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Synthesis of Isoquinoline Derivatives via Ag-Catalyzed Cyclization of 2-Alkynyl Benzyl Azides

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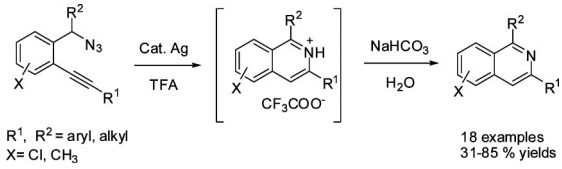

Ag-catalyzed cyclization of 2-alkynyl benzyl azides offers a novel and efficient method for the synthesis of substituted isoquinoline. The reaction proceeds smoothly in moderate to good yields and tolerates considerable functional groups. The reaction conditions and the scope of the process are examined, and a plausible mechanism is proposed.

The isoquinoline derivatives play an important role in organic chemistry, not only as key structural units in many natural products,[1] but also as building blocks in important pharmaceuticals.[2] Isoquinoline species are also utilized as chiral ligands for transition metal catalysts,[3] and their iridium complexes are used in organic light-emitting diodes.[4] For these reasons, the efficient synthesis of isoquinoline ring system continues to attract the interest of synthetic chemists.[5] The traditional approaches for the synthesis of the isoquinoline ring system, including the Bischler−Napieralski,[6] the Pictet−Spengler,[7] and the Pomeranz−Fritsch[8] reactions, have been frequently employed in the total synthesis of isoquinoline alkaloids. However, all the reactions usually required either harsh conditions or tedious reaction procedures. Over the last two decades, there has been growing interest to develop mild and efficient syntheses of isoquinoline. For instance, Pfeffer,[9] Heck,[10] and Widdowson[11] have reported palladium methodology to synthesize substituted isoquinolines. These syntheses utilize a stoichiometric amount of palladium salts, which is not very practical in organic synthesis. Later, Larock and co-workers developed a palladium catalytic revision, using the *tert*-butylamine, 2-iodobenzaldehydes, and alkynes (or allenes) as starting materials, to synthesize a wide variety of 3,4-disubstituted isoquinolines.[12] In addition, the transition metal chemistry focusing on isoquinoline synthesis has been expanded by exploring other elements, such as Ni,[13] Zr,[14] Rh,[15] and Cu.[16] Due to the importance of isoquinoline derivatives in organic chemistry, the development of new synthetic approaches with various reaction conditions remains an active research area.

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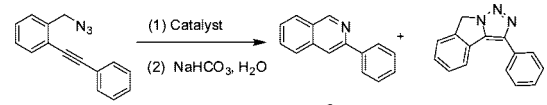
On the other hand, silver(I) complexes are generally used as stoichiometric oxidants for the oxidation of various organic or inorganic substrates. Many reports used silver(I) complexes as catalysts in oxidation or group-transfer reactions.[17,18d] Although recent studies have shown that silver species exhibited interesting catalytic activities functioning as a transition metal catalyst,[18,19] silver "catalysts" in a "transition metal" sense are commonly considered to have low efficiency and not to be as good as other late transition metals. Recently, Yamamoto's group reported the iodine-mediated electrophilic cyclization of 2-alkynyl benzyl azides into the corresponding 1,3,4-trisubstituted isoquinolines.[20] In our ongoing efforts to develop novel and efficient methodologies for the synthesis of heterocyclic compounds promoted by transition metal catalysts,[21] we herein wish to report that Ag-catalyzed cyclization of 2-alkynyl benzyl azides can produce the 3-substituted or 1,3-disubstituted isoquinolines.

Initially, we tested the reaction of substrate 1-(azidomethyl)-2-(phenylethynyl)benzene **1a** with 20 mol % of $AgSbF_6$ in 1,2-dichloroethane (DCE) at 80 °C, and the desired product **2a** was formed in 34% yield after 24 h (Table 1, entry 1). To our delight, when the reaction was run in the presence of 1 equiv of CF_3COOH (TFA), the more satisfactory result was observed, and the product was isolated in 55% yield (Table 1, entry 2). By increasing the amount of TFA to 2 equiv, a significant change occurred and the yield was 65% (Table 1, entry 3). Common protic acids such as acetic acid, TsOH, and chloroacetic acid have also been examined under the same condition, and no better results were obtained (Table 1, entries 4−6). Changing the catalyst to AgOTf, $AgBF_4$, CF_3COOAg, and CH_3COOAg, failed to improve the yield of the product **2a** (Table 1, entries 7−10). Other transition metals were also investigated for this cyclization. However, for the reactions of **1a** with $PtCl_2$, $PtCl_4$, $Cu(OTf)_2$, CuOTf, $AuCl_3$, and $PdCl_2$, no desired product **2a** was observed (Table 1, entries 11−16). The solvent effect on the cyclization reaction was then evaluated. This process revealed that solvents played a significant role in the formation of isoquinoline. In all solvents we examined, 1,2-dichloroethane is superior. The reactions can proceed in weak polar solvents such as toluene and benzene, although only 18% and 15% yields were observed, respectively (Table 1, entries 17 and 18). Disappointingly, none of product **2a** was obtained in acetonitrile, THF, or MeOH (Table 1, entries 19−21). Presumably, those solvents coordinated with silver catalyst to generate complexes, which decreased the catalytic activity of silver salt. The temperature also is a key factor in this catalytic reaction. The studies showed that the preferred temperature for the reaction was 80 °C. When the reaction was conducted in 1, 2-dichloroethane at 60 °C, only 42% product was obtained, even though the reaction was prolonged to 50 h (Table 1, entry 22). By increasing the temperature to 90 °C, a lower yield of 50% was observed along with the Huisgen 1,3-dipolar cycloaddition product **3a** in 25% yield (Table 1, entry 23).[22] A reduced yield was also observed when the loading of $AgSbF_6$ was lowered (Table 1, entry 24). From these results, the role of TFA in the reaction was doubted. Thus, the reaction without adding catalyst in the presence of TFA was examined. However, no desired isoquinoline was obtained (Table 1, entry 25). Thus, we chose the following reaction conditions as optimum for all subsequent cyclizations: 0.25 mmol of 2-alkynyl benzyl azides, 20 mol % of $AgSbF_6$, and 0.50 mmol of TFA in DCE were stirred at 80 °C for an appropriate amount of time.

With the optimized conditions in hand, the scope of this reaction was then investigated, and the results are summarized in Table 2. The scope of this reaction is quite general. When R^1 was a phenyl with an electron-donating $-CH_3$ group (Table 2, entries 2−4), the yields of **2** were higher than those substrates

TABLE 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	catalyst	additive	temp (°C)	solvent	yield **2a** (**3a**)
1	$AgSbF_6$	none	80	DCE	34 (0)
2	$AgSbF_6$	TFA[b]	80	DCE	55 (0)
3	$AgSbF_6$	TFA	80	DCE	65 (0)
4	$AgSbF_6$	CH_3COOH	80	DCE	36 (0)
5	$AgSbF_6$	TsOH	80	DCE	39 (0)
6	$AgSbF_6$	$ClCH_2COOH$	80	DCE	45 (0)
7	AgOTf	TFA	80	DCE	55 (0)
8	$AgBF_4$	TFA	80	DCE	49 (0)
9	CF_3COOAg	TFA	80	DCE	40 (0)
10	CH_3COOAg	TFA	80	DCE	5 (0)
11	$PtCl_2$	none	80	DCE	0 (0)
12	$PtCl_4$	none	80	DCE	0 (0)
13	$Cu(OTf)_2$	none	80	DCE	0 (0)
14	CuOTf	none	80	DCE	0 (0)
15	$AuCl_3$	none	80	DCE	0 (0)
16	$PdCl_2$	none	80	DCE	0 (0)
17	$AgSbF_6$	TFA	80	toluene	18 (0)
18	$AgSbF_6$	TFA	80	benzene	15 (0)
19	$AgSbF_6$	TFA	reflux	THF	0 (0)
20	$AgSbF_6$	TFA	reflux	CH_3CN	0 (0)
21	$AgSbF_6$	TFA	reflux	MeOH	0 (0)
22	$AgSbF_6$	TFA	60	DCE	42[c] (0)
23	$AgSbF_6$	TFA	90	DCE	50 (25)
24	$AgSbF_6$[d]	TFA	80	DCE	51 (0)
25	none	TFA	80	DCE	0 (0)

[a] Reaction conditions: unless indicated otherwise, all reactions were run by employing 0.25 mmol of **1a** in the presence of 20 mol % of catalysts and 2 equiv of additives in 3 mL of solvent at the indicated temperature for 24 h. [b] The reaction employed 1 equiv of TFA. [c] The reaction was run for 50 h. [d] The reaction was run by employing 10 mol % of $AgSbF_6$.

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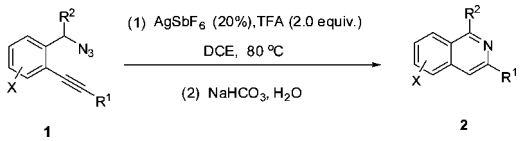
TABLE 2. Cyclization Reaction Catalyzed by $AgSbF_6$[a]

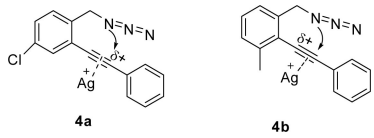


1 2

entry	substrate 1	R^1	R^2	X	product 2	yield (%)
1	**1a**	Ph	H	H	**2a**	65
2	**1b**	4-$CH_3C_6H_4$	H	H	**2b**	75
3	**1c**	3-$CH_3C_6H_4$	H	H	**2c**	78
4	**1d**	2-$CH_3C_6H_4$	H	H	**2d**	72
5	**1e**	4-ClC_6H_4	H	H	**2e**	56
6	**1f**	3-ClC_6H_4	H	H	**2f**	62
7	**1g**	2-ClC_6H_4	H	H	**2g**	60
8	**1h**	4-$CH_3COC_6H_4$	H	H	**2h**	48
9	**1i**	4-$CH_3OOCC_6H_4$	H	H	**2i**	46
10	**1j**	pentyl	H	H	**2j**	57
11	**1k**	R^{1b}	H	H	**2k**	55
12	**1*l***	Ph	H	Cl	**2*l***	80
13	**1m**	pentyl	H	Cl	**2m**	78
14	**1n**	3-$CH_3C_6H_4$	H	Cl	**2n**	85
15	**1o**	Ph	H	3-CH_3	**2o**	31
16	**1p**	Ph	ethyl	H	**2p**	60
17	**1q**	Ph	butyl	H	**2q**	63
18	**1r**	Ph	Ph	H	**2r**	76

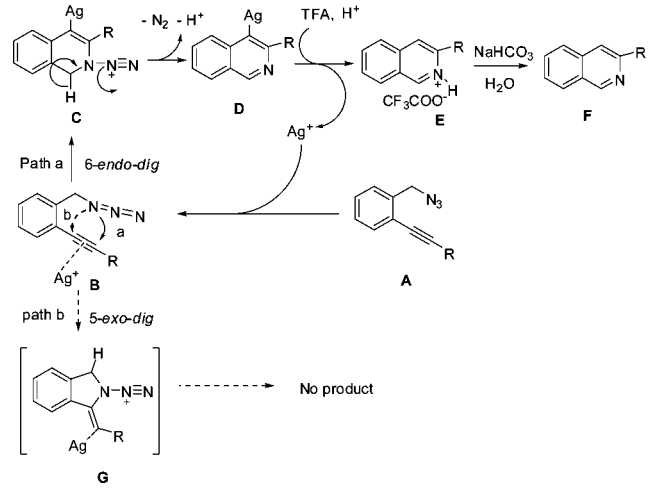
[a] Reaction conditions: unless indicated otherwise, all reactions were run by employing 0.25 mmol of **1a** in the presence of 20 mol % of $AgSbF_6$ and 0.50 mmol of TFA in 3 mL of DCE at 80 °C. [b] R^1 = CH_2O-(4-$CH_3OOCC_6H_4$).

SCHEME 1. Explanation of the Electronic Effects of the Substituents on the Aromatic Ring



with electron-withdrawing groups such as −Cl, $-COCH_3$, or $-COOCH_3$ (Table 2, entries 5−9). As can be seen, the position of the substituent on R^1 had only a slight influence in the yield of the products (Table 2, entries 2−4 and 5−7). Cyclization still proceeds when the terminus of the carbon−carbon triple bond is substituted by an alkyl group. Thus, 3-pentylisoquinoline **2j** can be synthesized in a moderate yield by the cyclization of benzyl azides **1j** (Table 2, entry 10). The reaction also proceeded smoothly when the $-CH_2O$-(4-$CH_3OOCC_6H_4$) substituent was introduced on the alkyne terminus. Therefore, substrate **1k** was successfully converted to methyl 4-(isoquinolin-3-ylmethoxy)-benzoate in 55% yield (Table 2, entry 11). We were also interested in investigating substituents on the aromatic ring. Introducing an electron-withdrawing Cl− group onto the aromatic ring significantly increased the yields to 85% (Table 2, entries 12−14). However, when the electron-donating CH_3- group was used, the yield of desired product was lowered to only 31% (Table 2, entry 15). The electronic effect of substituents on the aromatic ring can be explained as shown in Scheme 1. For intermediate **4a**, the positive charge on the alkyne carbon bearing the phenyl ring is better stabilized, and therefor closure to a six-membered ring and formation of the isoquinoline product are favored. For intermediate **4b**, more of the partial positive charge is located on the alkyne carbon bearing the (2-(azidomethyl)-6-methyl)phenyl ring, which disfavors the formation of a six-membered ring and results in a decrease in yield.

SCHEME 2. A Plausible Mechanism for the Formation of Isoquinolines



We continued to elucidate the scope of the reaction by replacing the hydrogen atom at the R^2 position with ethyl and phenyl groups (Table 2, entries 16−18). The reactions of **1p** and **1q** having aliphatic substituents at the R^2 position proceeded smoothly and gave the desired 1,3-disubstituted isoquinolines **2p** and **2q** in 60% and 63% yields (Table 2, entries 16 and 17), respectively. Very interestingly, in the case of R^2 changing as phenyl group (Table 2, entry 18), the more satisfactory result was obtained in 76% yield.

From the results shown in Tables 1 and 2, the reactions showed very high regioselectivity. Only the six-membered-ring isoquinoline from 6-*endo-dig* cyclization was obtained, and no five-membered exocyclic product was detected by TLC monitoring from the reaction mixture (Scheme 2, path b). Presumably, the reaction via 6-*endo-dig* cyclization can produce stable product and undergo a similar mechanism, which has been supported in the literature.[20]

On the base of the above results, we propose the following plausible mechanism for this process (Scheme 2, path a): (i) the alkynyl moiety of **A** is coordinated to the silver catalyst to generate complex **B**, (ii) the nitrogen atom undergoes regioselective attack at the electron-deficient triple bonds via 6-*endo-dig* cyclization, leading to the intermediate **C**, (iii) the intermediate **C** loses N_2 and H^+ and the organosilver isoquinoline **D** is formed, (iv) **D** then undergoes subsequent reaction with TFA and H^+ to afford isoquinoline salt **E** and to regenerate the silver catalyst, which enters the next catalytic cycle, and (v) finally, **E** reacts with saturated $NaHCO_3$ to afford the corresponding isoquinoline **F**.

In summary, we have described a novel and efficient method for the synthesis of substituted isoquinoline via Ag-catalyzed cyclization of 2-alkynyl benzyl azides. The reaction proceeds smoothly in moderate to good yields and tolerates considerable functional groups. Further application of the methodology to synthesize some natural alkaloids and pharmaceutical compounds is in progress in our laboratory and the results will be reported in due course.

Experimental Section

General Produce for the Silver-Catalyzed Cyclization of 2-Alkynyl Benzyl Azide. To a stirred solution of 2-alkynyl benzyl azides **1** (0.25 mmol) in 1,2-dichloroethane (3.0 mL) was added $AgSbF_6$ (17 mg, 20 mol %) and TFA (57 mg, 0.5 mmol) at 80 °C.

When the reaction was considered complete as determined by TLC analysis, saturated $NaHCO_3$ (15 mL) was added to the reaction mixture which was then stirred for 30 min. The mixtures were extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed with saturated NaCl solution (2 × 20 mL) and dried with Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography, eluting with hexanes/EtOAc (5:1) to affod pure **2.**

3-Phenylisoquinoline (2a): yield 33.4 mg (65%), white solid, mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1 H), 8.01−7.99 (d, J = 7.6 Hz, 2 H), 7.89 (s, 1 H), 7.81−7.79 (d, J = 8.4 Hz, 1 H), 7.69−7.67 (d, J = 8.0 Hz, 1 H), 7.53−7.49 (t, J = 7.2 Hz, 1 H), 7.42−7.36 (m, 3 H), 7.30−7.26 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.1, 139.5, 136.5, 130.4, 128.6, 128.4, 127.6, 127.4, 126.9, 126.7, 116.3; IR (KBr) 3352, 3033, 2925, 2854, 2251, 1624, 1584, 1452, 1279, 1199, 909, 883, 785, 760, 738, 686 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.79; H, 5.47; N, 6.75.

3-*p*-Tolylisoquinoline (2b): yield 41.2 mg (75%), white solid, mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1 H), 8.03−8.00 (m, 3 H), 7.94−7.92 (d, J = 8.4 Hz, 1 H), 7.82−7.79 (d, J = 8.4 Hz, 1 H), 7.65−7.61 (t, J = 7.6 Hz, 1 H), 7.54−7.50 (t, J = 7.6 Hz, 1 H), 7.30−7.28 (d, J = 8.0 Hz, 2 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.1, 138.3, 136.7, 136.6, 130.3, 129.4, 127.5, 127.4, 126.8, 126.7, 126.7, 115.8, 21.2; IR (KBr) 3053, 3032, 2914, 2856,1914, 1623, 1584, 1565, 1448, 1281, 1196, 943, 884, 822, 744 cm^{-1}. Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.59; H, 6.04; N, 6.43.

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Supporting Information Available: Experimental procedure, characterization details, and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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