Transition-Metal Catalysis

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Gold(I)-Catalyzed Annulation of Salicylaldehydes and Aryl Acetylenes as an Expedient Route to Isoflavanones**

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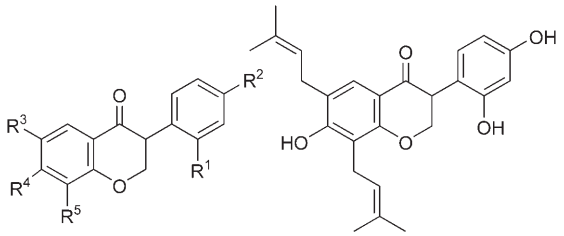
Isoflavanones are widely present in nature; the isoflavanone moiety is the key structural feature of many complex natural products, such as the pterocarpenoids and eriotrichin B (Scheme 1).[1] The classical methods for synthesizing isoflavanones are 1) the reduction of alkoxy isoflavones by using a complex metal hydride;[2,3] 2) the hydroboration of 3-phenylcoumarin or 4-hydroxy-3-phenylcoumarin followed by oxidation with chromic acid;[4] 3) Heck arylation of 4-acyloxy 2*H*-chromenes with aryl mercury(II) compounds in the presence of catalytic amounts of palladium acetate;[5] 4) the treatment of 2-hydroxyalkoxy deoxybenzoines with methylene iodide;[4] and 5) the Mannich reaction of 2-hydroxyalkoxy deoxybenzoines with paraformaldehyde in the presence of secondary amines, such as piperidine or dimethylamine, in boiling methanol.[6] However, these methods are limited by the use of expensive starting materials and, in some cases, toxic reagents.[5]

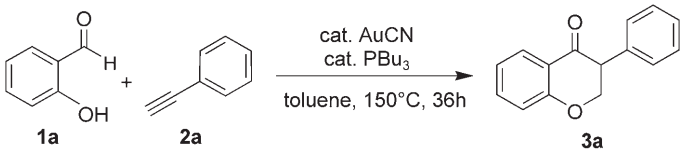


Isoflavanone structure Eriotrichin B

Scheme 1. The isoflavanone structure contained in many natural products, including eriotrichin B, a compound isolated from *Erythrina eriotricha*.[1b]

Gold catalysis has emerged recently as a powerful tool in synthesis.[7,8] For example, heterobicyclic molecules,[9] highly substituted pyrroles,[10] furans,[11] and chromanols[12] have been synthesized expediently by gold-based catalysis. A gold-catalyzed reaction has also been used as a key step in the total synthesis of angucyclinone antibiotics.[13] We have reported an efficient gold(III)-catalyzed multicomponent coupling that leads to propargylamines and benzylamines,[14] a highly efficient gold(III)-catalyzed annulation of phenols with dienes,[15a,c] and a gold(I)-catalyzed addition–cyclization cascade of terminal alkynes with *ortho*-alkynyl aryl aldehydes.[15b] Methodologies based on the reaction of C–H bonds provide more direct syntheses of complex molecules from relatively simple starting materials.[16] In 1997, Miura and co-workers reported a rhodium-catalyzed activation of the C–H bond of aldehydes.[17] Jun and co-workers have described rhodium-catalyzed hydroacylations of terminal olefins[18] and alkynes.[19]

Herein, we report a novel annulation of simple hydroxyaldehydes with alkynes under gold catalysis to give isoflavanone-type structures **3** directly and efficiently (Scheme 2). The isoflavanone derivative **3a** is a known compound. Its spectral data are consistent with those reported in the literature.[20] A doublet ($J = 7.1$ Hz) is observed in the ^{1}H NMR spectrum at $\delta = 4.68$ ppm for the two hydrogen atoms α to the oxygen atom of the ether group, and a triplet ($J = 7.1$ Hz) is observed at $\delta = 4.02$ ppm for the hydrogen atom α to the carbonyl group.



1a **2a** **3a**

Scheme 2. Gold-catalyzed annulation of salicylaldehyde with phenylacetylene.

In our initial studies, salicylaldehyde (**1a**) was treated with phenylacetylene (**2a**) under various conditions (Table 1). The inclusion of Au^{III}/PBu_3 as a potential catalyst combination led only to the recovery of starting material (Table 1, entries 1 and 2). With different ratios of Au^{I}/PBu_3 the desired product was formed in low to good yields (Table 1, entries 3–6 and 9–12). The best conditions found, which led to the isolation of **3a** in 78% yield, were the use of 1 mol% of an Au^{I} source and 25 mol% of PBu_3 (Table 1, entry 13). Finally, Au^{I} or PBu_3 alone provided none or only a trace amount of the desired product (Table 1, entries 7 and 8, respectively). When the alternative ligands triethylphosphane, tricyclohexylphosphane, and trimethylphosphane were used, the yield of the product decreased to 36, 19, and < 5%, respectively (Table 2, entries 2, 4, and 1). Among the organophosphine ligands examined for the annulation of hydroxyaldehydes with

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Table 1: The reaction of salicylaldehyde with phenylacetylene under various conditions.[a]

Entry	[b]	**1a** [mmol]	**2a** [mmol]	*t* [h]	*T* [°C]	Yield of **3a** [%][c]
1	$AuBr_3/PBu_3$ (10/50)	0.25	0.50	17	100	no reaction
2	$AuCl_3/PBu_3$ (10/50)	0.25	0.50	17	100	no reaction
3	AuI/PBu_3 (10/50)	0.25	0.50	17	100	11 (19)
4	$AuCl/PBu_3$ (10/50)	0.25	0.50	17	100	19 (69)
5	$AuCN/PBu_3$ (10/50)	0.25	0.50	17	100	21 (77)
6	$AuCN/PBu_3$ (10/50)	0.25	1.00	17	150	46 (75)
7	AuCN (10)	0.25	0.50	17	150	no reaction
8	PBu_3 (50)	0.25	0.50	17	150	trace (low)
9	$AuCN/PBu_3$ (10/50)	0.25	0.75	36	150	38 (98)
10	$AuCN/PBu_3$ (15/50)	0.25	0.75	36	150	38 (98)
11	$AuCN/PBu_3$ (1/50)	0.25	0.75	36	150	20 (98)
12	$AuCN/PBu_3$ (2.5/25)	0.25	0.75	36	150	66 (88)
13	$AuCN/PBu_3$ (1/25)	0.25	0.75	36	150	78 (81)
14	$AuCN/PBu_3$ (1/5)	0.25	0.75	36	150	< 5 (low)

[a] All reactions were conducted in a sealed tube in toluene (1 mL). [b] Catalyst combination and (in parentheses) amount of the components in mol%. [c] Based on ^{1}H NMR spectroscopic analysis with an internal standard; reaction conversion is shown in parentheses.

Table 2: The effect of various ligands on the gold-catalyzed annulation.[a]

Entry	Ligand (25 mol%)	Yield of **3** [%][b]
1	trimethylphosphane	< 5
2	triethylphosphane	36
3	tributylphosphane	78
4	tricyclohexylphosphane	19
5	tri-*tert*-butylphosphane	no reaction
6	triphenylphosphane	no reaction
7	tri-*o*-tolylphosphane	no reaction
8	tri-2-furylphosphane	no reaction
9	triphenyl phosphite	no reaction

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol, AuCN (1 mol%), ligand (25 mol%), toluene (1 mL); all reactions were carried out at 150°C for 36 h in a sealed tube under nitrogen. [b] Based on ^{1}H NMR spectroscopic analysis with an internal standard.

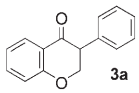
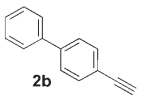
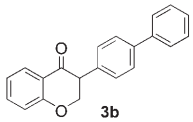
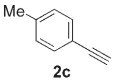
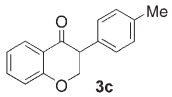
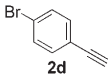
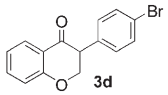
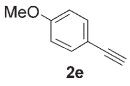
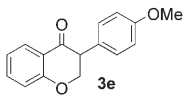
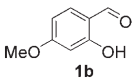
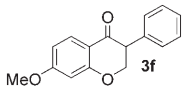
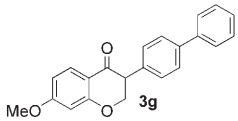
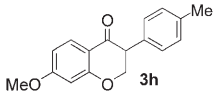
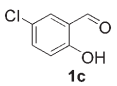
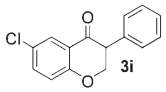
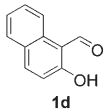
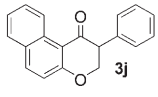
alkynes, PBu_3 appeared to be the most effective (Table 2, entry 3).

Subsequently, the reaction was examined with a range of substrates under the optimized conditions given in Scheme 2 (Table 3). The presence of a phenyl or electron-withdrawing substituent on the alkyne appears to be more beneficial (Table 3, entries 2 and 4) than the presence of an electron-donating substituent (Table 3, entries 3 and 5). On the other hand, no significant effect of substituents (H, MeO, Cl) on the hydroxyaldehyde was observed, and good yields were obtained in all cases. 2-Hydroxy-1-naphthaldehyde (**1d**) also reacted efficiently with **2a** to give the desired annulation product (Table 3, entry 10). The use of an aliphatic alkyne, 1-hexyne, under the same conditions led to the recovery of starting material.

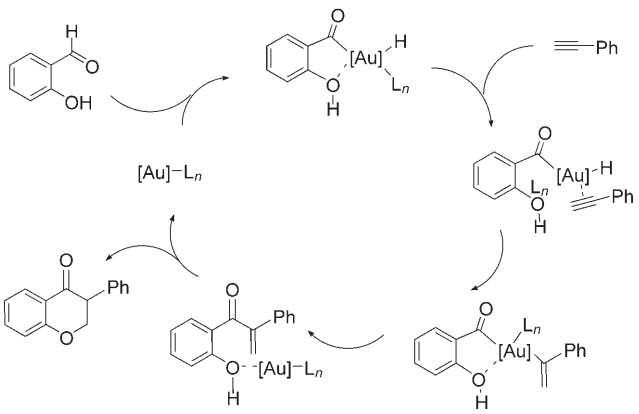
On the basis of the structure of compound **3a** as confirmed by ^{1}H NMR spectroscopy and thus the regioselectivity of the reaction, the following two mechanisms can be excluded: 1) initial reaction of the phenolic hydroxy group with the phenyl acetylene derivative (because the hydroxy group should add with Markovnikov regioselectivity, as reported by Yang and He:[21] the incorrect regioselectivity for the formation of compound **3a**); and 2) initial reaction of the terminal carbon atom of the alkyne with the aldehyde group, as described previously by us,[15b] followed by a Rupe[22] rearrangement to the α,β-unsaturated ketone and an intramolecular conjugate addition (because the phenyl substituent would then be β and not α to the carbonyl group). Thus, only a mechanism based on C–H activation of the aldehyde, possibly assisted by chelation, remains open to consideration.[19]

A tentative mechanism for the novel annulation is proposed in Scheme 3:

Table 3: Gold-catalyzed annulation of aldehydes with alkynes.[a]

Entry	Aldehyde	Alkyne	Product	Yield [%][b]
1	 **1a**	 **2a**	 **3a**	78 (75)
2	**1a**	 **2b**	 **3b**	73 (63)
3	**1a**	 **2c**	 **3c**	60 (57)
4	**1a**	 **2d**	 **3d**	71 (69)
5	**1a**	 **2e**	 **3e**	59 (55)
6	 **1b**	**2a**	 **3f**	75 (55)
7	**1b**	**2b**	 **3g**	65 (52)
8	**1b**	**2c**	 **3h**	75 (65)
9	 **1c**	**2a**	 **3i**	73 (65)
10	 **1d**	**2a**	 **3j**	70 (68)

[a] Reaction conditions: aldehyde (0.25 mmol), alkyne (0.75 mmol), AuCN (1 mol%), PBu_3 (25 mol%), toluene (1 mL); all reactions were carried out at 150°C for 36 h in a sealed tube under nitrogen. [b] Based on ^{1}H NMR spectroscopic analysis with an internal standard; the yield of the isolated product is shown in parentheses.



Scheme 3. Tentative mechanism for the gold-catalyzed annulation of salicylaldehyde with phenylacetylene.

Complexation of the gold(I) catalyst with salicylaldehyde followed by oxidative addition of the aldehyde C–H bond generates an acyl gold(III) hydride. This intermediate complexes with phenylacetylene, which undergoes hydrometalation. A subsequent conjugate addition of the hydroxy group to the α,β-unsaturated ketone now generated by reductive elimination gives the desired isoflavanone derivative and regenerates the gold catalyst. Alternatively, a gold–carbene intermediate[23] might be involved.

In conclusion, we have developed an annulation catalyzed by gold(I) of simple *o*-hydroxyaldehydes with alkynes. The annulation efficiently generates isoflavanone-type structures, which have many possible applications in the synthesis of isoflavanone natural products. Furthermore, this annulation incorporates all atoms in both starting materials into the product and thus has a theoretical atom economy of 100%.[24] The scope, mechanism, and synthetic applications of this reaction are under investigation in our laboratory.

Experimental Section

Typical procedure: A mixture of AuCN (0.6 mg, 0.0025 mmol), PBu_3 (15.4 μL, 0.0625 mmol), **1a** (26.6 μL, 0.25 mmol), and **2a** (82.5 μL, 0.75 mmol) in freshly distilled toluene (1 mL) was stirred in a sealed tube at 150 °C for 36 h under an atmosphere of nitrogen. The reaction mixture was then cooled to room temperature, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 15:1) to give **3a** ($R_f = 0.2$; 42 mg, 75%).

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[1] a) P. M. Dewich in *The Flavanoids: Advances in Research* (Ed.: J. B. Harborne, T. J. Mabry), Chapman and Hall, London, **1982**, pp. 535, 563, and 635; b) H. Wangensteen, M. Alamgir, S. Rajia, A.-B. Samuelsen, K.-E. Malterud, *Planta Med.* **2005**, *71*, 754–758.
[2] R. B. Bradbury, D. E. White, *J. Chem. Soc. I* **1953**, 871–876.
[3] K. H. Dudley, R. R. Corley, *J. Org. Chem.* **1967**, *32*, 2312–2317.
[4] B. S. Kirkiacharian, *J. Chem. Soc. Chem. Commun.* **1975**, 162–163.
[5] a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5535–5538; b) R. Saito, T. Isumi, A. Kasahara, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1776–1779.
[6] R. Gandhisadan, S. Neelakantan, P. V. Raman, *Synthesis* **1982**, 1110.
[7] A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150–7154; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990–6993; A. S. K. Hashmi, *Gold. Bull.* **2004**, *37*, 51–65.
[8] G. Dyker, *Angew. Chem.* **2000**, *112*, 4407–4409; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237–4242.
[9] L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963.
[10] D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261.
[11] a) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409–5412; b) M. H. Suhre, M. Reif, S. Kirsh, *Org. Lett.* **2005**, *7*, 3925–3927.
[12] Z. Shi, C. He, *J. Am. Chem. Soc.* **2004**, *126*, 5964–5965.
[13] K. Sato, N. Asao, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 8977–8981.
[14] a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585; b) Y. M. Luo, C.-J. Li, *Chem. Commun.* **2004**, 1930–1931.
[15] a) R.-V. Nguyen, C.-J. Li, *Org. Lett.* **2006**, *8*, 2397–2399; b) X. Yao, C.-J. Li, *Org. Lett.* **2006**, *8*, 1953–1955; c) X. Yao, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 6884–6885.
[16] a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770; c) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514.
[17] K. Kokubo, K. Matsumasa, M. Miura, M. Nomura, *J. Org. Chem.* **1997**, *62*, 4564–4565, and references therein.
[18] a) C.-H. Jun, H. Lee, J.-B. Hong, B.-I. Kwon, *Angew. Chem.* **2000**, *112*, 3214–3216; *Angew. Chem. Int. Ed.* **2000**, *39*, 3070–3072; b) C.-H. Jun, C.-W. Huh, S.-J. Na, *Angew. Chem.* **1998**, *110*, 150–152; *Angew. Chem. Int. Ed.* **1998**, *37*, 145–147; c) C.-H. Jun, K.-Y. Chung, J.-B. Hong, *Org. Lett.* **2001**, *3*, 785–787.
[19] C.-H. Jun, H. Lee, J.-B. Hong, B.-I. Kwon, *Angew. Chem.* **2002**, *114*, 2250–2251; *Angew. Chem. Int. Ed.* **2002**, *41*, 2146–2147.
[20] S. A. Ferrino, L. A. Maldonado, *Synth. Commun.* **1980**, *10*, 717–723.
[21] C.-G. Yang, C. He, *J. Am. Chem. Soc.* **2005**, *127*, 6966–6967.
[22] S. Swaminathan, K. V. Narayanan, *Chem. Rev.* **1971**, *71*, 429–438.
[23] a) D. Hildebrandt, G. Dyker, *J. Org. Chem.* **2006**, ASAP; b) H. H. Murray III, J. P. Fackler, Jr., D. A. Tocher, *J. Chem. Soc. Chem. Commun.* **1985**, *19*, 1278–1280, and reference [1a] cited therein; c) R. L. White-Morris, M. M. Olmstead, F. Jiang, D. S. Tinti, A. L. Balch, *J. Am. Chem. Soc.* **2002**, *124*, 2327–2336; d) S. K. Schneider, W. A. Herrmann, E. Herdtweck, *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363–2370; e) M. R. Fructos, T. R. Belderrain, P.-D. Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Angew. Chem.* **2005**, *117*, 5418–5422; *Angew. Chem. Int. Ed.* **2005**, *44*, 5284–5288.
[24] a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705.

