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Synthesis of 2,3-Dihydroquinolin-4(1*H*)-ones through Catalytic Metathesis of *o*-Alkynylanilines and Aldehydes

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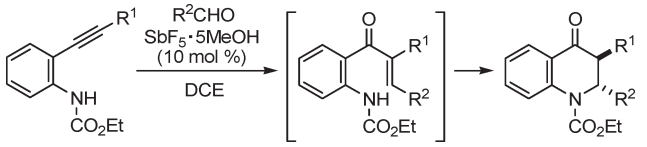

SbF_5−MeOH catalytic system efficiently promotes the alkyne−carbonyl metathesis of *o*-alkynylaniline derivatives and aldehydes to afford 2,3-disubstituted dihydroquinolinones in moderate to high yields with high *trans*-selectivity.

2,3-Dihydroquinolin-4(1*H*)-ones possess attractive pharmacological properties[1] and also serve as important synthetic intermediates for the preparation of biologically active compounds.[2] The cyclization of 2′-aminochalcones[3] or 3-anilinopropionic acid derivatives,[4] which often suffer from low yields, harsh conditions, or cumbersome synthesis of the substrates, has been widely used for the preparation of 2,3-dihydroquinolin-4(1*H*)-ones. Although the proline-catalyzed reaction of 2′-aminophenyl ketones and aldehydes has been reported as a relatively facile method for the direct preparation of 2,3-dihydroquinolin-4(1*H*)-ones, the procedure is limited to the formation of 2-substituted products.[5,6]

Metal-catalyzed metathesis of alkyne and carbonyl compounds has received attention as a straightforward and atom economical approach to the formation of conjugated enones via a formal [2 + 2] cycloaddition and cycloreversion (eq 1).[7,8] We recently developed a one-pot procedure for the SbF_5−alcohol complex-catalyzed synthesis of indanones through alkyne−carbonyl metathesis and the subsequent Nazarov cyclization.[9] Au-catalyzed synthesis of cyclopentanones by the similar approach was reported by Yamamoto et al.[10] These findings encouraged us to examine the formation of 2,3-dihydroquinolin-4(1*H*)-ones by means of the catalytic alkyne−carbonyl metathesis of *o*-alkynylaniline derivatives and aldehydes (eq 2). The metal-catalyzed cyclization of *o*-alkynylanilines to indoles has been established as an efficient synthetic method (eq 3).[11,12] Even in the presence of an aldehyde, Pd- or Cu-catalyzed reaction of *o*-alkynylaniline has been reported to afford the indole product.[12a,13] We herein describe the one-pot synthesis of

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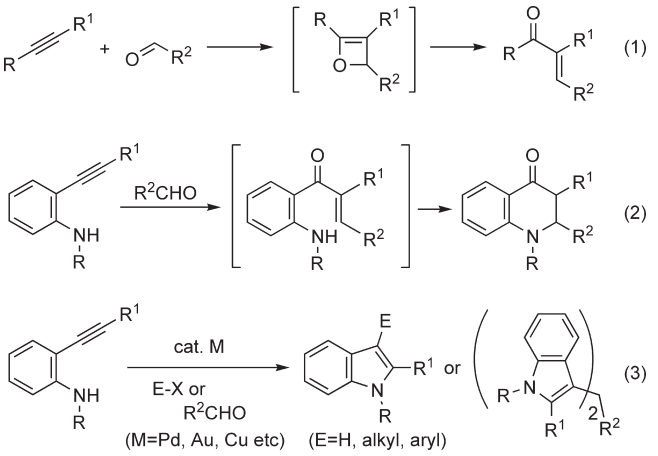
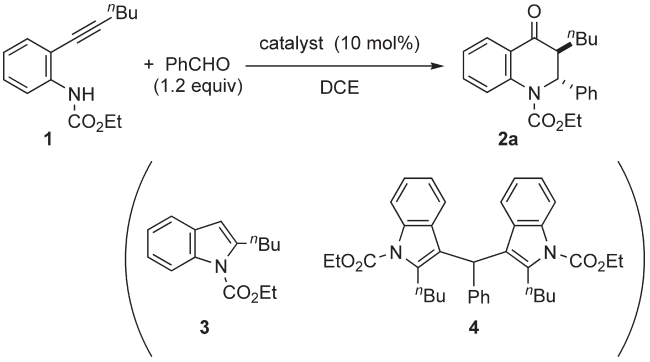
2,3-disubstituted dihydroquinolinones through the SbF_5-catalyzed metathesis of *o*-alkynylaniline derivatives and aldehydes.



At the outset, in the preliminary studies with *o*-alkynylaniline **1** and benzaldehyde (1.2 equiv) in 1,2-dichloroethane (DCE), it turned out that the use of $PtCl_2$, $PtCl_4$, or $AuCl_3$ resulted in the formation of indole compounds **3** and **4a** (runs 1−3, Table 1). By screening of miscellaneous catalysts in DCE for the formation of 2,3-dihydroquinolin-4(1*H*)-one **2a**, 20 mol % of $BF_3\cdot OEt_2$ was found to give the desired product **2a** as a diastereomeric mixture (*trans*/*cis* = 78:22) in 81% yield (run 7). SbF_5 and TfOH (trifluoromethanesulfonic acid) showed inferior results to $BF_3\cdot OEt_2$ (runs 8 and 10). An addition of MeOH, however, exerted a marked effect on the formation of **2a** catalyzed by SbF_5 or TfOH (runs 9 and 11). In particular, by the use of 10 mol % of $SbF_5\cdot 5$MeOH, which was prepared from SbF_5 and MeOH in a ratio of 1:5,[9] **1a** was consumed at 90 °C within 3 h to give **2a** in 94% yield with improved *trans*-selectivity (*trans*/*cis* = 88:12). It should be mentioned that $BF_3\cdot OEt_2$-catalyzed reaction in the presence of MeOH brought about results similar to those of the reaction in the absence of MeOH (run 7).

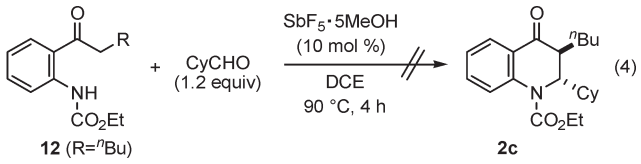
We next examined the reactions of various *o*-alkynylanilines and aldehydes under SbF_5/MeOH-catalyzed conditions. As shown in Figure 1, the optimum MeOH/SbF_5 ratio in the reaction of alkyne **1** with benzaldehyde (1.2 equiv) at 90 °C for 3 h in DCE is between 2 and 10. In particular, $SbF_5\cdot 5$MeOH could be applied to the reactions of *o*-alkynylanilines **1** and **5** with a variety of aldehydes (1.2 equiv) giving rise to the corresponding products in moderate to high yields (Table 2). In most cases, high *trans*-selectivities were observed (runs 1−8).[14,15] In the case of terminal alkyne **7**, however, product **8a** was obtained in low yield (28%) due to the formation of **9a**, which would be generated by the aldol condensation of **8a** with benzaldehyde (run 9). Thus, an increased amount of aldehyde (3 equiv) improved the yield of **9a** to 74% (run 10). Although the reaction of *o*-alkynylphenol **10** smoothly proceeded under the identical conditions to give the dihydrochromen-4-one **11a** (run 11), the other amine compounds (X = NH, NBn, and NTs) gave the complex mixtures. It should be mentioned that ketone compound **12**[16] was detected as a side product in all cases listed in Table 2 (8−38%). Although **12** could be considered to take part in the formation of 2,3-dihydroquinolin-4(1*H*)-one **2**, the reaction of **12** (R = ^{n}Bu) with cyclohexanecarbaldehyde scarcely proceeded under the present conditions (eq 4).

TABLE 1. Screening of Catalysts for the Formation of 2a



		condition			
run	catalyst	temp (°C)	time (h)	**2a** yield (%)[a]/(*trans*/*cis*)[a]	
1	$PtCl_2$	60	1	(**3** 53, **4a** 32)	
2	$PtCl_4$	rt	1	(**3** 81)	
3	$AuCl_3$	rt	1	(**3** 29, **4a** 50)	
4	$AgSbF_6$	90	4	31	(73:27)
5	$Cu(OTf)_2$	90	5	25	(72:28)
6	$In(OTf)_3$	90	18	24	(55:45)
7	$BF_3\cdot OEt_2$[b]	90	20	81	(78:22)
8	TfOH	90	16	63	(85:15)
9	TfOH·5MeOH[c]	90	20	93	(87:13)
10	SbF_5	60	20	63	(43:57)
11	$SbF_5\cdot 5$MeOH[c]	90	3	94	(88:12)

[a] Yields and ratio were determined by ^{1}H NMR analysis. [b] 20 mol %. [c] Catalyst/MeOH = 1:5 mixture.



In the reaction of *o*-alkynylanilines **1** with cyclohexanecarbaldehyde at 40 °C for 4 h under $SbF_5\cdot 5$MeOH-catalyzed conditions, enone **13c** was obtained in 56% yield (Scheme 1). **13c** was quantitatively converted into the corresponding product **2c** by heating at 90 °C within 1 h with an excellent *trans*-selectivity (Scheme 1). On the basis of the observations described in Scheme 1 and eq 4, we believe that **2c** would be formed through (i) the formal alkyne−carbonyl metathesis of **1** and aldehyde, followed by (ii) the intramolecular addition of the NH group to the conjugated enone moiety as shown in eq 2. Although the precise role of MeOH is

(14) The stereochemistry of products was determined by NOE experiments and/or by the values of the vicinal coupling constants between protons at 2- and 3-position. The relative configuration of **6a** was confirmed by single X-ray crystallographic analysis (see Supporting Information).

(15) The yields and *trans*/*cis* ratios of **2a**, **2d**, and **11a** with shorter and/or longer reaction times are as follows. **2a**: 1 h, 87% (90:10); 18 h, 93% (87:13). **2d**: 46 h, 62% (67:13). **11a**: 18 h, 79% (63:37). Regardless of the reaction times, these *trans*/*cis* ratios were nearly identical.

(16) In the absence of aldehyde, the reaction of *o*-alkynylanilines **1** catalyzed by 10 mol % of $SbF_5\cdot 5$MeOH at 90 °C for 18 h afforded **12** in 32% yield (see Supporting Information).

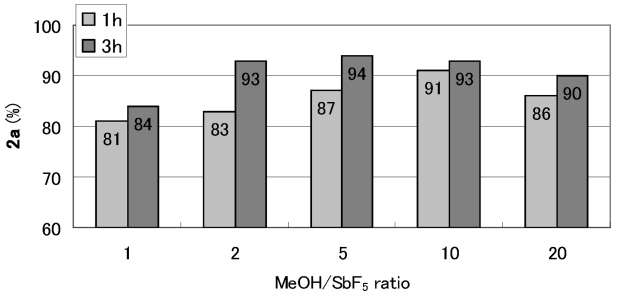
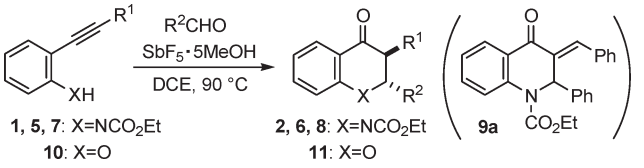


FIGURE 1. Optimum amount of MeOH to SbF_5 in the SbF_5/MeOH (10 mol %)-catalyzed reaction of **1** with benzaldehyde (1.2 equiv) at 90 °C for 1 or 3 h in DCE.

TABLE 2. SbF_5·5MeOH-Catalyzed Formation of Dihydroquinolinones[a]



run	alkyne/R^1	R^2CHO	time (h)	product	yield (%)[b]	*trans*/*cis*[c]
1	**1**/^{n}Bu	PhCHO	3	**2a**	94	(88:12)
2		$PhCH(OMe)_2$	20	**2a**	64	(88:12)
3		*p*-NO_2PhCHO	2	**2b**	69	(93:7)
4		CyCHO	4	**2c**	84	(100:0)
5		*n*-C_6H_{13}CHO	24	**2d**	63	(66:34)
6		^{t}BuCHO	20	**2e**	25[d]	(100:0)
7	**5**/Ph	PhCHO	46	**6a**	58	(100:0)
8		CyCHO	22	**6c**	60	(100:0)
9	**7**/H	PhCHO	13[e]	**9a**	13	(**8a** 28)
10		PhCHO[f]	16	**9a**	74	(**8a** 0)
11	**10**/^{n}Pr	PhCHO	2	**11a**	84	(67:33)

CyCHO: cyclohexanecarboaldehyde. [a] Unless noted otherwise, 10 mol % of SbF_5·5MeOH and 1.2 equiv of R^2CHO. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] SbF_5·10EtOH was used. [e] Temp = rt. [f] 3 equiv.

unclear, the SbF_5·MeOH catalyst might serve as an efficient Brønsted acid.[17]

As to the activation of *o*-alkynylanilines and aldehyde by the present catalytic system, we carried out NMR studies using **1** and benzaldehyde (Table 3). The ^{13}C NMR spectrum (75 MHz) of a 1:1 mixture of **1** and benzaldehyde in the presence of 5 equiv of MeOH in $CDCl_3$ at −60 °C showed that the signals of the sp-carbons (δ 75.0, $\Delta\delta$ = 0.1; δ 97.6, $\Delta\delta$ = 0) of **1** and the carbonyl carbon (δ 193.3, $\Delta\delta$ = 0.2) of benzaldehyde scarcely shifted (run 2) by comparison with the original signals of the sp-carbons (δ 75.1, 97.6) and the carbonyl carbon (δ 193.1, run 1). The mixture of **1**, benzaldehyde, and 1 equiv of SbF_5·5MeOH showed two sets of both sp-carbons (δ 74.8 and 74.9, δ 97.9 and 98.0) and the carbonyl carbons (δ 195.9 and 196.4, run 4). In both cases, the larger shifts of carbonyl carbons to a lower field ($\Delta\delta$ = 2.8 and 3.3) were observed, albeit the slight shift of sp-carbons ($\Delta\delta$ = 0.2 and 0.3, $\Delta\delta$ = 0.4 and 0.3). The use of 1 equiv of TfOH·5MeOH also showed the larger shift of carbonyl carbon (δ 194.1, $\Delta\delta$ = 1.0) than the shift

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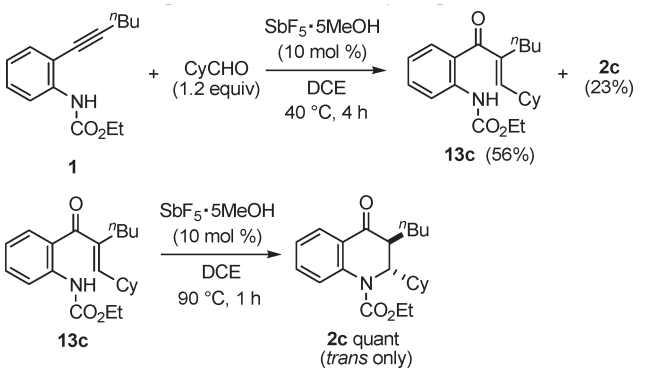
TABLE 3. ^{13}C NMR Spectrum of *o*-Alkynylaniline 1 and Benzaldehyde (1:1) in the Presence of Additive in $CDCl_3$ at −60 °C

		chemical shift (ppm)		
		PhCHO	Ar−Cα≡Cβ-^{n}Bu (**1**)	
run	additive (equiv)	δ (C=O)	δ (Cα)	δ (Cβ)
1	none	193.1	97.6	75.1
2	MeOH (5)	193.3	97.6	75.0
3	SbF_5·5MeOH (0.1)	193.5	97.7	75.2
4	SbF_5·5MeOH (1)	196.4	98.0	74.9
		195.9	97.9	74.8
5	TfOH·5MeOH (1)	194.1	97.7	74.9

SCHEME 1. Stepwise Formation of Dihydroquinolinones



of sp-carbons (δ 74.9, $\Delta\delta$ = 0.2; δ 97.7, $\Delta\delta$ = 0.1, run 5). A similar observation has been reported in the reaction of alkyne and aldehyde catalyzed by SbF_5−alcohol complex.[9] Since the present catalytic system would preferentially activate aldehyde rather than alkyne, the formation of **2** would proceed prior to the generation of indole **3**.

In conclusion, we have demonstrated the facile synthesis of *trans*-2,3-dihydroquinolin-4(1*H*)-ones from *o*-alkynylanilines and aldehydes via a formal alkyne−carbonyl metathesis and cyclization. SbF_5−MeOH catalytic system was found to be very efficient. Synthetic applications and detailed mechanistic studies of the present reaction are underway.

Experimental Section

A typical experimental procedure for the formation of 2,3-dihydroquinolin-4(1*H*)-one derivatives (**2a**): to a solution of *o*-alkynylaniline **1a** (98.1 mg, 0.4 mmol) and benzaldehyde (50 μL, 0.48 mmol) in DCE (1.5 mL) was added a solution of SbF_5·5MeOH (0.1 M in DCE, 40 μL, SbF_5; 40 μmol, MeOH; 0.2 mmol) at room temperature. After being refluxed until the consumption of the starting material (by TLC analysis), the mixture was diluted with ether and filtered through a short silica gel column chromatography. Concentration of the filtate to dryness and then purification by silica gel column chromatography (hexane/AcOEt = 25:1) gave **2a** (132.7 mg, 94% yield, *trans*/*cis* = 88:12) as a colorless oil: IR (neat) ν 1716, 1685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, J = 7.2 Hz), 1.32−1.68 (m, 7H), 1.72−1.84 (m, 2H), 3.16 (td, 1H, J = 7.4, 1.7 Hz), 4.24−4.49 (m, 2H), 6.01 (d, 1H, J = 1.7 Hz), 7.04−7.11 (m, 1H), 7.12−7.24 (m, 5H), 7.46−7.51 (m, 1H), 7.85−7.92 (m, 2H); the following signals were assigned to *cis*-isomer: 6.04 (d, 1H, J = 5.9 Hz), 7.72−7.75 (m, 1H), 8.02−8.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.5, 22.5, 29.2, 29.8, 51.1, 59.9,

62.8, 123.5, 123.8, 126.6, 127.4, 128.6, 134.5, 138.5, 141.2, 155.1, 195.7; the following signals were assigned to *cis*-isomer: 22.6, 25.8, 29.9, 51.3, 60.7, 128.1, 128.3, 128.4, 134.2, 136.5; FAB-LM *m*/*z* 352 ($M^+ + H$); FAB-HM calcd for $C_{22}H_{25}NO_3$ 352.1913, found 352.1923. Anal. Calcd for $C_{22}H_{24}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.94; H, 7.17; N, 4.05.

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Supporting Information Available: Experimental procedures and physical data for novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.