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Gold(I)-catalyzed stereoselective cyclization of *ortho* alkynyl benzaldehyde chromium complexes with nucleophiles

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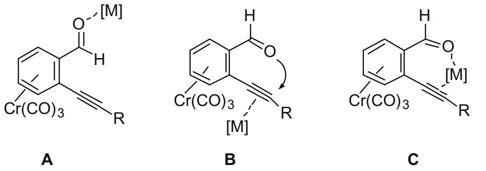
ABSTRACT

Gold(I)-catalyzed cyclization of *o*-alkynyl benzaldehyde chromium complexes gave stereoselectively 1-*anti*- and *syn*-functionalized 1*H*-isochromene chromium complexes, respectively, depending on the nature of nucleophiles. Enantiomerically pure *trans*- and *cis*-1,3-dimethylisochromans were stereoselectively prepared from a single planar chiral *o*-(1-propynyl)benzaldehyde chromium complex.

Oxygen and nitrogen heterocycles are common structural components of a wide range of naturally occurring and biologically active molecules.[1] The development of efficient methods for the synthesis of heterocyclic compounds is of central importance in organic synthesis. An attractive route to the functionalized heterocycles is via X–H bond of nitrogen or oxygen nucleophile across the carbon–carbon multibond. An activation of the triple bond is normally required for the achievement of this process. Thus, halogen,[2] ArSeBr,[2] Ipy_2BF_4[3] or transition metals[4] are employed for the activation of alkyne. Transition metal-catalyzed electrophilic activation of alkynes has attracted much attention as a useful method, and the generated metal-containing benzopyrylium-type intermediates is considered a common process, which upon further treatment with various partners, such as nucleophiles, alkynes, alkenes, and carbonyl compounds, result in diverse products.[5] In particular, gold has emerged as a powerful homogeneous catalyst for the electrophilic activation of alkynes, and has been demonstrated in useful organic transforming reactions.[6] However, the cyclized 1-functionalized heterocycles are normally obtained as achiral compounds by this methodology, although a chiral center is created. Directed toward the synthesis of optically active 1-functionalized-1*H*-isochromenes, we studied gold(I)-catalyzed electrophilic cyclization of planar chiral chromium complexes of *ortho* alkynyl benzaldehyde with nucleophiles.

In the case of tricarbonylchromium-complexed *o*-alkynyl benzaldehydes, the structure of the metal-coordinated intermediates is significant for a relative stereochemistry of the cyclized 1-functionalized 1*H*-isochromene tricarbonylchromium complexes. Three activation modes by the coordination with metal are devised (Fig. 1). In the transition state **A**, metal activates carbonyl group in which carbonyl oxygen is an *anti*-conformation with *ortho* alkyne substituent due to a steric interaction. On the other hand, the alkyne in the intermediate **B** is activated by metal giving metal-contained benzopyrylinium ion intermediate.[7] The transition state **C** has dual carbophilic and oxophilic activations[8] by metal such as $In(OTf)_3$ catalyst at the same time. Since nucleophiles attack the metal-coordinated intermediates from an opposite side of the tricarbonylchromium fragment, a relative stereochemistry at the benzylic position of the cyclized 1-functionalized 1*H*-isochromene chromium complexes obtained from the transition state **A** is distinct from that of derived from the other intermediates **B** and **C**. Thus, the substituent at the benzylic position of 1-functionalized 1*H*-isochromene chromium complexes derived from the transition state **A** is *syn*-configuration with the tricarbonylchromium fragment, while the corresponding substituent arised from intermediates **B** or **C** is *anti*-configuration.

With this in mind, we initially studied metal-catalyzed reaction of *o*-alkynyl benzaldehyde chromium complexes **1** with alcohols **2** as nucleophile. Among various metal catalysts studied in this research, gold bis(trifluoromethanesulfonyl)imidate, $Ph_3PAuNTf_2$, gave best result.[9] The reaction took place stereo- and regioselectively with primary and secondary alcohols in good yields to give 6-*endo*-*dig* cyclization products, 1-*anti*-alkoxy-1*H*-isochromene chromium complexes **3** (Table 1). The methoxy group of **3aa** was confirmed as an *anti*-configuration by X-ray crystallography. The



oxophilic activation: *anti*-: C=O / alkyne

carbophilic activation: benzopyrylinium ion intermediate

dual carbophilic and oxophilic activation: *syn*-: C=O / alkyne

Figure 1. Activated form of *o*-alkynyl benzaldehyde chromium complex with metal.

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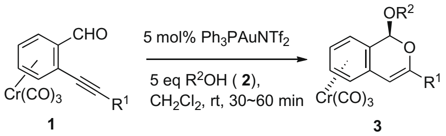
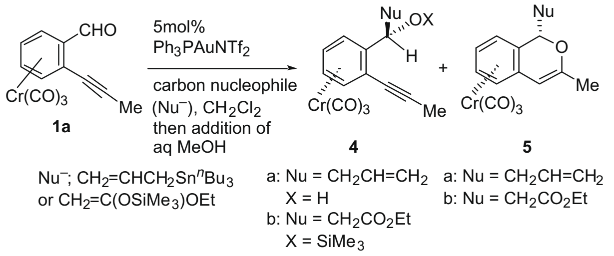
Table 1
Gold(I)-catalyzed reaction of *o*-alkynyl benzaldehyde chromium complexes with alcohols



Entry	1	R^1	R^{2}OH (**2**)	3	Yield (%)
1	**1a**	Me	MeOH (**2a**)	**3aa**	80
2	**1a**	Me	^{i}PrOH (**2b**)	**3ab**	60
3	**1a**	Me	CH$_2$=CHCH$_2$OH (**2c**)	**3ac**	83
4	**1a**	Me	HC≡CCH$_2$OH (**2d**)	**3ad**	62
5	**1b**	^{n}Bu	MeOH (**2a**)	**3ba**	71
6	**1c**	Ph	MeOH (**2a**)	**3ca**	73
7	**1d**	SiMe$_3$	MeOH (**2a**)	**3da**	66

cyclization products **3** were derived from *anti*-addition of alcohols to the generated chromium-complexed benzopyrinium intermediates derived from the transition state **B**. TMS-substituted alkyne chromium complex **1d** gave also 6-*endo-dig* cyclization product **3da** (entry 7), while the treatment of **1d** with 2 M aqueous NaOH in MeOH at room temperature produced stereoselectively 5-*exo-dig* cyclization product with loss of TMS group.[10] It is worthwhile that the cyclization mode of *o*-alkynyl benzaldehyde chromium complexes is distinct between Au(I)-catalyzed reaction and base-mediated cyclization.

We next turned attention to the metal-catalyzed cyclization of *o*-alkynyl benzaldehyde tricarbonylchromium complexes **1** with carbon pronucleophiles. Treatment of **1a** with allyl tri-*n*-butylstannane in the presence of 5 mol % gold(I) catalyst at room temperature for 30 min, then the addition of 10 equiv MeOH and further stirring at rt for 4.5 h gave interestingly 1-*syn*-allyl-1*H*-isochromene chromium complex **5a** in 17% yield along with the formation of a single diastereomeric-allylated benzyl alcohol chromium complex **4a** in 40% yield (Scheme 1). The corresponding *anti*-allyl isomer was not detected. The *syn* stereochemistry of allyl group of the cyclization product **5a** was confirmed by X-ray crystallography. Similarly, ketene trimethylsilyl ethyl acetal afforded a mixture of *syn*-functionalized isochromene chromium complex **5b** and benzylalcohol trimethylsilyl ether **4b** in 19% and 38% yields, respectively, by treatment with Au(I) catalyst at −20 °C for 10 min and following reflux for overnight after the addition of 10 equiv MeOH and H$_2$O for cleavage of the generated alkoxy–metal bond. The *syn*-functionalized-1*H*-isochromene chromium complexes **5a** and **5b** would be formed *via* diastereoselective nucleophilc addition to the *anti*-oriented carbonyl group in the metal-coordinated intermediate **A** and subsequent intramolecular cyclization of hydroxy group with metal-activated alkyne group. Thus, gold bis(trifluoromethanesulfonyl)imidate catalysis in the reaction of chromium-complexed *o*-alkynyl benzaldehyde with carbon nucleophile serves as a multicatalysis[11] for the activation of carbonyl and subsequently alkyne groups with catalytic transformation stepwise. The low yield of the cyclized isochromene chromium complexes **5** would be contributed to the slow cleavage of the generated benzyl trimethylsilyl ether intermediate, and decrease of activity of the gold catalyst by the addition of aqueous MeOH.

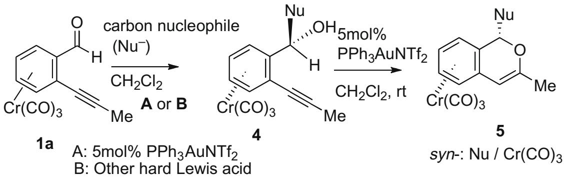


Scheme 1. Gold(I)-catalyzed reaction of *o*-alkynyl benzaldehyde chromium complex with carbon nucleophile.

The low yield of 1-*syn*-functionalized isochromene chromium complexes by one-pot synthesis was improved by stepwise reaction via benzyl alcohol derivatives as follows. Chromium complex **1a** was reacted with allyl tri-*n*-butylstannane in the presence of 5 mol % Ph$_3$PAuNTf$_2$ in CH$_2$Cl$_2$ at −20 °C to give diastereomerically single-allylated secondary benzyl alcohol chromium complex **4a** in 73% yield (Table 2). Similarly, ketene enolsilyl acetal produced the corresponding benzylalcohol chromium complex **4b** (entry 2). Thus, a highly efficient addition of nucleophiles to the aldehyde was achieved with catalytic amount of the Au(I) catalyst or other hard Lewis acids, for example, BF$_3$·OEt$_2$ or TiCl$_4$. The obtained *o*-alkynyl benzyl alcohol chromium complexes **4** were treated with 5 mol % gold(I) catalyst at rt to give 1-*syn*-functionalized 1*H*-isochromene chromium complexes **5** in good yields without the formation of the corresponding 5-*exo-dig* cyclization products.[12,5b]

The alkoxy group of 1-*anti*-alkoxy 1*H*-isochromene chromium complexes **3** can be used as a key for further manipulation. Thus, methoxy group of 1-*anti*-methoxy-1*H*-isochromene chromium complex **3aa** was substituted with carbon nucleophiles by treatment with Lewis acid to afford 1-*anti*-functionalized 1*H*-isochromene chromium complexes **6** via chromium-complexed benzylic carbocation[13] (Table 3). In this manner, both 1-*anti*- and 1-*syn*-functionalized 1*H*-isochromene tricarbonylchromium complexes can be stereoselectively prepared from a single *o*-substituted benzaldehyde chromium complex.

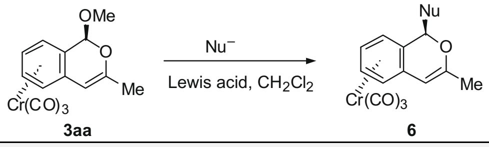
Table 2
Two-step synthesis of 1-*syn*-functionalized isochromene chromium complexes



Entry	Nu$^-$	4	Yield (%)		5	Yield (%)
			A	B (Lewis acid)		
1	CH$_2$=CHCH$_2$Sn(n-Bu)$_3$	**4a**	73	60 (BF$_3$ OEt$_2$)	**5a**	68
2[a]	CH$_2$=C(OSiMe$_3$)OEt	**4b**	56	58	**5b**	69
3	Et$_2$AlC≡CBu^n	**4c**	97	—	**5c**	31
4	MeLi	**4d**	91[b]	—	**5d**	80

[a] TBAF was added to the reaction mixture for deprotection of O–SiMe$_3$ bond.
[b] The reaction took place in ether without Au(I) or Lewis acid.

Table 3
Lewis acid-mediated transformation of 1-*anti*-methoxy isochromene chromium complex **3a**



Entry	Nu$^-$	Lewis acid	6	Nu	Yield (%)
1	Me$_3$Al	—	**6a**	Me	99
2	CH$_2$=CHCH$_2$Sn(n-Bu)$_3$	BF$_3$·OEt$_2$	**6b**	CH$_2$CH=CH$_2$	60
3	CH$_2$=C(OSiMe$_3$)OEt	TiCl$_4$	**6c**	CH$_2$CO$_2$Et	72
4	Me$_3$SiCN	BF$_3$·OEt$_2$	**6d**	CN	56
5	Et$_2$AlC≡CBu^n	BF$_3$·OEt$_2$	**6e**	C≡CBu^n	74