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Gold-catalyzed synthesis of isoquinolines via intramolecular cyclization of 2-alkynyl benzyl azides

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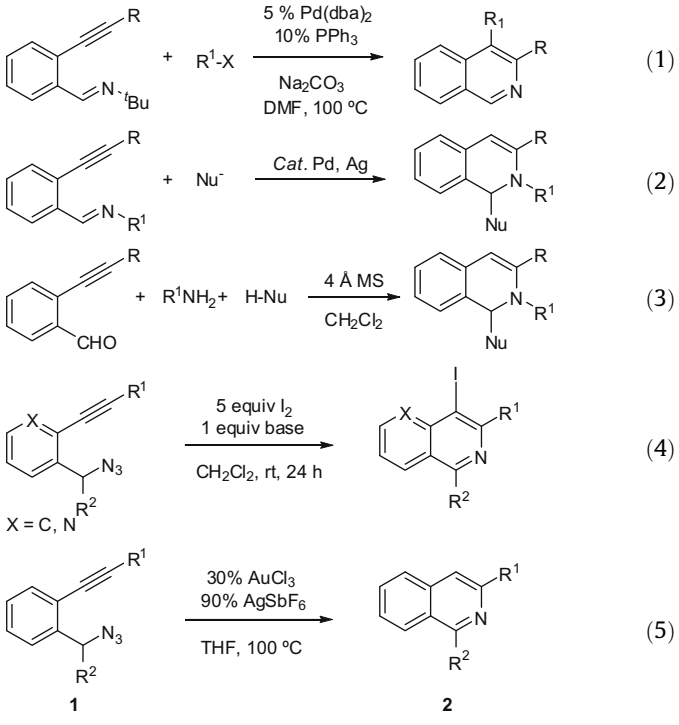
ABSTRACT

Intramolecular cyclization of 2-alkynyl benzyl azides in the presence of $AuCl_3$ and $AgSbF_6$ in THF under a pressured vial at 100 °C gives the corresponding isoquinolines in good yields. Similarly, the five-membered analogs afford the corresponding isoquinolines.

Isoquinolines are an important class of alkaloids and many biologically active natural products contain the isoquinoline framework.[1] Their biological activities have made them useful in pharmaceutical compounds, and their physical properties make them beneficial as functional materials.[2] Furthermore, they are utilized as chiral ligands for transition metal catalysts.[3] Accordingly, a number of synthetic methods for isoquinolines have been developed. For example, (1) classic methods such as the Pomeranz–Fritsch,[4] Bischler–Napieralski,[5] and Pictet–Spengler[6] reactions, although all have considerable drawbacks such as the use of strong acids and elevated temperatures, and (2) transition metal-catalyzed synthesis of substituted isoquinolines from phenylacetylene substrates (Eq. 1).[7] These reactions have proven to be extremely efficient in the synthesis of a wide variety of isoquinolines. However, the development of additional synthetic methods is still highly desirable.

Recently, we reported the synthesis of 1,2-dihydroisoquinolines via palladium- or AgOTf-catalyzed direct addition of nucleophiles to *o*-alkynylarylaldimines (Eq. 2).[8] Asao et al. reported the three-component coupling reaction with *ortho*-alkynylbenzaldehydes, primary amines, and pronu-cleophiles in the presence of molecular sieves (Eq. 3).[9] More recently, we reported an entirely new method for the synthesis of 1,3,4-trisubstituted isoquinolines through iodine-mediated electrophilic cyclization of 2-alkynyl benzyl azides (Eq. 4).[10] It occurred to us that cyclization of **1** may take place using coinage metal catalysts. Herein, we report that the gold-catalyzed intramolecular cyclization of 2-alkynyl benzyl azides **1** using $AuCl_3$ and $AgSbF_6$ in THF at 100 °C gives isoquinolines **2** in good yields (Eq. 5).



(1) (2) (3) (4) (5)

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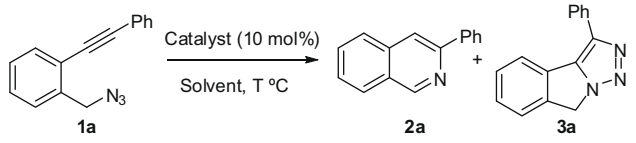
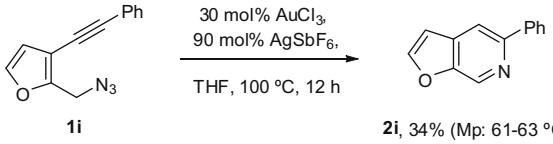
Table 1
Effect of catalysts and solvents on formation of isoquinoline **2a** from **1a**[a]



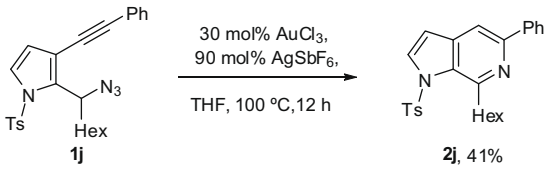
Entry	Catalyst	Time (h)	Solvent	Yield[b] of (%)		
				2a	**3a**	**1a**
1	$AgSbF_6$	12	DCE	30	55	10
2	$AgNTf_2$	12	DCE	28	37	8
3	AgOTf	12	DCE	32	33	10
4	$In(OTf)_3$	12	DCE	0	94	0
5	$Cu(OTf)_2$	12	DCE	0	90	0
6	TfOH	3	DCE	0	97	0
7	$PtBr_2$	7	DCE	10	80	5
8	$AuCl/AgSbF_6$	12	DCE	31	46	6
9	$AuCl_3/AgSbF_6$	12	DCE	36	38	0
10	$AuCl_3/AgSbF_6$	5	DCE	(43)	0	0
11	$AuCl_3/AgSbF_6$	5	CH_3NO_2	(48)	0	0
12	$AuCl_3/AgSbF_6$	12	Toluene	31	18	0
13	$AuCl_3/AgSbF_6$	12	1,4-Dioxane	31	20	0
14	$AuCl_3/AgSbF_6$	12	CH_3CN	28	34	0
15	$AuCl_3/AgSbF_6$	12	THF	(52)	(18)	0
16[c]	$AuCl_3/AgSbF_6$	12	THF	(67)	0	0
17[c,d]	$AuCl_3/AgSbF_6$	24	THF	58	10	0

[a] The reaction of **1a** in a pressured vial was carried out in the presence of the catalyst at reflux (entries 1–10) and at 100 °C (entries 11–16).
[b] ^1H NMR yield was determined using CH_2Br_2 as an internal standard. Isolated yield is shown in parentheses.
[c] 30 mol % $AuCl_3$/90 mol % $AgSbF_6$ was used.
[d] Reaction temperature was 80 °C.

Initially, we tested the reaction of substrate **1a** in order to optimize the reaction conditions, and the results are summarized in Table 1. Treatment of azide **1a** with 10 mol % of silver catalysts in 1,2-dichloroethane (DCE) at reflux for 12 h gave a mixture of the desired product **2a** and triazole **3a** (entries 1–3). Other Lewis acid and protic acid catalysts, such as $In(OTf)_3$, $Cu(OTf)_2$, and TfOH, were ineffective for the production of **2a**, instead, only triazole **3a** was obtained in high yields (entries 4–6). Surprisingly, $PtBr_2$,[11] which was reported as an effective catalyst for the synthesis of isoquinolines, gave only trace amounts of the product **2a** along with triazole **3a** in 80% NMR yield (entry 7). The use of $AuCl/AgSbF_6$ and $AuCl_3/AgSbF_6$, afforded **2a** in moderate yields (entries 8 and 9). Increasing the catalyst loading up to 20 mol % enhanced the yield of **2a** (entry 10). Various solvents such as CH_3NO_2, toluene, 1,4-dioxane, CH_3CN, and THF, instead of 1,2-dichloroethane (DCE), were examined; we found that THF gave the best result among the solvents tested and the product **2a** was obtained in 52% yield along with triazole **3a** in 18% yield (entries 11–15). To our delight, increasing the amount of catalyst gave the best result, the product was obtained in 67% yield without formation of **3a** (entry 16). Decreasing the reaction temperature led to a lower yield of the product even after prolonged reaction time (entry 17).

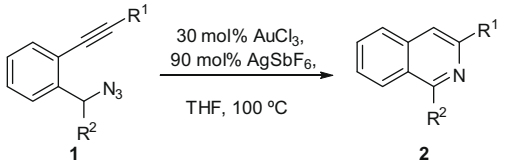


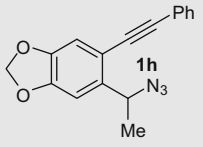
(6)



(7)

Table 2
Gold-catalyzed synthesis of isoquinolines **2**[a]

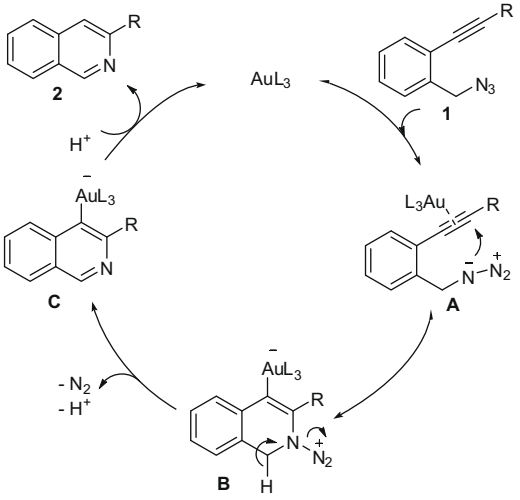


Entry	R^1		R^2	Product **2**	Yield[b] of **2** mp (°C)
1	Ph	**1a**	H	**2a**	67 (97–98)
2	*p*-$MeOC_6H_4$	**1b**	H	**2b**	80 (97–99)
3	*n*-Butyl	**1c**	H	**2c**	77
4	1-Cyclohexenyl	**1d**	H	**2d**	59 (104–106)
5	Ph	**1e**	OAc	**2e**	36
6	Ph	**1f**	Hex	**2f**	60
7	Ph	**1g**	Ph	**2g**	51
8				**2h**	48 (92–93)

[a] The reaction of **1** (0.2 mmol) in the presence of 30 mol % $AuCl_3$ and 90 mol % $AgSbF_6$ was carried out at 100 °C in THF under a pressured vial for 12 h.
[b] Isolated yield.

The scope of the intramolecular cyclization of 2-alkynyl benzyl azides **1** is summarized in Table 2.[12] An arylacetylene bearing a methoxy group on the aromatic ring afforded the corresponding cyclized product **2b** in 80% yield (entry 2). The reactions of substrates having *n*-butyl and 1-cyclohexenyl groups at the alkyne terminus, under the standard conditions, proceeded smoothly to give the desired products **2c** and **2d**, respectively, in good yields (entries 3 and 4). For secondary azides, the yields of the isoquinolines **2e–g** were lower than those of the primary azides (entries 5–7). Azide **1h** gave the corresponding isoquinoline **2h** in 48% yield (entry 8). With five-membered heterocyclic derivatives, the cyclization proceeded similarly, although the yields of the desired products were lower than those of the corresponding six-membered derivatives; the furan and pyrrole substrates **1i** and **1j** gave the products **2i** and **2j** in 34% and 41% yields, respectively (Eqs. 6 and 7).

A plausible mechanism for the gold-catalyzed cyclization of **1** is shown in Scheme 1. Initially, coordination of the triple bond of **1** to the gold catalyst enhances the electrophilicity of the alkyne to gen-



Scheme 1. A plausible mechanism for the formation of **2**.

erate intermediate **A**, and subsequent nucleophilic attack of the nitrogen atom on the electron-deficient alkyne forms the intermediate **B**. Elimination of N_2 and H^+ forms **C**. Protonolysis of **C** then results in the formation of isoquinoline **2** and regenerates the gold catalyst.

In conclusion, we have developed an efficient method for the synthesis of isoquinolines from 2-alkynyl benzyl azides. The cyclization proceeds very smoothly in the presence of $AuCl_3$ and $AgSbF_6$. Further studies to extend the scope of this procedure are in progress in our laboratory.

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12. *General procedure for the synthesis of isoquinoline* **2a** *from 2-alkynyl benzyl azide* **1a**: To a THF (2 mL, 0.1 M) solution of $AuCl_3$ (18.2 mg, 0.06 mmol) and $AgSbF_6$ (61.8 mg, 0.18 mmol) which were weighed in a glove box, was added 2-alkynyl benzyl azide **1a** (46.6 mg, 0.2 mmol) at room temperature under an Ar atmosphere in a pressured vial. The mixture was stirred at 100 °C for 12 h. The reaction progress was monitored by TLC (hexane/ethyl acetate; 2:1). After consumption of **1a**, the reaction mixture was cooled to room temperature and filtered through a short Florisil pad using ethyl acetate as eluent. After concentration, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate; 20:1–5:1) to afford product **2a** in 67% yield as a white solid (27.5 mg). Mp: 97–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.35 (s, 1H), 8.13 (d, J = 7.5 Hz, 2H), 8.08 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 152.3, 151.1, 139.2, 136.4, 130.3, 128.6, 128.4, 127.6, 127.4, 126.8, 126.6, 126.5, 116.0; IR (KBr) 3346, 2859, 1626, 1455, 684 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{11}NNa$ ([M+Na]$^+$) 228.0784. Found 228.0783.
Data for **3a**. See: Chowdhury, C.; Mandal, S. B.; Achari, B. *Tetrahedron Lett.* **2005**, *46*, 8531.