Asymmetric Catalysis

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Relay Catalysis Using a Rhodium Complex/Chiral Brønsted Acid Binary System: Enantioselective Reduction of a Carbonyl Ylide as the Reactive Intermediate**

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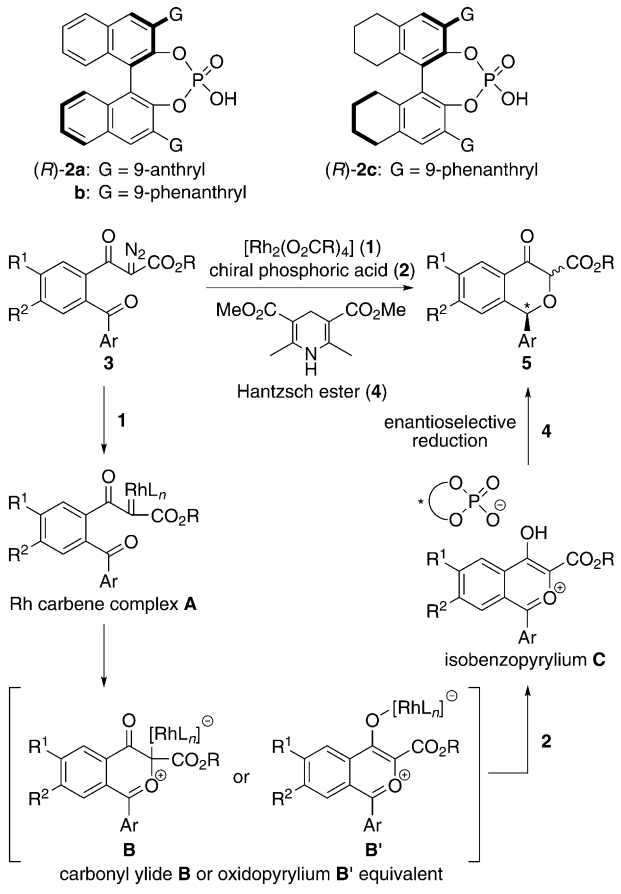
Carbonyl ylides are generally non-isolable reactive intermediates and have been extensively utilized as the dipole in 1,3-dipolar cycloaddition reactions with electron-deficient and electron-rich dipolarophiles to afford polycyclic compounds including five-membered oxacycles.[1] The most efficient method for generating the carbonyl ylide is the interaction of a metal carbene complex with the oxygen atom of a carbonyl group. One practical way of generating metal carbene complexes as a precursor of carbonyl ylides is the decomposition of α-diazocarbonyl compounds by rhodium catalysts,[1,2] and significant progress has been made in developing stepwise sequences for rhodium carbene/carbonyl ylide formation. However, this sequential process with carbonyl ylides has been applied only to 1,3-dipolar cycloaddition reactions and, to the best of our knowledge, further utilization of this attractive intermediate has never been demonstrated in any range of organic transformations. To broaden the scope of the synthetic applicability of the carbonyl ylide, we envisioned the combination of an organocatalytic method with a rhodium-catalyst-initiated reaction sequence in one pot.[3]

Combined use of a transition-metal catalyst and an organocatalyst has stimulated intensive interest in recent years,[3] as it could potentially enable highly efficient and/or unprecedented transformations in a one-pot operation. Indeed, excellent transformations have been established by taking advantage of both of these catalytic approaches, where two types of catalyst combinations have been developed in the binary catalytic system. One is that each reactant is activated simultaneously by one type of catalyst; for instance, a metal catalyst is used to activate the nucleophile while an organocatalyst is used to activate the electrophile in a cooperative manner.[4] The other is the consecutive transformation using a binary catalytic system, that is, relay catalysis for a multistep sequence in which each catalyst promotes one type of reaction in the sequence in one pot.[5] Herein, we report an unprecedented relay catalysis[5] for a carbonyl ylide formation/enantioselective reduction sequence using a binary catalytic system[6] that consisting of the dirhodium(II) tetracarboxylate **1** and chiral phosphoric acid **2** as a chiral Brønsted acid catalyst[7,8] (Scheme 1). The proposed relay catalysis involves a four-step transformation: a) decomposition of the α-diazocarbonyl compound **3** by **1** to generate



Scheme 1. Relay catalysis using a dirhodium(II) tetracarboxylate/chiral phosphoric acid binary system for consecutive transformations.

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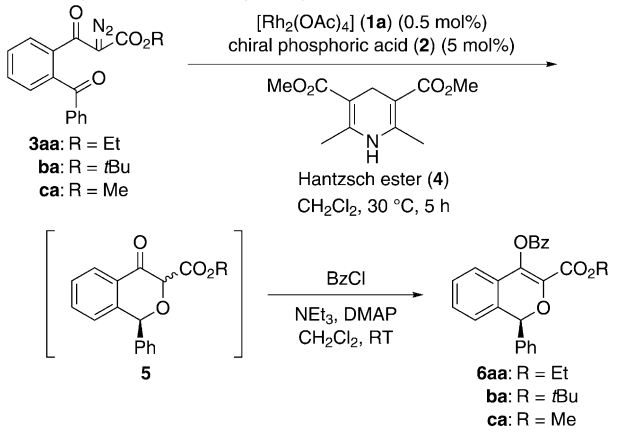
the rhodium carbene complex **A**; b) subsequent intramolecular cyclization to afford the carbonyl ylide equivalent **B** (or tautomerization to oxidopyrylium equivalent **B′**); c) protonation of this transient species by **2** to afford ion pairs of the stable isobenzopyrylium ion **C** and the conjugate base of **2**; and d) termination through a reduction of the cationic intermediate **C** using the Hantzsch ester (**4**)[9] under the influence of chiral conjugate base $\mathbf{2}^-$ to afford the isochroman-4-one derivative **5** in an optically active form.

At the outset of our studies, we conducted a control experiment in the absence of the chiral catalyst **2**. The reaction was performed using the α-diazocarbonyl compound **3aa**, 0.5 mol% of $[Rh_2(OAc)_4]$ (**1a**), and 1.5 equivalents of the Hantzsch ester (**4**) in CH_2Cl_2 at 30°C for 5 hours (Table 1, entry 1). The reaction proceeded cleanly to afford the racemic

Table 1: Optimization of relay catalysis reaction conditions.[a]



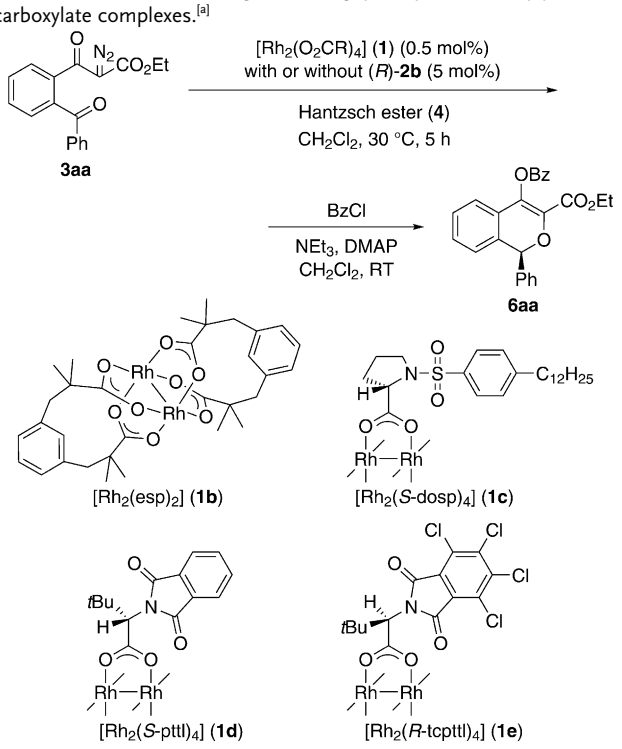
Entry	2	3	6	Yield [%][b]	*ee* [%][c]
1	none	**3aa**	**6aa**	91	–
2	**2a**	**3aa**	**6aa**	88	89
3	**2b**	**3aa**	**6aa**	90	90
4	**2c**	**3aa**	**6aa**	85	80
5[d]	**2b**	**3aa**	**6aa**	81	84
6[e]	**2b**	**3aa**	**6aa**	82	88
7	**2b**	**3ba**	**6ba**	85	60
8	**2b**	**3ca**	**6ca**	83	90

[a] Unless otherwise noted, all reactions were carried out using **1a** (0.001 mmol, 0.5 mol%), (*R*)-**2** (0.01 mmol, 5 mol%), **3** (0.2 mmol), and **4** (0.3 mmol) at 30°C for 5 h. The solution of **3** in CH_2Cl_2 (1 mL) was added to the solution of **1a**, (*R*)-**2**, and **4** in CH_2Cl_2 (1 mL) by syringe pump over a 1 h period. [b] Yield of isolated **6** (2 steps). [c] The enantiomeric excess of **6** was determined by HPLC analysis using a chiral stationary phase. The absolute configuration at the C1 of **5aa** was determined to be *S* by X-ray crystallographic analysis after derivatization to the 4-bromobenzoyloxy isochromene derivative. See the Supporting Information for details. [d] At 10°C for 48 h. [e] At 40°C for 4 h.

isochromanone derivative **5aa**. The enol tautomer of **5aa** was then entrapped by a benzoyl group to afford the benzoyloxy isochromene derivative **6aa** as a racemic sample for chiral stationary phase HPLC analysis. Although **3aa** underwent the transformation without **2**, we investigated the proposed one-pot relay catalysis in the presence of 5 mol% of the chiral acid **2a** where G is a 9-anthryl group (Table 1, entry 2).[10,11] Delightfully, the reaction sequence gave rise to **6aa** with high enantioselectivity, despite the fact that the reaction proceeded without the chiral acid **2** under the same reaction conditions (30°C, 5 h; see entry 1 in Table 1).[12] Additional optimization of the catalyst through changes in the substituent G and the backbone of the binaphthyl unit revealed that slightly higher chemical yields and enantioselectivities were obtained with the use of **2b** bearing 9-phenanthryl substituents (Table 1, entry 3). Modification of the catalyst backbone, thus the octahydrobinaphthyl **2c**, however, resulted in a decrease in the enantioselectivity (Table 1, entry 4). Screening of reaction temperature led to disappointing results; the enantioselectivities were reduced when the temperature was decreased to 10°C or increased to 40°C (Table 1, entries 5 and 6). Additional investigation of the effect of the ester substituent in diazocarbonyl compound **3** demonstrated that the introduction of sterically less demanding substituents proved to be beneficial for enantioselectivity; the enantioselectivity of methyl ester **6ca** is as high as that of ethyl ester **6aa** (Table 1, entries 3, 7, and 8).

In an effort to gain mechanistic insight into the present binary catalytic system, we attempted the reaction using several dirhodium(II) tetracarboxylates **1**, including chiral dirhodium(II) complexes **1c–e** (Table 2). As shown in Table 1, entry 1, the diazocarbonyl **3aa** underwent the consecutive reaction to give **5aa** without the chiral acid **2**, whereas the enantioenriched **5aa** was obtained in the presence of the chiral acid **2**. One plausible pathway to afford the enantioenriched **5aa** is that a chiral dirhodium(II) complex possessing chiral phosphate ligand(s) may serve as an enantioselective catalyst.[13] Thus, ligand exchange would partially occur between the acetate groups in $[Rh_2(OAc)_4]$ (**1a**) and **2** to generate a chiral dirhodium(II) complex. We therefore employed $[Rh_2(esp)_2]$ (**1b**) having tethered dicarboxylate ligands[14] to prevent the plausible ligand exchange reaction. As shown in entry 1 in Table 2 and entry 3 in Table 1, comparable enantioselectivities were observed despite the fact that the extent of the ligand exchange should be different between **1a** and **1b**.[15] These results imply that dirhodium(II) complexes, even when chiral dirhodium(II) complexes might be generated, do not participate in the stereo-determining step, which is the transient assembly of the C–H bond-forming step to generate the stereogenic centers at C1 (and C3) of the isochromanone derivative **5aa**. To obtain direct evidence as to whether a dirhodium(II) complex is involved in the stereo-determining step, we investigated the consecutive transformation using the chiral dirhodium(II) complexes **1c–e**.[16,17] Although these three chiral complexes have been reported as efficient enantioselective catalysts in a range of organic transformations, these complexes yielded the racemic products **5aa** in the absence of **2** (Table 2, entries 2, 4, and 6). In sharp contrast, the combined use of the chiral acid **2b** with chiral dirhodium(II) complexes resulted in the formation of the enantioenriched **5aa** (Table 2, entries 3, 5, and 7), with enantioselectivities as high as that obtained by the original method using the achiral dirhodium(II) **1a** (see Table 1, entry 3). These results strongly suggest that the present transformation sequence involves a four-step process as proposed in Scheme 1 and, in the final step, a rhodium-free intermediate, that is isobenzopyrylium **C**,

Table 2: Mechanistic investigation using (chiral) dirhodium(II) tetracarboxylate complexes.[a]



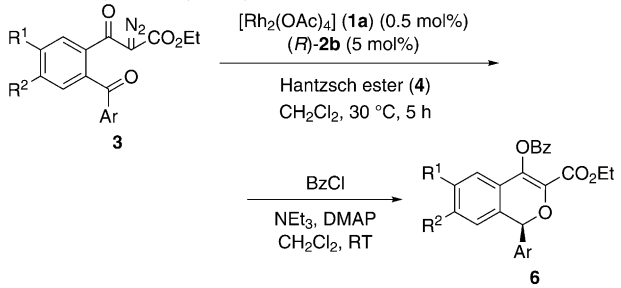
Entry	1	2b [mol%]	Yield [%][b]	*ee* [%][c]
1	**1b**	5	90	89
2	**1c**	none	84	<1
3	**1c**	5	83	90
4	**1d**	none	73	<1
5	**1d**	5	75	89
6	**1e**	none	78	<1
7	**1e**	5	79	90

[a] Unless otherwise noted, all reactions were carried out using **1** (0.001 mmol, 0.5 mol%), (*R*)-**2b** (0.01 mmol, 5 mol%), **3aa** (0.2 mmol), and of **4** (0.3 mmol). The solution of **3aa** in CH_2Cl_2 (1 mL) was added to the solution of **1**, [(*R*)-**2b**], and **4** in CH_2Cl_2 (1 mL) by syringe pump over a 1 h period. [b] Yield of isolated **6aa** (2 steps). [c] The enantiomeric excess of **6aa** was determined by HPLC analysis using a chiral stationary phase.

undergoes enantioselective reduction under the influence of the chiral conjugate base of **2**. It should be emphasized that the use of the chiral phosphoric acid is crucial for obtaining the corresponding products in optically active form.

Having clarified the relay catalysis and the process involving four consecutive transformations, we additionally investigated the present binary catalytic system using a range of α-diazocarbonyl compounds **3**. Table 3 summarizes experiments carried out to probe the scope of the present transformation. Investigation of the effect of the substituent on the Ar group showed that comparable enantioselectivities were observed irrespective of the electronic character and position of the substituent introduced on the phenyl ring (Table 3, entries 1–5). The α-diazocarbonyl compounds **3** having substituents on the basal aromatic ring also underwent the consecutive transformation to afford isochromene derivatives **6** in good yields (Table 3, entries 6 and 7). In these cases,

Table 3: Scope of relay catalysis.[a]



Entry	3	Yield [%][b]	*ee* [%][c]
1	**3ab**: Ar = 4-ClC_6H_4-, $R^1 = R^2 = H$	93	86
2	**3ac**: Ar = 4-$MeOC_6H_4$-, $R^1 = R^2 = H$	84	87
3	**3ad**: Ar = 4-MeC_6H_4-, $R^1 = R^2 = H$	90	89
4	**3ae**: Ar = 3-MeC_6H_4-, $R^1 = R^2 = H$	89	90
5	**3af**: Ar = 2-MeC_6H_4-, $R^1 = R^2 = H$	92	88
6	**3ag**: Ar = Ph, $R^1 = H$, $R^2 = Br$	85	92
7	**3ah**: Ar = Ph, $R^1 = Cl$, $R^2 = Cl$	81	74

[a] Unless otherwise noted, all reactions were carried out using **1a** (0.001 mmol, 0.5 mol%), (*R*)-**2b** (0.01 mmol, 5 mol%), of **3** (0.2 mmol), and of **4** (0.3 mmol). The solution of **3** in CH_2Cl_2 (1 mL) was added to the solution of **1a**, (*R*)-**2b**, and **4** in CH_2Cl_2 (1 mL) by syringe pump over a 1 h period. [b] Yield of isolated **6** (2 steps). [c] The enantiomeric excess of **6** was determined by HPLC analysis using a chiral stationary phase.

however, the enantioselectivities were significantly dependent upon the substituent pattern, with the highest enantioselectivity achieved when $R^1 = H$.

In conclusion we have demonstrated a one-pot relay catalysis for a carbonyl ylide formation/enantioselective reduction sequence using a binary catalytic system consisting of a dirhodium(II) tetracarboxylate and a chiral phosphoric acid as a chiral Brønsted acid catalyst. The proposed relay catalysis is composed of four consecutive reactions involving isobenzopyrylium as a reactive key intermediate. More importantly, the use of the chiral phosphoric acid was found to be essential for obtaining the corresponding products in an enantioselective fashion, which was confirmed by mechanistic investigations using chiral dirhodium(II) complexes. By virtue of the reactive isobenzopyrylium intermediate under the influence of chiral conjugate base $\mathbf{2}^-$, the present method would be applicable to the reactions with nucleophilic components other than the Hantzsch ester, thus yielding isochromanone derivatives in an enantioenriched form. Additional studies to elucidate the reaction mechanism in detail and determine the origin of the stereochemical outcome of the present consecutive transformation are in progress, with the aim of developing efficient enantioselective transformations on the basis of the present relay catalysis.

Experimental Section

$[Rh_2(OAc)_4]$ (**1a**, 0.5 mol%, 0.44 mg, 0.001 mmol), (*R*)-**2b** (5 mol%, 7.01 mg, 0.01 mmol), and Hantzsch ester (**4**, 67.6 mg, 0.30 mmol) were added to a dried test tube. The atmosphere was replaced with argon and then the mixture was dissolved in CH_2Cl_2 (1 mL). **3aa** (89% purity, 72.4 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was added to the solution at 30°C over a 1 h period using a syringe pump. After

completion of the addition, the mixture was stirred at 30 °C for additional 4 h and then the reaction mixture was cooled to 0 °C. NEt_3 (139 μL, 1.0 mmol), BzCl (46.4 μL, 0.40 mmol), and DMAP (10 mol %, 2.44 mg, 0.02 mmol) were added to the reaction mixture at 0 °C and then the mixture was stirred at RT for 12 h. The reaction mixture was directly purified by flash column chromatography on silica gel (CH_2Cl_2) to give **6aa** in 90 % yield as a white solid. The enantiomeric excess was determined by chiral stationary phase HPLC analysis.

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[10] Chiral phosphoric acids **2** were washed with aqueous HCl solution (2 M) and then water, after purification by silica gel column chromatography. See the Supporting Information for details.

[11] The decrease in the amount of acid catalyst **2** from 5 mol % led to a marked reduction in reproducibility of the enantioselectivity.

[12] The reaction of **3aa** with Hantzsch ester (**4**) was conducted using the chiral phosphoric acid **2a** alone under similar reaction conditions (30 °C, 24 h). Substantial amount of **3aa** remained unchanged in the absence of $[Rh_2(OAc)_4]$ (**1a**), although decomposition of **4** to a pyridine derivative was occurred.

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[15] $[Rh_2(esp)_2]$ (**1b**) also accelerated the consecutive transformation without acid catalyst **2** under the same reaction conditions (87 % yield).

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[17] For selected examples of $[Rh_2(pttl)_4]$ (**1d**) and $[Rh_2(tcpttl)_4]$ (**1e**) as enantioselective catalysts for 1,3-dipolar cycloaddition reactions, see: a) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417 – 1418; b) S. Kitagaki, M. Yasugahira, M. Anada, M. Nakajima, S. Hashimoto, *Tetrahedron Lett.* **2000**, *41*, 5931 – 5935; c) H. Tsutsui, N. Shimada, T. Abe, M. Anada, M. Nakajima, S. Nakamura, H. Nambu, S. Hashimoto, *Adv. Synth. Catal.* **2007**, *349*, 521 – 526; d) N. Shimada, M. Anada, S. Nakamura, H. Nambu, H. Tsutsui, S. Hashimoto, *Org. Lett.* **2008**, *10*, 3603 – 3606; e) H. Nambu, M. Hikime, J. Krishnamurthi, M. Kamiya, N. Shimada, S. Hashimoto, *Tetrahedron Lett.* **2009**, *50*, 3675 – 3678; f) N. Shimada, T. Hanari, Y. Kurosaki, K. Takeda, M. Anada, H. Nambu, M. Shiro, S. Hashimoto, *J. Org. Chem.* **2010**, *75*, 6039 – 6042.

