A Facile Route to *H*-Pyrazolo[5,1-*a*]isoquinolines through a Multicomponent Reaction of 2-Alkynylbenzaldehyde, Sulfonylhydrazine, and Benzyne

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Abstract: A facile and efficient route for the generation of *H*-pyrazolo[5,1-*a*]isoquinolines via a silver triflate catalyzed three-component reaction of 2-alkynylbenzaldehyde, tosylhydrazine, and benzyne is reported. This reaction proceeds smoothly under mild conditions with high efficiency.

Key words: 2-alkynylbenzaldehyde, benzyne, *H*-pyrazolo[5,1-*a*]isoquinoline, silver triflate, tosylhydrazine

Great advances have been in the use of metal salts as catalysts to facilitate chemical transformations.[1] It is well recognized that metal catalysis has historically dominated organic synthesis, although organocatalysis has been developed over the last decade.[2] Extensive efforts have been made to understand of the properties of metals and the applications of their versatile reactivity patterns in various transformations.

Diversity-oriented synthesis is a known strategy in the drug discovery process,[3] and multicomponent reactions[4] are a powerful tool for the preparation of libraries of small molecules. A wide range of advantages offered by multicomponent reactions, such as a high degree of atom economy, convergence, ease of execution, and access to complex molecules, have now been identified. Therefore, it would be attractive to construct complex small molecules using multicomponent reactions.

As a privileged scaffold, pyrazole derivatives are found broadly in lead drug identification and drug discovery programs, such as cyclooxygenase inhibitors (e.g., SC-558, tepoxalin, and celecoxib) and cannabinoid-1 inverse agonists, which are very promising for reducing obesity (e.g., rimonabant).[5] Some derivatives of fused heterocycles containing a pyrazole framework, such as *H*-pyrazolo[5,1-*a*]isoquinolines, also exhibited remarkable biological activity for the inhibition of CDC25B, TC-PTP, and PTP1B.[6] Thus, efforts have been made to synthesize *H*-pyrazolo[5,1-*a*]isoquinoline derivatives. So far, there are several approaches for the construction of the skeleton of *H*-pyrazolo[5,1-*a*]isoquinoline.[6–9] One convenient route starts from an *N*′-(2-alkynylbenzylidene)hydrazide,[7] which could be easily accessed by condensation of 2-alkynylbenzaldehyde with a sulfonylhydrazine; during the tandem process, isoquinolinium-2-ylamide was demonstrated to be the key intermediate.

It is known that aryne is a highly reactive species and it is readily generated in situ from 2-(trimethylsilyl)aryl triflate in the presence of a fluoride source. A wide range of heterocycles and carbocycles have been constructed using aryne as the starting material.[10] Moreover, excellent reactivity has been shown when aryne is used as a dipolarophile in 1,3-dipolar cycloaddition reactions.[11] As mentioned above, isoquinolinium-2-yl amide is readily formed from *N*′-(2-alkynylbenzylidene)hydrazide via a 6-*endo* cyclization catalyzed by a suitable Lewis acid or promoted by electrophiles, and *N*′-(2-alkynylbenzylidene)hydrazide is produced from the reaction of 2-alkynylbenzaldehyde with a sulfonylhydrazine. Prompted by these results and the advancement of aryne chemistry, we anticipated that aryne could participate in a reaction of 2-alkynylbenzaldehyde **1** with a sulfonylhydrazine. As shown in Scheme 1, in the presence of silver(I) catalyst and fluoride source, isoquinolinium-2-yl amide **A** would react with the aryne via a [3+2] cycloaddition to afford compound **B**; subsequent aromatization would give the corresponding *H*-pyrazolo[5,1-*a*]isoquinolines.

Initial studies focused on the model reaction of 2-alkynylbenzaldehyde **1a** and tosylhydrazine with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2**) in the presence of 10 mol% of silver triflate at room temperature. The results of the preliminary screening are presented in Table 1. The target product **3a** was obtained in 41% yield when the reaction was performed in 1,2-dichloroethane in the presence of cesium fluoride (entry 1). A better yield was observed when benzyltriethylammonium chloride (25 mol%) was added as an additive (entry 2). Different solvents were subsequently screened. It was found that toluene and ethanol were not suitable for this transformation (entries 3 and 4), leading to either a low yield, or a trace amount of the desired product. In contrast, the yields dramatically improved when acetonitrile, tetrahydrofuran, or 1,4-dioxane were used as the solvent (entries 5–7). Grati-

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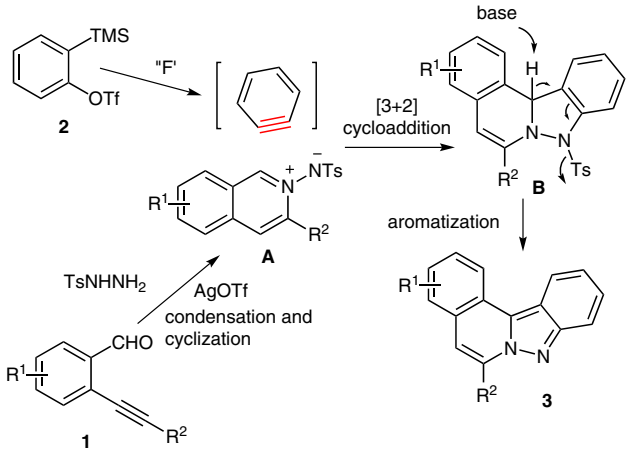
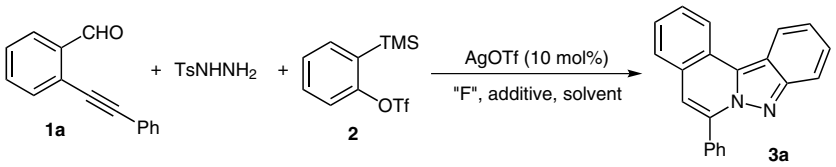


Scheme 1 A proposed route to *H*-pyrazolo[5,1-*a*]isoquinolines through a three-component reaction

fyingly, the use of a mixed solvent, 1,4-dioxane–acetonitrile, gave the best 86% yield (entry 8), while other combinations of solvents only provided relatively low yields of **3a** (entries 9–11). However, using potassium fluoride or tetrabutylammonium fluoride as the fluoride source instead of cesium fluoride to promote the generation of benzyne did not improve the yield (entries 12 and 13). Moreover, reducing the amount of the additive (Et_3NBnCl) from 25 mol% to 10 mol% also resulted in lower yield (entry 14).

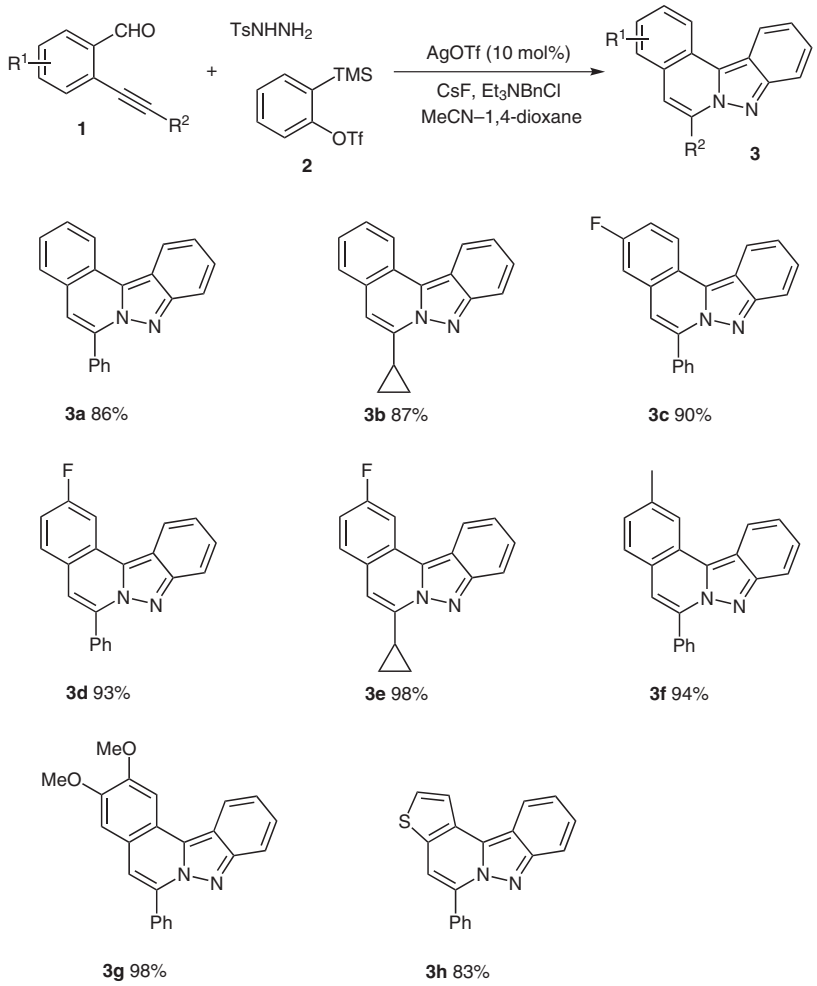
With the optimized conditions in hand, we next explored the scope of this three-component reaction of 2-alkynylbenzaldehyde, tosylhydrazine, and benzyne. The results are summarized in Scheme 2. It was found that the substituents on the aromatic ring, such as fluoro, methyl, and methoxy, were well tolerated in the reactions, giving the corresponding products **3c–g** in good to excellent yields. When substrate with heteroaromatic ring (thienyl group) was employed in the transformation, the corresponding product **3h** was obtained in 83% yield. Additionally, substrates **1** bearing a cyclopropyl substituent on the triple bond worked efficiently under the standard conditions, producing the expected products of **3b** and **3e** in 87% and 98% yields, respectively. This result indicated that the cyclopropyl group is also compatible with these conditions. The structures of all the products were unambiguously characterized by NMR and HRMS. Moreover, the structure of compound **3g** was further confirmed by X-ray single crystal diffraction (Figure 1).[12]

Table 1 Initial Studies for the Three-Component Reaction of 2-Alkynylbenzaldehyde **1a**, Tosylhydrazine, and Benzyne **2**



Entry	'F'	Additive	Solvent	Yield[b] (%)
1	CsF	–	DCE	41
2	CsF	Et_3NBnCl	DCE	52
3	CsF	Et_3NBnCl	toluene	18
4	CsF	Et_3NBnCl	EtOH	trace
5	CsF	Et_3NBnCl	MeCN	70
6	CsF	Et_3NBnCl	THF	72
7	CsF	Et_3NBnCl	1,4-dioxane	71
8	CsF	Et_3NBnCl	1,4-dioxane–MeCN	86
9	CsF	Et_3NBnCl	THF–MeCN	70
10	CsF	Et_3NBnCl	1,4-dioxane–CH_2Cl_2	50
11	CsF	Et_3NBnCl	1,4-dioxane–DMF	64
12	KF	Et_3NBnCl	1,4-dioxane–MeCN	58
13	TBAF	Et_3NBnCl	1,4-dioxane–MeCN	75
14[c]	CsF	Et_3NBnCl	1,4-dioxane–MeCN	72

[a] Reaction conditions: 2-alkylbenzaldehyde **1a** (0.3 mmol), $TsNHNH_2$ (0.3 mmol), benzyne precursor **2** (0.45 mmol), AgOTf (10 mol%), 'F' source (3 equiv), additive (25 mol%), solvent (3.0 mL).
[b] Isolated yield based on 2-alkynylbenzaldehyde **1a**.
[c] In the presence of 10 mol% of additive.



Scheme 2 Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines through a three-component reaction of 2-alkynylbenzaldehyde, tosylhydrazine, and benzyne

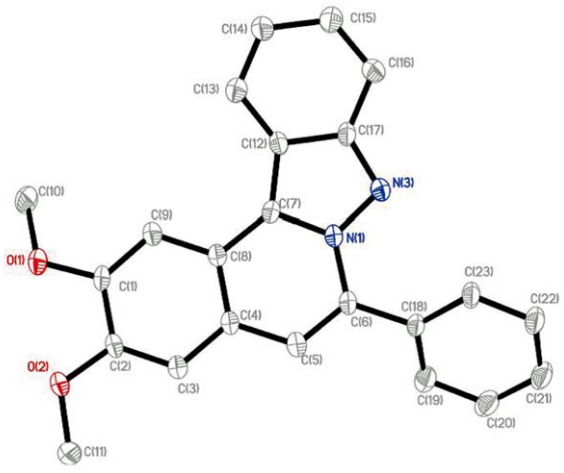


Figure 1 ORTEP illustration of compound **3g** (30% probability ellipsoids)

In conclusion, we have provided a facile and efficient route for the generation of *H*-pyrazolo[5,1-*a*]isoquinolines via a silver triflate catalyzed three-component reaction of 2-alkynylbenzaldehyde, tosylhydrazine, and benzyne. This reaction proceeds smoothly under mild conditions with high efficiency, producing the corresponding products in good to excellent yields.

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr at 25–35°C. Nuclear magnetic resonance (NMR) spectra are quoted in ppm on the δ scale with tetramethylsilane as the internal standard; coupling constants are quoted in Hz. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. High-resolution mass spectrometry (HRMS) was carried out using a micrOTOF II instrument.

Silver Triflate Catalyzed Three-Component Reaction of 2-Alkynylbenzaldehyde 1, Tosylhydrazine, and Benzyne 2; General Procedure

2-Alkynylbenzaldehyde **1** (0.3 mmol) was added to a solution of $TsNHNH_2$ (0.3 mmol) in 1,4-dioxane (1.0 mL). The mixture was stirred at r.t. for 30 min. Then AgOTf (7.7 mg, 10 mol%) was added

and the mixture was heated to 70 °C with vigorous stirring for 1 h. Subsequently, benzyne precursor **2** (0.45 mmol, 1.5 equiv), CsF (0.9 mmol, 3.0 equiv), Et_3NBnCl (0.075 mmol, 0.25 equiv), and MeCN (2.0 mL) were added. The mixture was stirred vigorously at 50 °C until completion of the reaction. The mixture was diluted with EtOAc (5.0 mL), and quenched with H_2O (5.0 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) to provide the desired product **3**.

6-Phenylindazolo[3,2-*a*]isoquinoline (3a)
Yellow solid; yield: 75.8 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 7.6 Hz, 1 H), 7.34 (s, 1 H), 7.47–7.56 (m, 5 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.92–7.97 (m, 3 H), 8.41 (d, *J* = 8.2 Hz, 1 H), 8.62 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.8, 116.9, 117.7, 121.2, 121.5, 122.7, 125.7, 127.2, 127.6, 128.2, 128.6, 129.6, 129.8, 131.5, 134.1, 138.4, 148.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}N_2$: 295.1235; found: 295.1247.

6-Cyclopropylindazolo[3,2-*a*]isoquinoline (3b)
White solid; yield: 67.3 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.93 (m, 2 H), 1.23–1.30 (m, 2 H), 2.84–2.91 (m, 1 H), 6.88 (s, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.1 Hz, 1 H), 7.49–7.54 (m, 2 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 8.02 (d, *J* = 8.7 Hz, 1 H), 8.34 (d, *J* = 8.7 Hz, 1 H), 8.49 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 12.0, 110.8, 116.9, 117.4, 121.2, 121.3, 122.5, 124.8, 126.9, 127.2, 127.3, 128.4, 131.0, 140.8, 148.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2$: 259.1235, found: 259.1247.

3-Fluoro-6-phenylindazolo[3,2-*a*]isoquinoline (3c)
White solid; yield: 84.2 mg (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.28 (m, 2 H), 7.36–7.54 (m, 6 H), 7.89–7.95 (m, 3 H), 8.30 (d, *J* = 8.2 Hz, 1 H), 8.54–8.55 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.2 (d, $^2J_{CF}$ = 22 Hz), 115.9, 116.3, 117.1 (d, $^2J_{CF}$ = 24 Hz), 117.8, 120.9, 121.6, 122.4, 124.9 (d, $^3J_{CF}$ = 9 Hz), 127.4, 128.6, 129.8, 129.9, 130.2 (d, $^3J_{CF}$ = 9 Hz), 131.2, 133.7, 139.4, 149.0, 161.3 (d, $^1J_{CF}$ = 247 Hz).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{14}FN_2$: 313.1141; found: 313.1147.

2-Fluoro-6-phenylindazolo[3,2-*a*]isoquinoline (3d)
Yellow solid; yield: 87.0 mg (93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.25 (m, 2 H), 7.32–7.39 (m, 2 H), 7.43–7.54 (m, 4 H), 7.88–7.93 (m, 3 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 8.49–8.50 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.2 (d, $^2J_{CF}$ = 21 Hz), 115.9, 116.3, 117.1 (d, $^2J_{CF}$ = 24 Hz), 117.8, 120.8, 121.6, 122.4, 124.9 (d, $^3J_{CF}$ = 9 Hz), 127.4, 128.6, 129.8, 129.9, 130.2 (d, $^3J_{CF}$ = 9 Hz), 131.2, 133.7, 139.4, 148.9, 161.3 (d, $^1J_{CF}$ = 247 Hz).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{14}FN_2$: 313.1141; found: 313.1144.

6-Cyclopropyl-2-fluoroindazolo[3,2-*a*]isoquinoline (3e)
Yellow solid; yield: 81.1 mg (98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.89 (m, 2 H), 1.20–1.25 (m, 2 H), 2.79–2.86 (m, 1 H), 6.66 (s, 1 H), 7.15–7.23 (m, 3 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 8.7 Hz, 1 H), 8.11 (d, *J* = 8.7 Hz, 1 H), 8.24–8.28 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8, 11.8, 109.5, 109.6, 111.3 (d, $^2J_{CF}$ = 21 Hz), 116.1 (d, $^2J_{CF}$ = 24 Hz), 116.3, 117.4, 120.9, 121.2, 124.5 (d, $^3J_{CF}$ = 9 Hz), 127.3, 129.9 (d, $^3J_{CF}$ = 9 Hz), 130.4, 141.9, 148.8, 161.1 (d, $^1J_{CF}$ = 248 Hz).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_2$: 277.1141; found: 277.1145.

2-Methyl-6-phenylindazolo[3,2-*a*]isoquinoline (3f)
Yellow solid; yield: 86.9 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 7.21–7.26 (m, 3 H), 7.43–7.56 (m, 5 H), 7.90–7.94 (m, 3 H), 8.29 (s, 1 H), 8.37 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 116.8, 116.9, 117.6, 121.2, 122.2, 125.8, 126.5, 127.1, 127.4, 128.5, 128.9, 129.5, 129.8, 131.2, 134.2, 137.5, 138.3, 148.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2$: 309.1392; found: 309.1402.

2,3-Dimethoxy-6-phenylindazolo[3,2-*a*]isoquinoline (3g)
White solid; yield: 104.1 mg (98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 4.13 (s, 3 H), 7.16 (s, 1 H), 7.24–7.30 (m, 2 H), 7.48–7.56 (m, 4 H), 7.90–7.98 (m, 4 H), 8.33 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 56.2, 103.1, 107.5, 115.9, 116.2, 117.4, 120.4, 120.6, 120.8, 123.8, 127.1, 128.5, 129.3, 129.7, 131.2, 134.3, 136.7, 149.0, 149.7, 150.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_2$: 355.1447; found: 355.1450.

5-Phenylthieno[3′,2′:3,4]pyrido[1,2-*b*]indazole (3h)
Yellow solid; yield: 74.7 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 7.3 Hz, 1 H), 7.42–7.43 (m, 1 H), 7.52–7.57 (m, 6 H), 7.89 (d, *J* = 8.7 Hz, 1 H), 7.99 (d, *J* = 7.3 Hz, 2 H), 8.17 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.4, 114.8, 116.7, 120.4, 120.5, 124.0, 127.1, 128.0, 128.1, 128.6, 128.8, 129.5, 129.7, 131.1, 134.2, 137.2, 149.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{13}N_2S$: 301.0799; found: 301.0813.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are experimental procedure, characterization data, and ^{1}H and ^{13}C NMR spectra of compounds **3**.

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