightforward synthesis of functionalized indolines by a direct addition process.[12]

Upon discovering that carbamate derivatives could produce formal [3+2] cycloadducts, we broadened our search to include other dehydroamino esters, specifically enamide variants (Table 2). Again, an addition reaction occurred between the aryne and the enamine derivative; however, in this case the adduct was an isoquinoline.[13] This product arises via a [4+2] addition reaction between the *N*-acyl enamine and aryne followed by dehydrative aromatization.[14] Under optimized conditions (TBAT, THF, 23 °C, 6 h), reaction of benzyne and *N*-acetyl dehydroalanine ester produced methyl 1-methylisoquinoline-3-carboxylate in 87% yield (entry 1). We have found the scope of this reaction to be quite broad and have successfully synthesized a range of structurally diverse, polyfunctionalized isoquinoline derivatives. Notably, this reaction tolerates a variety of substitution α to the amide carbonyl, including alkyl (entries 1−5), aryl (entry 6), and several heteroatom-functionalized alkyl groups (entries 7−9). Importantly, alkyl substituents can be added in place of an ester on the enamine moiety (entries 10, 11). In fact, the enamine may even be incorporated within a carbocycle, providing access to a number of tricyclic isoquinoline derivatives (entries 12−15).[15]

Scheme 1.

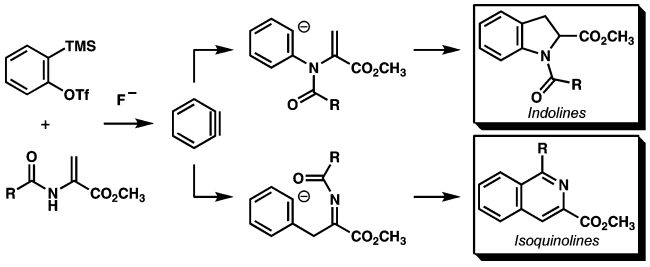
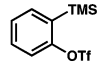
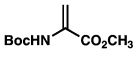
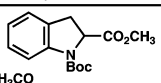
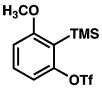
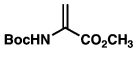
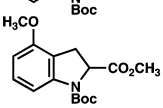
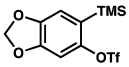
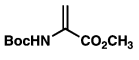
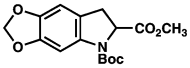
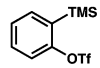
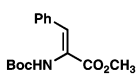
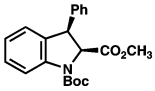


Table 1. Synthesis of Indolines[a]

entry	silyl aryl triflate	ene carbamate	product	yield
1				61%
2				49% [b]
3				39%
4				40%

[a] Performed by treating 2.0 mmol silyl aryl triflate and 1.0 mmol ene carbamate with TBAT (2.0 mmol) in THF (50 mL) at 23 °C for 6 h. [b] Isolated as a 2.3:1 mixture of 4- and 7-methoxyindolines.

In order to probe the effect of aryne substitution on reactivity, methyl 2-acetamidoacrylate was added to a variety of functionalized arynes to produce 6-, 7-, and 8-substituted isoquinolines (Table 3). Interestingly, ortho-functionalized arynes bearing the inductively electron-withdrawing methoxy substituent provided a single product (entry 1).[10,11] In the case of a meta methyl aryne, the product was observed as a 1:1 mixture of isomers (entry 2). Finally, electron-rich (entries 3, 4) and electron-poor (entry 5) arynes each perform well in the reaction and provide ready access to functionalized isoquinolines.

Having developed this powerful condensation reaction for generating isoquinolines, we sought to demonstrate its utility in a rapid total synthesis of papaverine[16] (Scheme 2), a clinically used non-narcotic antispasmotic agent that is a biosynthetic precursor of several pavine natural products and one of the four major constituents of opium.[17] Our synthesis began with the condensation of homoveratric acid (**1**) and serine methyl ester·HCl (**2**), followed by elimination to provide *N*-acyl enamine **3**.[18] In the key step, enamide **3** undergoes dehydrative addition to the aryne produced from silyl aryl triflate **4** to furnish isoquinoline **5** in 70% yield. Last, saponification and thermal decarboxylation[19] afforded papaverine (**6**) in 29% overall yield in three steps from commercially available materials, marking the shortest reported synthesis of this important alkaloid.[20,21]

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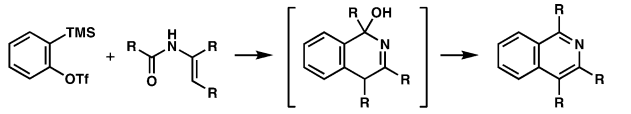
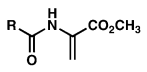
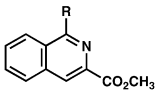
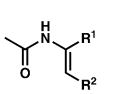
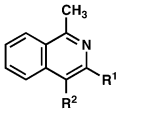
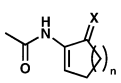
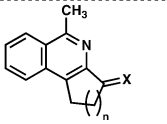
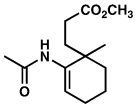
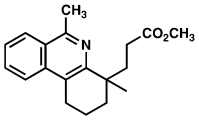
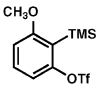
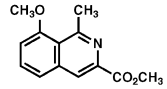
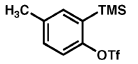
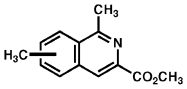
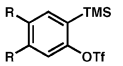
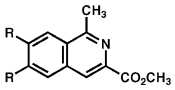
Table 2. Synthesis of Isoquinolines from 2-(TMS)phenyl Triflate[a]



entry	substrate	product		yield
1			R = CH_3	87%
2			R = *n*-Bu	76%
3			R = cyclohexyl	65%
4			R = *i*-Pr	66%
5			R = Bn	72%
6			R = Ph	55%
7			R = CF_3	57%
8			R = CO_2CH_3	51%
9			R = CH_2OCH_3	68%
10			R^1 = Et, R^2 = CH_3	72%
11			R^1 = *t*-Bu, R^2 = H	83%
12			n = 1 X = H_2	66%
13			n = 2 X = H_2	67%
14			n = 2 X = O	66%
15				71%

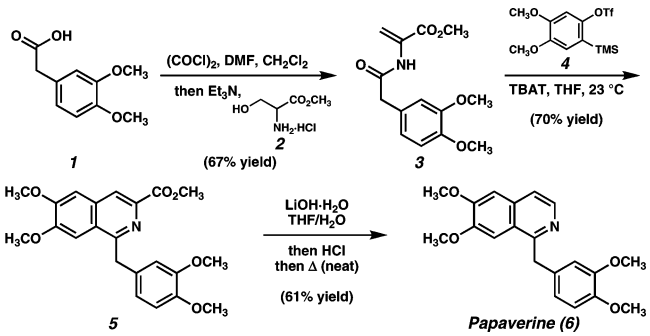
[a] Performed by treating 2.0 mmol 2-(TMS)phenyl triflate and 1.0 mmol enamide with TBAT (2.0 mmol) in THF (100 mL) at 23 °C for 6−8 h.

Table 3. Isoquinoline Synthesis from Methyl 2-Acetamidoacrylate[a]

entry	substrate	product		yield
1				66%
2				59% (1:1)
3			R = $O(CH_2)O$	63%
4			R = OCH_3	60%
5			R = F	78%

[a] Performed by treating 2.0 mmol silyl aryl triflate and 1.0 mmol enamide with TBAT (2.0 mmol) in THF (100 mL) at 23 °C for 6−8 h.

Scheme 2. Total Synthesis of Papaverine



In summary, we have developed a direct, metal-free, and divergent process for the synthesis of diversely substituted indolines and isoquinolines by the coupling reaction of *N*-acyl dehydroamino esters with arynes. This methodology exploits orthogonal modes of reactivity displayed by differentially substituted enamine derivatives in the presence of arynes. Finally, we have applied this chemistry to a concise total synthesis of the opiate alkaloid papaverine. The utilization of this methodology in more complex settings is currently underway in our laboratories and will be reported in due course.

Acknowledgment. The authors thank Abbott, Amgen, Bristol-Myers Squibb, Merck, and Caltech for generous funding.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Decarboxylated products of this type (e.g., **6**) constitute those originally targeted in the *N*-vinyl acetamide case (see ref 15), thereby circumventing the undesired ene reactivity previously displayed by these substrates.

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