Asymmetric Catalysis

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Chiral Silver Phosphate Catalyzed Transformation of *ortho*-Alkynylaryl Ketones into 1*H*-Isochromene Derivatives through an Intramolecular-Cyclization/Enantioselective-Reduction Sequence**

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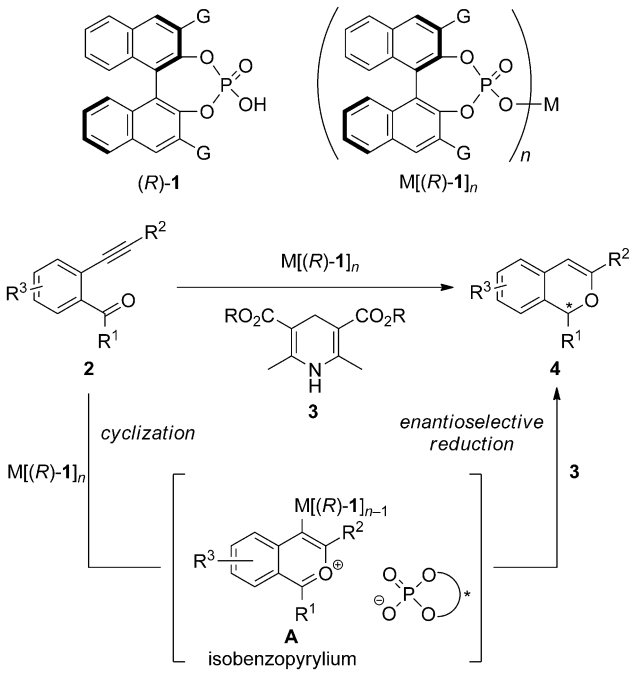
Abstract: *The transformation of ortho-alkynylaryl ketones through a cyclization/enantioselective-reduction sequence in the presence of a chiral silver phosphate catalyst afforded 1H-isochromene derivatives in high yield with fairly good to high enantioselectivity. An asymmetric synthesis of the 9-oxabicyclo[3.3.1]nona-2,6-diene framework, which has been found in some biologically active molecules, is presented as a demonstration of the synthetic utility of this method.*

Isobenzopyrylium ions are stable oxonium cations owing to their aromaticity as a 10 π-electron system. In general, these cationic species have been generated in situ by various methods for further manipulation, although the corresponding salts can be isolated as air-stable solids with less nucleophilic anions, such as BF_4^-, and are utilized both for the characterization of these distinctive species and in electrophilic transformations.[1–5] Their high and unique reactivity has attracted great attention during the past decade, because these oxonium species undergo a diverse array of transformations, including Diels–Alder reactions and nucleophilic addition reactions,[2–4] and can be applied to the synthesis of natural products and biologically relevant molecules.[5] However, catalytic enantioselective reactions of the isobenzopyrylium ions remain largely unexploited despite their unique reactivity and synthetic utility, presumably owing to the planar structure of the isobenzopyrylium ion, which lacks apparent coordination sites that can interact with chiral metal catalysts or organocatalysts.[6,7] Indeed, successful examples are quite limited and have been based on the use of metal catalysts with electronically neutral chiral ligand(s).[6] Hence, the development of enantioselective transformations involving the isobenzopyrylium ion as a reactive intermediate is still a challenging topic in synthetic organic chemistry.[8,9] To develop such a catalytic enantioselective transformation, we took advantage of the chemical properties of the isobenzopyrylium ion; notably, the formation of ion-pair salts between the isobenzopyrylium ion and less nucleophilic counteranions. In principle, the use of a chiral instead of an achiral counteranion should enable reactions to take place in an enantioselective fashion.[9]

Chiral-counteranion-induced enantioselective transformations in metal-catalyzed reactions, namely, chiral-anion catalysis,[10] has emerged as a powerful and attractive tool in asymmetric synthesis in recent years owing to its distinct advantages over conventional methods that rely on metal complexes coupled with electronically neutral chiral ligand(s). Chiral-anion catalysis offers another approach to the enantioselective reaction of isobenzopyrylium ions with a controlled stereochemical outcome.[8a,9] In this context, we envisioned an enantioselective sequential transformation based on chiral-anion catalysis in which the key intermediate, the isobenzopyrylium ion, is generated in situ through metal-



Scheme 1. Enantioselective transformation involving an isobenzopyrylium cation as the reactive intermediate.

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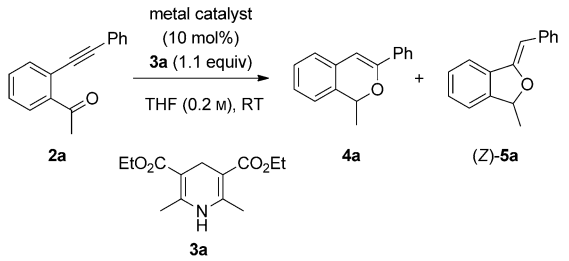
complex-catalyzed intramolecular cyclization of *ortho*-alkynylaryl ketones **2**. The proposed sequence involves a two-step transformation (Scheme 1): 1) intramolecular cyclization of **2** catalyzed by a π-Lewis acidic metal complex with a binol-derived phosphate **1** (binol = 1,1′-binaphthalene-2,2′-diol) as the chiral counteranion[11] to generate an ion pair comprised of the isobenzopyrylium intermediate **A** and chiral phosphate $\mathbf{1}^-$, and 2) enantioselective reduction of this key intermediate **A** with a Hantzsch ester **3**[12] to afford the final product **4** in an enantioselective manner under the influence of $\mathbf{1}^-$. Herein, we report the enantioselective transformation of *ortho*-alkynylaryl ketones **2** into optically active 1*H*-isochromene derivatives **4** through a cyclization/enantioselective reduction sequence with a chiral silver phosphate catalyst and **3** as the reducing agent.

We began our investigation by exploring achiral π-Lewis acidic metal complexes with the *ortho*-alkynylaryl ketone **2a** (R^1 = Me, R^2 = phenyl, R^3 = H) as the primary substrate for the precursor of the isobenzopyrylium ion. The sequential transformation was performed with 10 mol% of the metal catalyst and 1.1 equivalents of Hantzsch ester **3a** in THF at room temperature. The reactivity and mode of cyclization were highly dependent on the metal catalyst employed (Table 1). Ag^I and Cu^{II} catalysts afforded the desired 6-*endo* cyclization product **4a** exclusively in excellent yield (Table 1, entries 1 and 2, respectively). In contrast, the reactions with Pt^{II}, Au^{III}, and Au^I catalysts afforded not only the desired 6-*endo* product **4a**, but also the 5-*exo* product **5a** (Table 1, entries 3, 4, and 6, respectively), although the Au^{III} and Au^I catalysts exhibited higher catalytic activity than that of the Ag^I catalyst (Table 1, entries 4 and 6 versus entry 1). To verify the participation of the π-Lewis acidic metal species in this reaction, trifluoromethanesulfonic acid (TfOH) was employed as a metal-free Brønsted acid catalyst (Table 1, entry 7). As expected, this strong Brønsted acid did not afford any product, and the starting material **2a** was almost completely recovered. As the catalyst AgOTf exhibited exclusive formation of the 6-*endo* product **4a** and higher reactivity than $Cu(OTf)_2$, Ag^I was chosen as the metal species for further studies on an enantioselective variant of the present sequential transformation.

Table 1: Initial screening of π-Lewis acidic metal catalysts for the cyclization/reduction of **2a**.[a]

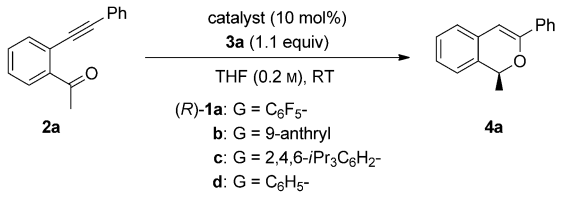


Entry	Metal catalyst	*t* [h]	Conversion of **2a** [%][b]	Yield of **4a** [%][b]	Yield of **5a** [%][b]
1	AgOTf	3	100	96	–
2	$Cu(OTf)_2$	24	96	96	–
3	$PtCl_2$	24	35	18	5
4	$AuCl_3$	1	100	38	50
5	AuCl/AgOTf	24	trace	–	–
6	$[AuCl(PPh_3)]$/AgOTf	1	100	24	58
7	TfOH	24	trace	–	–

[a] Reaction conditions: transition-metal catalyst (0.02 mmol, 10 mol%), **2a** (0.2 mmol), **3** (0.22 mmol, 1.1 equiv), THF (1 mL), room temperature. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product. Tf = trifluoromethanesulfonyl.

The enantioselective variant of the reaction was conducted with the chiral silver phosphate Ag[(*R*)-**1**] (10 mol%), **2a**, and **3a** (1.1 equiv) in THF at room temperature. Ag[(*R*)-**1**] was preprepared from Ag_2CO_3 and the corresponding binol-derived phosphoric acid (*R*)-**1** (2 equiv).[11a,13] We screened a range of chiral silver phosphates by changing the substituents at the 3- and 3′-positions of the binaphthol backbone (Table 2, entries 1–4). The pentafluorophenyl-substituted chiral silver phosphate Ag[(*R*)-**1a**] was found to provide the highest chemical yield and enantioselectivity (Table 2, entry 1). Ag[(*R*)-**1a**] promoted the consecutive reactions smoothly to afford the desired product **4a** in 94% yield with fairly good enantioselectivity (85% *ee*). The use of Ag_2CO_3 or the chiral phosphoric acid alone did not afford any product, and the starting ketone **2a** was recovered in a nearly quantitative manner (Table 2, entries 5 and 6). These control experiments strongly suggest that Ag[(*R*)-**1**] is essential for this reaction sequence to proceed in an enantioselective

Table 2: Screening of chiral silver catalysts for the cyclization/enantioselective reduction of **2a** to **4a** and control experiments.[a]

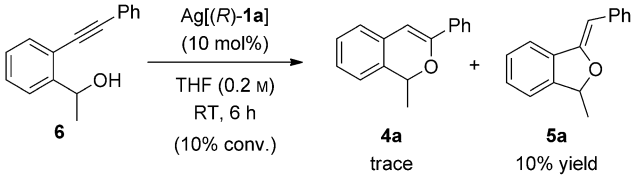


Entry	Catalyst	*t* [h]	Additive	Yield [%][b]	*ee* [%][c]
1	Ag[(*R*)-**1a**]	4	–	94	85
2	Ag[(*R*)-**1b**]	9	–	84	37
3	Ag[(*R*)-**1c**]	7	–	94	66
4	Ag[(*R*)-**1d**]	5	–	77	41
5	Ag_2CO_3[d]	24	–	trace[e]	–
6	(*R*)-**1a**	24	–	trace[e]	–
7[f]	Ag_2CO_3/(*R*)-**1a**	5	–	94	83
8[g]	Ag[(*R*)-**1a**]	48	3 Å MS	80[h]	86
9[g]	Ag[(*R*)-**1a**]	54	4 Å MS	32[i]	77
10[g]	Ag[(*R*)-**1a**]	6	5 Å MS	95	87

[a] Reaction conditions (unless otherwise noted): catalyst (0.02 mmol, 10 mol%), **2a** (0.2 mmol), **3a** (0.22 mmol, 1.1 equiv), THF (1 mL), room temperature. [b] Yield of isolated **4a**. The consumption of **2a** was monitored by TLC. [c] The *ee* value of **4a** was determined by chiral-stationary-phase HPLC analysis. [d] The reaction was carried out with Ag_2CO_3 (0.01 mmol, 5 mol%). [e] Ketone **2a** was recovered in nearly quantitative yield. [f] The catalyst was generated in situ from Ag_2CO_3 (0.01 mmol, 5 mol%) and (*R*)-**1a** (0.02 mmol, 10 mol%). [g] The reaction was carried out with MS (75 mg), Ag[(*R*)-**1a**] (0.015 mmol, 10 mol%), **2a** (0.15 mmol), and **3a** (0.165 mmol, 1.1 equiv) in THF (0.75 mL). [h] Ketone **2a** was recovered in 19% yield. [i] Ketone **2a** was recovered in 66% yield.

manner. The chiral silver phosphate generated in situ from (*R*)-**1a** and Ag_2CO_3 was also examined (Table 2, entry 7). However, preprepared Ag[(*R*)-**1a**] displayed slightly higher enantioselectivity than that of the catalyst generated in situ. We then explored the use of other additives to improve the enantioselectivity of the reaction (Table 2, entries 8–10). The addition of 3 Å and 4 Å molecular sieves (MS) significantly retarded the reaction, and the starting ketone **2a** was not consumed completely, even after 2 days (Table 2, entries 8 and 9, respectively). In particular, a considerable reduction in both the chemical yield and the *ee* value was observed in the presence of 4 Å MS. In contrast, when 5 Å MS were used as an additive, even higher enantioselectivity was observed without any detrimental effect on the chemical yield (Table 2, entry 10).

Next, we explored the mechanism of the silver phosphate catalyzed sequential transformation of **2** into **4** to confirm the participation of the isobenzopyrylium ion as the reactive intermediate. From a mechanistic viewpoint, it can be considered that there are two possible reaction pathways. One pathway involves intramolecular cyclization followed by enantioselective reduction of the isobenzopyrylium intermediate (Scheme 1). However, the same product would be obtained if the reactions occurred in the reverse order, that is, reduction to the alcohol, followed by cyclization.[14] To verify the order of the reaction sequence, we conducted a control experiment with alcohol **6** as a possible intermediate (Scheme 2). When compound **6** was subjected to the catalytic

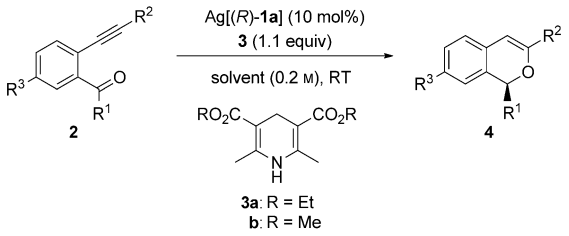


Scheme 2. Mechanistic study: control experiment.

reaction under the influence of Ag[(*R*)-**1a**] (10 mol%) without the Hantzsch ester, the reaction proceeded with very low conversion, even after 6 h, and product **5a** of 5-*exo* cyclization was obtained in 10% yield, whereas almost none of the desired 6-*endo* cyclization product **4a** was observed. This behavior is in contrast to that of the present reaction of the primary substrate **2a**, which afforded the 6-*endo* cyclization product **4a** exclusively in excellent yield within 4 h in the presence of the Hantzsch ester (Table 2, entry 1). Therefore, these results strongly suggest that alcohol **6** is not involved as an intermediate in the present sequential transformation, and that the isobenzopyrylium species participates as the key intermediate, as shown in Scheme 1. Thus, it was concluded that the reaction is initiated by the coordination of Ag[(*R*)-**1**] to the C–C triple bond of **2**. This interaction induces intramolecular nucleophilic attack by the carbonyl oxygen atom to generate an ion pair consisting of the isobenzopyrylium ion and the chiral phosphate. Subsequent enantioselective reduction by Hantzsch ester **3**, followed by metal–proton exchange, regenerates the catalytic species and releases the isochromene product **4**.[15,16]

Having identified the sequential process involving an isobenzopyrylium reactive intermediate, the scope of the reaction was then investigated with a range of alkynylaryl ketones **2** under the optimized reaction conditions. A broad range of alkynylaryl ketones are applicable to the present sequential transformation, although reactivity and enantioselectivity are highly dependent on the nature of the substituents (Table 3). When alkyl and aryl groups were introduced at

Table 3: Scope of the chiral silver phosphate catalyzed transformation of **2** into **4**.[a]



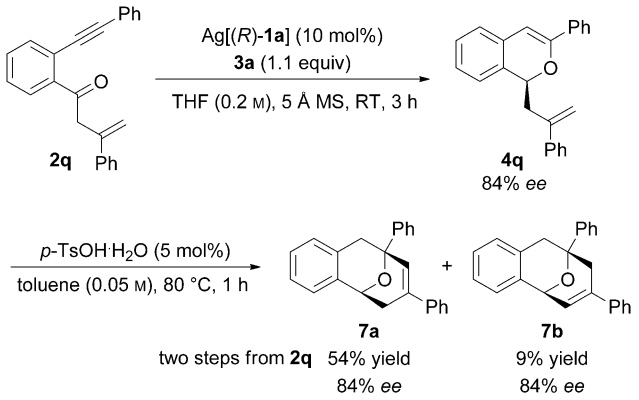
Entry	**2** (R^1, R^2, R^3)	*t* [h]	**4**	Yield [%][b]	*ee* [%][c]
1	**2b** (Me, 4-MeC_6H_4-, H)	11	**4b**	98	81
2	**2c** (Me, 4-$CF_3C_6H_4$-, H)	10	**4c**	87	67
3	**2d** (Me, 4-MeOC_6H_4-, H)	5	**4d**	92	80
4	**2e** (*n*Pr, Ph, H)	9	**4e**	95	81
5	**2f** (*i*Bu, Ph, H)	6	**4f**	89	82
6	**2g** (Me, Ph, F)	6	**4g**	89	87
7	**2h** (Me, *n*Bu, H)	2	**4h**	89	22
8	**2i** (Ph, Ph, H)	24	**4i**	85	92
9	**2j** (4-MeOC_6H_4-, Ph, H)	26	**4j**	81	90
10	**2k** (4-BrC_6H_4-, Ph, H)	26	**4k**	81	91[d]
11	**2l** (4-$CF_3C_6H_4$-, Ph, H)	30	**4l**	84	91
12	**2m** (3-MeOC_6H_4-, Ph, H)	29	**4m**	81	91
13	**2n** (2-TBSOC_6H_4-, Ph, H)	24	**4n**	90	88
14	**2o** (Ph, Ph, F)	28	**4o**	68	90
15	**2p** (Ph, *n*Bu, H)	8	**4p**	86	49

[a] Reactions were carried out with Ag[(*R*)-**1a**] (0.015 mmol, 10 mol%), **2** (0.15 mmol), and **3** (0.165 mmol, 1.1 equiv). For **2b–h**, reactions were carried out with **3a** (R = Et) in THF (0.75 mL) in the presence of 5 Å MS (75 mg). For **2i–p**, reactions were carried out with **3b** (R = Me) in EtOAc (0.75 mL) in the absence of MS. [b] Yield of isolated **4**. [c] The *ee* value of **4** was determined by chiral-stationary-phase HPLC analysis. [d] The absolute configuration of **4k** was determined to be *S* by X-ray crystallographic analysis.[17] See the Supporting Information for details.

the R^1 and R^2 positions, respectively (Table 3, entries 1–6), these substrates exhibited relatively high reactivity and afforded isochromene derivatives **4** in high yields. However, in terms of the enantioselectivity, the introduction of a *para* substituent on the aromatic group at the R^2 position (substrates **2b–d**) led to a slight decrease in enantioselectivity as compared to that observed with the primary substrate **2a** (R^2 = Ph). Substrates bearing linear or branched alkyl chains at the R^1 position (**2e** and **2f**, respectively) also underwent the reaction with a slight reduction in enantioselectivity, whereas fluoro substitution on the tethering benzene ring (**2g**) did not compromise the stereochemical outcome. However, the introduction of an alkyl substituent at the R^2 position led to

a considerable decrease in enantioselectivity (Table 3, entry 7). The reactions of substrates **2i**–**o** bearing aromatic substituents at the R^1 position and a phenyl group at the R^2 position were very sluggish under the optimized conditions and proceeded in low chemical yields, although the *ee* values of the products were around 90%. To our delight, however, these substrates were smoothly converted under modified reaction conditions [with **3b** (R = Me) in ethyl acetate instead of THF and in the absence of 5 Å MS] to give the corresponding isochromene products **4i**–**n** in good yields with high enantioselectivity (Table 3, entries 8–13). A variety of aryl groups at the R^1 position were tolerated in this reaction (substrates **2j**–**n**; Table 3, entries 9–13). Even with a bulky *tert*-butyldimethylsilyloxy (OTBS) substituent in the *ortho* position, the corresponding product **4n** was obtained in 90% yield with 88% *ee* (Table 3, entry 13). The introduction of a fluoro substituent on the tethering benzene ring of a diaryl-substituted ketone (substrate **2o**) did, however, result in a slight decrease in chemical yield, but with little detrimental effect on the enantioselectivity (Table 3, entry 14). However, when an alkyl substituent was introduced at the R^2 position, a considerable reduction in enantioselectivity was observed (Table 3, entry 15).

Finally, the synthetic utility of the present method was demonstrated (Scheme 3). 1-Allyl 1*H*-isochromenes, such as **4q**, have been utilized as key intermediates for the synthesis



Scheme 3. Derivatization of the reaction product. Ts = *p*-toluenesulfonyl.

of the 9-oxabicyclo[3.3.1]nona-2,6-diene framework,[18] and this bicyclic ring structure has been found in some biologically active molecules.[19] We thus attempted to construct the fundamental structure of these compounds in an optically active form by utilizing our methodology followed by an acid-catalyzed annulation reaction. Compound **2q** was subjected to the optimized reaction conditions, and the 1*H*-isochromene product **4q** was obtained with fairly good enantioselectivity (84% *ee*). In the presence of *p*-TsOH·H_2O (5 mol%), **4q** was then converted into the desired bicyclic product **7a** and the regioisomer **7b** in moderate overall yield for the two steps. During the course of the acid-catalyzed annulation, no loss of enantiomeric purity was observed.

In conclusion, we have successfully developed a cyclization/enantioselective-reduction sequence for the transformation of *ortho*-alkynylaryl ketones under the catalysis of a chiral silver phosphate complex to afford 1*H*-isochromene derivatives in high yields with fairly good to high enantioselectivity. A mechanistic study strongly suggested that an isobenzopyrylium cation is involved as the key intermediate in this transformation. We also demonstrated the utility of this methodology for the asymmetric synthesis of the 9-oxabicyclo[3.3.1]nona-2,6-diene framework, which has been found in some biologically active molecules. Further development of the present methodology for application not only to other types of nucleophiles, but also to other transformations involving cationic species that are difficult to perform by other conventional methods will be completed in due course.

Experimental Section

Typical procedure for the reaction of **2a**–**h**: MS (5 Å; 75.0 mg), Hantzsch ester **3a** (41.8 mg, 0.165 mmol), and Ag[(*R*)-**1a**] (10 mol%, 11.8 mg, 0.015 mmol) were placed in a dry test tube. The atmosphere was replaced with argon, THF (0.75 mL) was added to the mixture, and the resulting mixture was stirred vigorously for 10 min. Ketone **2a** (32.8 mg, 0.15 mmol) was then added, and the reaction mixture was stirred for 6 h at room temperature and then filtered through a pad of Al_2O_3 (with EtOAc as the eluent). The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel with hexane/EtOAc/Et_3N (100:1:1) as the eluent to afford **4a** (31.5 mg, 95%) as a white solid. The *ee* value was determined by chiral-stationary-phase HPLC analysis. See the Supporting Information for the reaction of **2i**–**p**.

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[16] When the 4,4-dideuterium-substituted Hantzsch ester was employed, deuterium was introduced at the C1 position exclusively. This result strongly suggests that the reaction proceeded through the formation of an isobenzopyrylium ion as the reactive intermediate. See the Supporting Information for details.

[17] CCDC 954470 [(*S*)-**4k**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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