Asymmetric Catalysis

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Chiral Copper(II) Phosphate Catalyzed Enantioselective Synthesis of Isochromene Derivatives by Sequential Intramolecular Cyclization and Asymmetric Transfer Hydrogenation of *o*-Alkynylacetophenones**

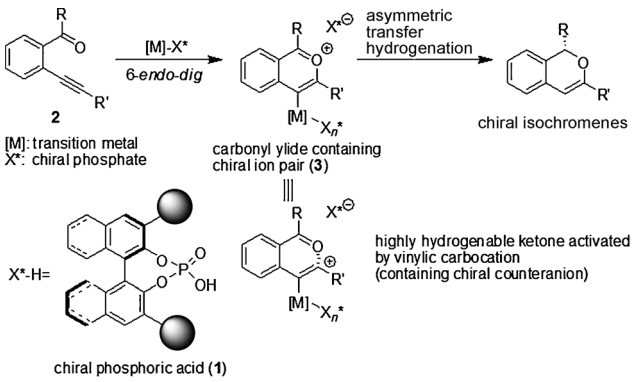
*Kodai Saito, Yuki Kajiwara, and Takahiko Akiyama**

Chiral binaphthyl phosphoric acids (CPAs) have been used for the activation of imines through hydrogen-bonding interactions and a range of enantioselective reactions have been developed.[1] Recently, the conjugate base of a CPA has emerged as a chiral counteranion catalyst for asymmetric synthesis, wherein electrostatic interactions are responsible for the high enantioselectivity. This concept has been recognized as a powerful tool, and is termed asymmetric counterion-directed catalysis (ACDC).[2] By using this concept, catalytic reactions which proceed via cationic intermediates can be performed with high enantioselectively by the incorporation of a chiral counteranion into the catalyst. One of the most powerful uses of ACDC involves the incorporation of transition-metal catalysis.[3] The cationic metallic intermediate can form a tight ion pair with the chiral counteranion. Intramolecular cyclization initiated by activation of the alkyne moiety using transition-metal catalysis has been extensively investigated,[4] and cyclized metal-containing intermediates could also be employed for further reactions in a tandem manner. Recently, reactions initiated by alkyne activation, combined with the use of CPA have also been developed.[5]

Transition-metal-containing carbonyl ylides are highly reactive intermediates, which are generated by 6-*endo*-dig cyclization reactions of alkynyl carbonyl compounds. Although the carbonyl ylides are employed for [4+2] and [3+2] cycloaddition reactions,[6] its application to asymmetric synthesis is limited. As far as we know, Iwasawa and co-workers reported the [3+2] cycloaddition reaction of a platinum-carbonyl ylide with vinyl ethers by means of chiral platinum bisphosphine complex, and bicyclic ether structures were efficiently constructed in good yields with excellent enantioselectivities.[7] There are no preceding examples for enantiocontrol of the carbonyl ylide intermediate using the ACDC concept, and the development of asymmetric reactions using metal-containing carbonyl ylide intermediates based on the new concept is thus, an important challenge.

More recently, Yao and co-workers reported the $Pd(OAc)_2$/CPA-catalyzed asymmetric cascade annulation based on an oxa-Diels–Alder cycloaddition using a metal-containing carbonyl ylide intermediate to afford tetrahydronapthalene derivatives with multiple stereogenic centers including quaternary carbon atoms, thus taking advantage of the metallo/organo binary catalytic methodology.[8]

Although a CPA (**1**)-catalyzed transfer hydrogenation of imines using a hydrogen donor has been recently developed by many research groups,[9] the application of this method for ketones, in place of imines, is limited to a few examples.[10] We could view the carbonyl ylide **3** as an easily hydrogenated intermediate, in which the carbonyl oxygen atom would be strongly activated by a vinylic carbocation (Scheme 1). Our approach to achieve asymmetric synthesis of chiral skeletons is based on the asymmetric transfer hydrogenation of the carbonyl ylide intermediate **3**. When a transition-metal/phosphate complex activates the alkyne moiety of **2** selectively, nucleophilic attack by the carbonyl oxygen atom would occur to afford **3**, containing a chiral phosphate as the counteranion. We envisioned that the metal-containing carbonyl ylide intermediate, which would interact with chiral phosphate as an ion pair, would be subsequently reduced enantioselectively to furnish chiral isochromenes by the use of a hydrogen donor.



Scheme 1. Transition-metal/phosphate-catalyzed asymmetric transfer hydrogenation of metal-containing carbonyl ylide based on ACDC.

As an initial examination, the substrate **2a** was treated with a cationic transition-metal/phosphate catalyst prepared from the reaction of CPA, bearing a 3,4,5-trifluorophenyl group (**1a**; 10 mol%), silver carbonate (5 mol%), and a transition-metal salt (5 or 10 mol%) in the presence of 4 Å molecular sieves and the Hantzsch ester **4a** (1.4 equiv), as

[*] Dr. K. Saito, Y. Kajiwara, Prof. Dr. T. Akiyama
Department of Chemistry, Gakushuin University
1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588 (Japan)
E-mail: takahiko.akiyama@gakushuin.ac.jp

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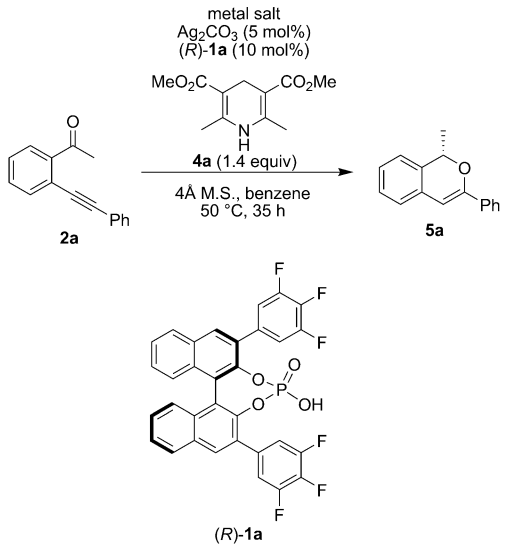
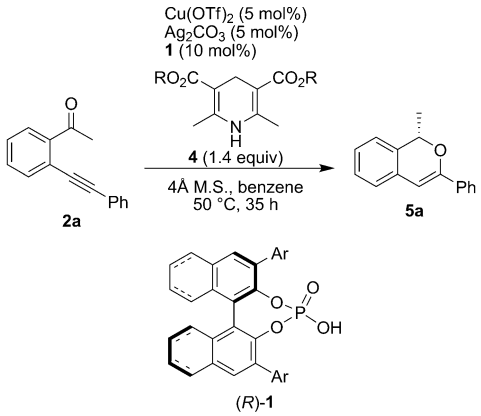
Table 1: Screening of transition-metal salts.



Entry[a]	Metal salt	Yield [%][a]	e.r.[b]
1	$[AuCl(PPh_3)]$	5	52.6:47.4
2	$[\{PtCl_2(CH_2CH_2)\}_2]$	57	51.1:48.9
3	$Pd(OAc)_2$	35	52.1:47.9
4	$[Ni(acac)_2]$	43	81.2:18.8
5	none	84	80:9:19.1
6	$Cu(NO_3)_2$	24	85.4:14.6
7	$Cu(TFA)_2$	51	85.4:14.6
8	$Cu(OTf)_2$	25	86.6:13.4

[a] Yield of isolated product. [b] Enantiomer ratios were determined by HPLC analysis on a chiral stationary phase (chiralcel OZ-H). acac = acetylacetonate, M.S. = molecular sieves, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetate.

Table 2: Screening of CPA and Hantzsch esters.



Entry	Ar	R	Yield [%][a]	e.r.[b]
1	3,4,5-$F_3C_6H_2$ (**1a**)	Me	25	86.6:13.4
2	Ph (**1b**)	Me	17	58.4:41.6
3	4-$NO_2C_6H_4$ (**1c**)	Me	28	64.2:35.8
4	9-anthryl (**1d**)	Me	50	67.4:32.6
5	2,4,6-(iPr)$_3C_6H_2$ (**1e**)	Me	36	68.1:31.9
6	$SiPh_3$ (**1f**)	Me	68	89.1:10.9
7	$SiPh_3$ (**1g**)[c]	Me	82	93.0:7.0
8	Si(4-tBu$C_6H_4)_3$ (**1h**)	Me	16	87.5:12.5
9	$SiPh_3$ (**1g**)[c]	Et	68	86.5:13.5
10	$SiPh_3$ (**1g**)[c]	iPr	20	89.6:10.4
11	$SiPh_3$ (**1g**)[c]	tBu	29	87.9:12.1
12	$SiPh_3$ (**1g**)[c,d]	Me	86	93.6:6.4

[a] Yield of isolated product. [b] Enantiomer ratios were determined by HPLC analysis on a chiral stationary phase (chiralcel OZ-H). [c] CPA derived from H_8-BINOL was used. [d] THF was used as solvent.

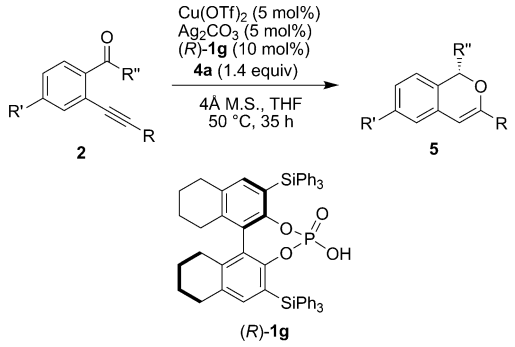
a hydrogen source, at 50 °C for 35 h (Table 1). When gold(I), platinum(II), and palladium(II) salts were used, the expected product **5a** was obtained in 5, 57, and 35 % yield, respectively, with modest enantioselectivities (Table 1, entries 1–3). Although nickel(II) salts are rarely used for the activation of the alkyne moiety, the selectivity was improved (Table 1, entry 4). Interestingly, the sole use of the silver phosphate catalyst resulted in the formation of **5a** in higher yield and with 71 % *ee* (Table 1, entry 5). Finally, it was found that copper(II) trifluoromethanesulfonate exhibited the highest enantioselectivity (Table 1, entry 8).

Next, we investigated the effect of the CPA (Table 2). The use of a CPA bearing either a Ph or 4-$NO_2C_6H_4$ group resulted in low yield with diminished enantioselectivity (Table 2, entries 2 and 3). Yields and *ee* values were improved by means of CPAs bearing bulky substituents such as a 9-anthryl and 2,4,6-(iPr)$_3C_6H_2$ group (Table 2, entries 4 and 5). Pleasingly, a CPA having a triphenylsilyl group exhibited higher catalytic activity, and more importantly, promising enantioselectivity (Table 2, entry 6). Use of (*R*)-**1g**, bearing a H_8-BINOL backbone, further improved the enantioselectivity to 86 % *ee*.[11] Examination of the ester moiety of Hantzsch ester showed that the methyl ester **4a** gave the best result. Use of THF as a solvent improved both the yield and *ee* value of **5a**.[12]

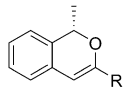
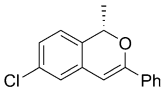
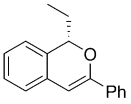
We explored the scope of the copper/phosphate-catalyzed cyclization/transfer hydrogenation of various *o*-alkynylacetophenone derivatives under the optimized reaction conditions. The results are summarized in Table 3. For substrates bearing *p*-substituted aryl groups at the alkyne termini, the electron-donating or electron-withdrawing substituents have marginal effects, and good enantioselectivities were obtained (Table 3, entries 2–4). Interestingly, electron-donating groups on the *m*-position of the aryl ring at the alkyne termini played a very important role in enantiocontrol, and the enantiomeric excesses were increased to 91 % *ee* (Table 3, entries 5–7). Introduction of halogen atoms to the *m*-position on the aryl group showed almost the same enantiomeric ratio as with the *p*-substituted analogues (Table 3, entries 8 and 9). Substrates bearing a disubstituted aryl group were also applicable, and 3,5-disubstitution of the aryl group was the most effective for enantiocontrol. When the substrates **2k** and **2l** were subjected to the optimized reaction conditions, **5k** and **5l**, respectively, were obtained with the corresponding 96 % *ee* and 97 % *ee* values (Table 3, entries 11 and 12). Additionally, **2m**, containing a halogen atom at the 5-position and the propiophenone derivative **2n**, were also suitable substrates for this tandem process, and excellent enantiomer ratios were realized with good conversions (Table 3, entries 13 and 14).[13]

A plausible mechanism is shown in Scheme 2. An electrophilic activation of the alkyne moiety of **2** by the cationic copper/phosphate complex led to the formation of the

Table 3: Substrate scope of copper/phosphate-catalyzed asymmetric synthesis of isochromenes.



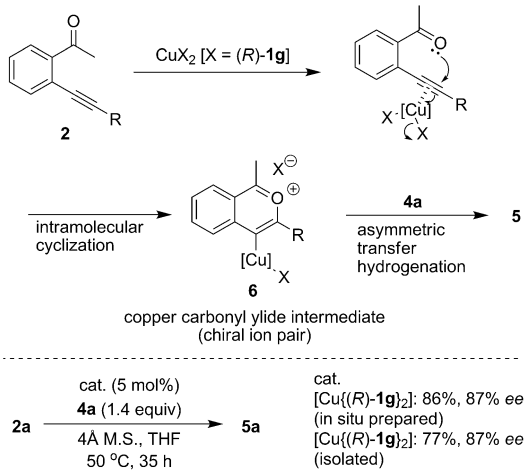
(*R*)-**1g**

Entry	Product		Yield [%][a]	e.r.[b]
				
1	R = Ph (**5a**)		86	93.6:6.4
2	R = PMP (**5b**)		89	95.7:4.3
3	R = 4-ClC_6H_4 (**5c**)		86	94.1:5.9
4	R = 4-BrC_6H_4 (**5d**)		84	92.7:7.3
5	R = 3-MeC_6H_4 (**5e**)		89	94.2:5.8
6	R = 3-$MeOC_6H_4$ (**5f**)		81	95.6:4.4
7	R = 3-*i*PrC_6H_4 (**5g**)		90	95.5:4.5
8	R = 3-ClC_6H_4 (**5h**)		75	93.3:6.7
9	R = 3-BrC_6H_4 (**5i**)		81	92.4:7.6
10	R = 3,4-$Me_2C_6H_3$ (**5j**)		82	93.5:6.5
11	R = 3,5-$Me_2C_6H_3$ (**5k**)		75	98.1:1.9
12	R = 3,5-$(MeO)_2C_6H_3$ (**5l**)		79	98.5:1.5
13		**5m**	84	90.1:9.9
14		**5n**	80	93.0:7.0

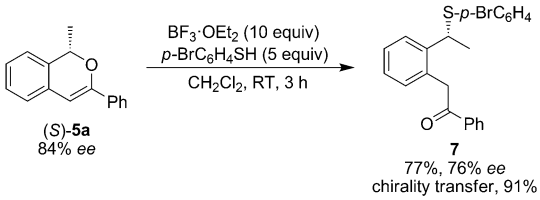
[a] Yield of isolated product. [b] Enantiomer ratios were determined by HPLC analysis on a chiral stationary phase (chiralcel OZ-H). PMP = *p*-methoxyphenyl, THF = tetrahydrofuran.

copper-containing carbonyl ylide **6**, wherein one phosphate anion was eliminated from the copper complex and coordinated as a counteranion to the oxonium part. Subsequent transfer hydrogenation of the ion-pair intermediate **6** afforded the chiral isochromene **5**. The use of the isolated [Cu{(*R*)-**1g**}$_2$] resulted in the formation of **5a** in 77% yield with 87% *ee*, and clearly shows that the present reaction was catalyzed by the in situ generated chiral copper/phosphate complex.[14,15]

Further transformation of the chiral isochromenes was explored (Scheme 3). When (*S*)-**5a** was treated with an excess amount of boron trifluoride etherate in the presence of *p*-bromobenzenethiol in CH_2Cl_2, the chiral sulfide **7** was obtained in 77% yield with 91% chirality transfer.[16] The absolute configuration of the major enantiomer of **7** was determined to be *R*.[17] It was confirmed that the present



Scheme 2. A plausible reaction mechanism.



Scheme 3. Derivatization of chiral isochromene.

reaction proceeded with inversion of the configuration at the benzylic carbon.

In conclusion, we have developed a highly efficient asymmetric synthesis of chiral isochromenes through the copper(II)/phosphate-catalyzed intramolecular cyclization/asymmetric transfer hydrogenation sequence of *o*-alkynylacetophenone derivatives. This sequence allows the synthesis of multisubstituted isochromenes containing various substituents in high yields with good to excellent enantioselectivities. The method features the efficient construction of an oxacyclic skeleton by the successive cyclization and hydrogenation. Further investigation of the mechanistic insights and application to the synthesis of more complex molecules are currently underway in our laboratory.

Experimental Section

A typical procedure for the reaction of **2a** is described. A magnetic stirrer bar and powdered molecular sieves 4 Å (4 Å M.S.; 100 mg) were placed in a test tube under a nitrogen atmosphere. The 4 Å M.S. were then dried with a heat gun under reduced pressure and the test tube was refilled with nitrogen. Ag_2CO_3 (1.4 mg, 5.0 μmol), and the phosphoric acid (*R*)-**1g** (8.8 mg, 0.010 mol) were added to the test tube successively under a nitrogen atmosphere and the test tube was covered by aluminum film. THF (1 mL) was added to the test tube. After being stirred for 2 h at room temperature, $Cu(OTf)_2$ (1.8 mg, 5.0 μmol) was added quickly to the test tube. After being stirred for 2 h at room temperature, **2a** (22.0 mg, 0.10 mmol) and **4a** (31.5 mg, 0.14 mmol) were added to the test tube using THF (2 mL). After being stirred for 35 h at 50 °C, the mixture was filtered through Celite pad (washed with CH_2Cl_2) and the filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin-

layer chromatography on silica gel (AcOEt/hexanes = 1:20) to give 19.1 mg (0.086 mmol, 86%) of (*S*)-**5a** as a colorless solid.

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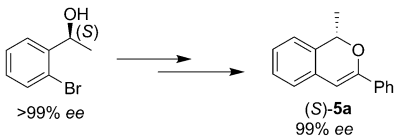
[11] Absolute configuration of *ent*-**5a** was determined by comparison of the sign of the optical rotation and retention time of HPLC analysis on a chiral stationary phase to that of the derived product from (*S*)-2-bromo-α-methylbenzyl alcohol. See the Supporting Information for more results and experimental details. The configurations of other products were assigned by analogy.



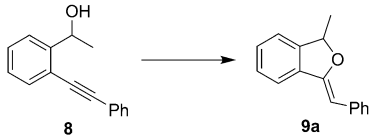
$[\alpha]_D^{25}$ + 26.5 (*c* 0.40, $CHCl_3$)
Table 2, entry 1; $[\alpha]_D^{25}$ + 32.1 (*c* 0.55, $CHCl_3$)

[12] The reaction in the absence of $Cu(OTf)_2$ under the otherwise identical reaction conditions of entry 12 in Table 2 furnished **5a** in 27% yield with 70% *ee*. This result clearly implies that the formation of copper phosphate is responsible for the high catalytic activity in this reaction.

[13] A substrate bearing an aliphatic substituent at the alkyne termini exhibited low enantioselectivity.

[14] For examples of the reactions using chiral copper(I)/phosphate complex, see R. Yazaki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2011**, *133*, 10275 – 10282. See also Ref. [3c]. Chiral copper(II)/phosphate-catalyzed reaction is also reported in Ref. [3j].

[15] Treatment of the alkynyl benzyl alcohol **8** with a variety of metal salts preferentially gave the five-membered product **9a**.



8 **9a**

This result clearly shows that sequential cyclization/asymmetric transfer hydrogenation of carbonyl ylide intermediate did proceed. For recent examples of the synthesis of isochromenes using *o*-alkynyl benzylalcohol derivatives, see: a) A. S. K. Hashmi, S. Schäfer, M. Wölfle, C. D. Gil, P. Fischer, A. Laguna, M. C. Blanco, M. C. Gimeno, *Angew. Chem.* **2007**, *119*, 6297 – 6300; *Angew. Chem. Int. Ed.* **2007**, *46*, 6184 – 6187; b) G. Le Bras, A. Hamze, S. Messaoudi, O. Provot, P.-B. Le Calvez, J.-D. Brion, M. Alami, *Synthesis* **2008**, 1607 – 1611; c) A. Varela-Fernández, C. González-Rodríguez, J. A. Varela, L. Castedo, C. Saá, *Org. Lett.* **2009**, *11*, 5350 – 5353; d) P. N. Liu, F. H. Su, T. B. Wen, H. H.-Y. Sung, I. D. Williams, G. Jia, *Chem. Eur. J.* **2010**, *16*, 7889 – 7897.

[16] Y. Ren, M. Li, J. Yang, J. Peng, Y. Gu, *Adv. Synth. Catal.* **2011**, *353*, 3473 – 3484.

[17] Absolute configuration of **7** was determined by comparison of the sign of the optical rotation and retention time from HPLC analysis on a chiral stationary phase to that of the product derived from (*S*)-2-bromo-α-methylbenzyl alcohol. See the Supporting Information for details.

