Asymmetric Catalysis

DOI: 10.1002/ange.200904024

Synthesis of Chiral Tetrasubstituted Alkenes by an Asymmetric Cascade Reaction Catalyzed Cooperatively by Cationic Rhodium(I) and Silver(I) Complexes**

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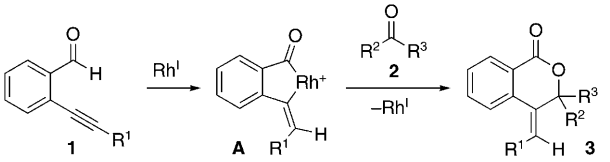
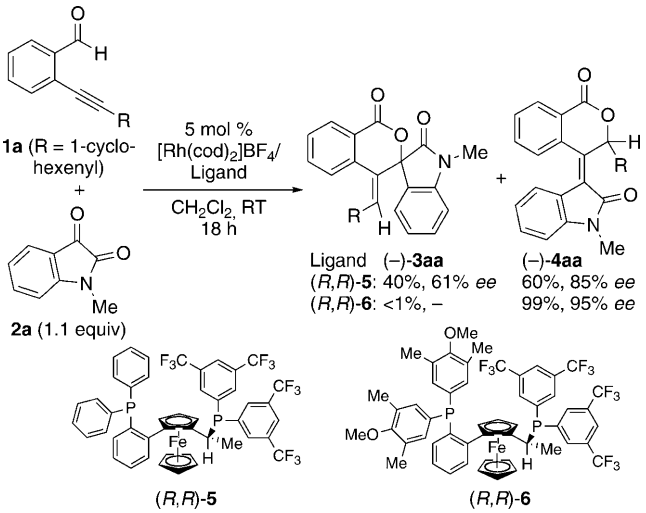
Cascade reactions that can furnish complex organic molecules in one step have attracted much attention in organic synthesis.[1] Obviously, asymmetric cascade reactions that can control the chirality of the product are more attractive.[2] Herein, we describe a novel asymmetric cascade reaction that is catalyzed cooperatively by cationic rhodium(I) and silver(I) complexes. The reaction can produce tetrasubstituted alkenes which possess helical and/or central chirality.[3] Feringa and co-workers have demonstrated that tetrasubstituted helical alkenes, which possess both central and helical chirality, can be applied to light-driven molecular motors.[4] Therefore helical alkenes are attracting growing interest. Furthermore, the present asymmetric cascade reaction might include unprecedented sequential activation of π- and σ-bonds by cationic transition-metal complexes.

Our research group has recently reported that a cationic rhodium(I)/chiral bisphosphine complex catalyzes a highly enantioselective [4+2] annulation of 2-alkynylbenzaldehydes **1** with carbonyl compounds **2**, and the reaction leads to benzopyranones **3** in high yields and with high *ee* values (Scheme 1).[5] The mechanism of the [4+2] annulation is proposed as follows:[5,6] A rhodium hydride species is generated through activation of the C–H bond of the formyl group of **1**, which adds intramolecularly to the pendant alkyne to give five-membered acylrhodacycle **A**. An intermolecular [4+2] cycloaddition between **A** and the carbonyl group of **2**, and subsequent reductive elimination furnishes optically active benzopyranone **3**.

On the other hand, when the reaction of 2-alkynylbenzaldehyde **1a**, possessing a cyclohexenyl group at the alkyne terminus, and *N*-methylisatin (**2a**) was conducted in the presence of a cationic rhodium(I)/(*R*,*R*)-SL-W001-1 ((*R*,*R*)-**5**) catalyst, the unexpected benzopyranone **4aa**, possessing a tetrasubstituted alkene moiety, was obtained along with the expected benzopyranone **3aa** (Scheme 2). Screening of chiral ligands revealed that the use of (*R*,*R*)-SL-W005-1 ((*R*,*R*)-**6**) furnished **4aa** in almost quantitative yield with a high *ee* value (Scheme 2). However the reactions of 2-alkynylbenzaldehydes **1**, possessing an alkyl, isopropenyl, or aryl group at the alkyne terminus, and **2a** in the presence of the cationic rhodium(I) catalyst with (*R*,*R*)-**5** or (*R*,*R*)-**6** furnished benzopyranones **3** in high yields, and only trace amounts (< 2% yield) of benzopyranones **4** were generated.



Scheme 1. Rhodium-catalyzed enantioselective [4+2] annulation of 2-alkynylbenzaldehydes **1** with carbonyl compounds **2**.



Scheme 2. Rhodium-catalyzed enantioselective synthesis of tetrasubstituted alkene **4aa** from **1a** and **2a**. cod = cycloocta-l,5-diene.

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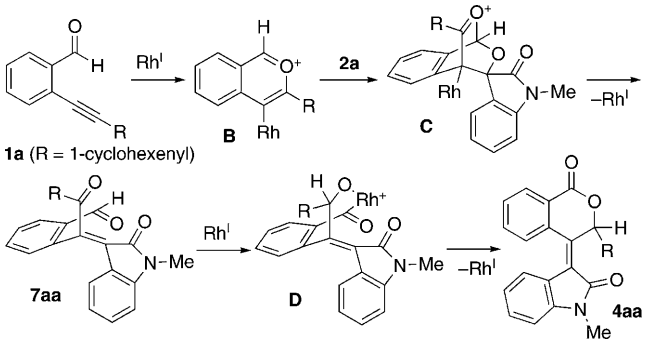
[**] This work was supported by Grants-in-Aid for Scientific Research from MEXT (Japan) (grant nos. 20675002, 19028015, and 21·7999). We thank Solvias AG for the gift of walphos ligands (*R*,*R*)-**5** and (*R*,*R*)-**6**, Takasago Int. Co. for the gift of (*R*)-segphos, and Umicore for generous support in supplying a rhodium complex.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200904024.

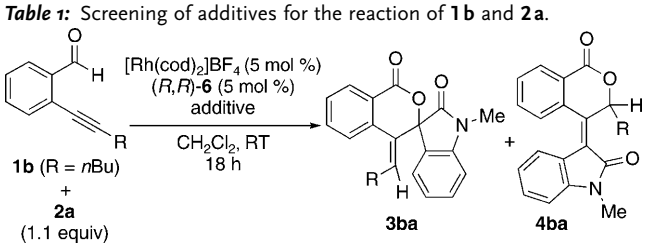


Scheme 3. Possible mechanism for the formation of **4aa**.

precedents for the formation of a metalbenzopyrilium intermediate [7] through the reaction of the 2-alkynylbenzaldehyde and a π-electrophilic transition-metal complex, which reacts intermolecularly with alkenes[8] or alkynes[9] to form various six-membered compounds.[10] Therefore the π-electrophilic cationic rhodium(I) complex would react with an alkyne moiety of **1a** to form rhodiumbenzopyrilium intermediate **B**. Although there is no precedent for a cycloaddition between the metalbenzopyrilium intermediate and a C=O bond, cyclic dicarbonyl compound **2a** might react with intermediate **B** to form ketoaldehyde **7aa** through intermediate **C**.[11] Enantioselective intramolecular ketone hydroacylation of **7aa** proceeds through rhodacycle **D** to give tetrasubstituted alkene **4aa**.[12]

As the π-electrophilicity of the cationic rhodium(I) complex might not be strong enough to promote the formation of intermediate **B**, the reaction of 2-(1-hexynyl)-benzaldehyde (**1b**) and **2a** was investigated in the presence of the cationic rhodium(I)/(*R*,*R*)-**6** complex (5 mol%) and an additional strongly π-electrophilic transition-metal complex (10 mol%, Table 1, entries 1–4). Although $AgBF_4$ showed the highest selectivity for the formation of tetrasubstituted alkene **4ba** (Table 1, entry 4), the yield was extremely low. As the brownish CH_2Cl_2 solution of the cationic rhodium(I)/(*R*,*R*)-**6** complex became green by adding $AgBF_4$, we anticipated that $AgBF_4$ might interact with rhodium to form the greenish

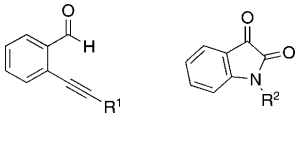
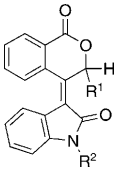
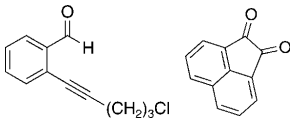
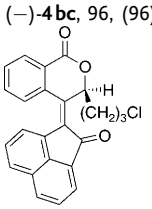
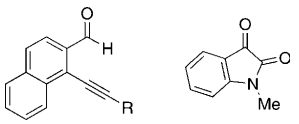
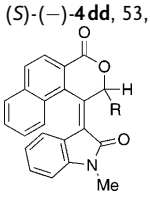
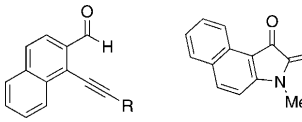
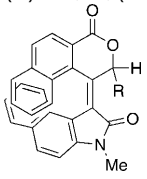
Table 1: Screening of additives for the reaction of **1b** and **2a**.



Entry	Additives	Conv. [%]	Yield of (−)-**3ba** [%][a]	Yield of (−)-**4ba** [%][a]	*ee* of (−)-**4ba** [%][b]
1	$[Pd(MeCN)_4](BF_4)_2$ (10 mol%)	100	10	2	98
2	$PtCl_2$ (10 mol%)	100	89	3	87
3	$Cu(OTf)_2$ (10 mol%)	30	5	<1	–
4	$AgBF_4$ (10 mol%)	30	3	6	98
5	$AgBF_4$ (10 mol%), PPh_3 (10 mol%)	100	4	53	98
6	$AgBF_4$ (10 mol%), PPh_3 (5 mol%)	100	3	82	98
7	$AgBF_4$ (5 mol%), PPh_3 (5 mol%)	100	17	82	98

[a] Yield of isolated product. [b] Determined by chiral HPLC methods. Tf = trifluoromethanesulfonyl.

Table 2: Enantioselective synthesis of chiral tetrasubstituted alkenes **4** from alkynylarylaldehydes **1b–k** and carbonyl compounds **2a–e**.[a]

Entry	**1** (R^1)	**2** (R^2)	**4**, Yield [%][a], (*ee* [%][g]), [d.r.]
			
1	**1b** (*n*Bu)	**2a** (Me)	(−)-**4ba**, 82, (98)
2	**1c** (Cy)	**2a**	(−)-**4ca**, 67[c], (98)
3	**1d** ($Cl(CH_2)_3$)	**2a**	(−)-**4da**, 86, (98)
4	**1e** (2-isopropenyl)	**2a**	(−)-**4ea**, 75, (>99)
5	**1f** (Ph)	**2a**	(−)-**4fa**, 96, (96)
6	**1g** ($2\text{-}ClC_6H_4$)	**2a**	(−)-**4ga**, 74, (99)
7	**1b**	**2b** (Ph)	(−)-**4bb**, 82, (98)
8	**1b**	**2c** (H)	(−)-**4bc**, 96, (96)
			
9	**1b**	**2d**	(−)-**4bd**, 52, (94)
10	**1d**	**2d**	(*S*)-(−)-**4dd**, 53, (95)
			
11	**1h** (*n*Bu)	**2a**	(+)-**4ha**, 72, (94), [>99:1]
12	**1i** ($Cl(CH_2)_3$)	**2a**	(+)-**4ia**, 68[d], (95), [>99:1]
13	**1j** (2-isopropenyl)	**2a**	(+)-**4ja**, 79, (>99), [>99:1]
14	**1k** (Ph)	**2a**	(−)-**4ka**, 95, (>99), [>99:1]
			
15[e]	**1h**	**2e**	(−)-**4he**, 58, (30), [>99:1]
			(−)-**4he**, 19, (99), [>99:1][f]
16[e]	**1k**	**2e**	(+)-**4ke**, 79, (20), [>99:1]

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (5 mol%), (*R*,*R*)-**6** (5 mol%), PPh_3 (5 mol%), $AgBF_4$ (10 mol%), **1b–k** (1.0 equiv), and **2a–e** (1.1 equiv) in CH_2Cl_2 at RT for 18–72 h. [b] Yield of isolated product. [c] Conversion of **1c** was about 85% after 66 h. [d] Conversion of **1i** was about 80% after 72 h. [e] (*R*)-Segphos was used as a ligand. [f] After a single recrystallization from *n*-hexane/EtOAc (3:1). [g] The *ee* values were determined by chiral HPLC methods. Cy = cyclohexyl, (*R*)-Segphos = (*R*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine).

mixture, which lowers the catalytic activity towards both π- and σ-bond activation. Indeed, addition of 10 mol% of PPh_3, which would occupy free coordination sites of rhodium, significantly increased the yield of **4ba** (Table 1, entry 5).[13] Decreasing the amount of PPh_3 to 5 mol% further increased the yield of **4ba** (Table 1, entry 6), while decreasing the amount of $AgBF_4$ to 5 mol% increased the yield of **3ba**, which was not easily separable from **4ba** by silica gel chromatography (Table 1, entry 7). It was reported that a cationic silver(I) complex reacts with a 2-alkynylbenzaldehyde to form the corresponding benzopyrilium intermediate.[14] Therefore, $AgBF_4$ might catalyze the formation of ketoaldehyde **7ba** (R = *n*Bu in Scheme 3). Contrary to our expectation, the reaction of **1b**, **2a**, and $AgBF_4$ (10 mol%) at room temperature did not furnish **7ba** and an unidentified mixture of products, derived from **1b**, was generated. This result suggests that rhodium(I) and silver(I) complexes cooperatively catalyze the present cascade reaction, although the precise role of $AgBF_4$ is not clear at present.

Thus, we explored the scope of this process by using 5 mol% of the cationic rhodium(I)/(*R*,*R*)-**6**/PPh_3 complex and 10 mol% of $AgBF_4$ at room temperature as shown in Table 2. Alkyl- (Table 2, entries 1–3), alkenyl- (Table 2, entry 4), and aryl-substituted 2-alkynylbenzaldehydes (Table 2, entries 5 and 6) could participate in this reaction. Not only *N*-methylisatin (Table 2, entries 1–6) but also *N*-phenylisatin (Table 2, entry 7), NH-isatin (Table 2, entry 8), and acenaphthenequinone (Table 2, entries 9 and 10) could be employed for this reaction.[15–17] Also, this reaction was successfully applied to the enantio- and diastereoselective synthesis of tetrasubstituted helical alkenes possessing both central and helical chirality. 1-Alkynyl-2-naphthaldehyde **1h** reacted with **2a** to give helical alkene **4ha** as a single diastereomer in good yield with a high *ee* value (Table 2, entry 11). Chroloalkyl- (Table 2, entry 12), isopropenyl- (Table 2, entry 13), and phenyl-substituted 2-alkynyl-1-naphthaldehydes (Table 2, entry 14) could also participate in this reaction. Sterically more demanding helical alkenes **4he** and **4ke** could be synthesized using (*R*)-segphos as a ligand (Table 2, entries 15 and 16). Although low enantioselectivity was observed, the *ee* value could be readily improved after a single recrystallization (Table 2, entry 15). The relative configuration of **4ha** and **4he** were determined by X-ray crystallographic analysis (Figure 1).[17]

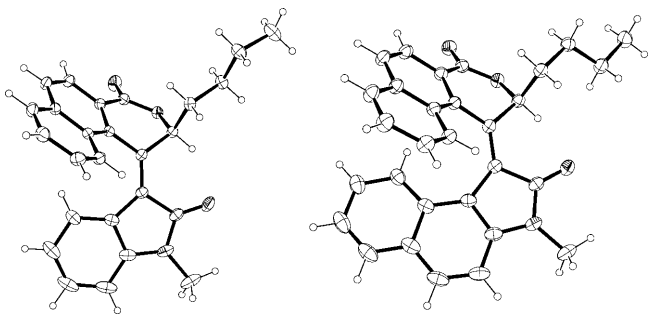


Figure 1. ORTEP diagrams of tetrasubstituted helical alkenes (±)-**4ha** (left) and (±)-**4he** (right) drawn at the 30% probability level.

Photophysical properties of helical alkenes **4** were briefly examined (Table 3). As expected, overcrowded helical alkenes **4he** and **4ke** (Table 3, entries 5 and 6) exhibit larger optical rotation values and bathochromic shifts in UV absorption values in comparison with the less crowded helical alkenes **4ha**–**4ka** (Table 3, entries 1–4).

Table 3: Photophysical data of helical alkenes **4**.[a]

Entry	4	$[\alpha]_D^{25}$[b]	UV absorption λ_{max} [nm][c]
1	(+)-**4ha**	+340	368
2	(+)-**4ia**	+301	369
3	(+)-**4ja**	+238	368
4	(−)-**4ka**	−28	369
5	(−)-**4he**	−1219	479
6	(+)-**4ke**	+2064	483

[a] Measured in $CHCl_3$. [b] Values are calculated as 100% *ee*. [c] Only the longest absorption maximum wavelengths are given.

Future studies will focus on elucidation of the precise mechanism of this cooperative catalysis and the behavior of helical alkenes under UV irradiation.[18]

Received: July 21, 2009
Published online: September 22, 2009

Keywords: alkenes · asymmetric catalysis · cascade reactions · helical chirality · rhodium

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[11] Alternatively, a carbonyl alkyne metathesis between the C=O bond of **2a** and the alkyne moiety of **1a** might proceed to yield **7aa**. However, the reactions of diphenylacetylene and **2a** in the presence of the cationic rhodium(I) and silver(I) complexes at room temperature did not furnish the corresponding metathesis product and the starting materials were recovered. Therefore the mechanism of the carbonyl alkyne metathesis might be excluded. For Ag^{I}-catalyzed carbonyl alkyne metathesis, see: a) J. U. Rhee, M. J. Krische, *Org. Lett.* **2005**, *7*, 2493; for Rh^{I}-catalyzed carbonyl alkyne metathesis, see: b) K. Tanaka, K. Sasaki, K. Takeishi, K. Sugishima, *Chem. Commun.* **2005**, 4711.

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[13] The color of the catalyst mixture became brown upon the addition of PPh_3.

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[15] Acyclic 1,2-dicarbonyl compounds, such as α-ketoesters and 1,2-diketones, failed to react with **1b**.

[16] The absolute configuration of (−)-(*E*)-**4dd** was determined to be *S* by X-ray crystallographic analysis of the corresponding *Z* isomer.

[17] CCDC 738708 (**4aa**), 738707 ((*S*)-(−)-(*Z*)-**4dd**), 738706 (**4ha**), and 738705 (**4he**) contain 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.

[18] Our preliminary study revealed that a red $(CH_2Cl)_2$ solution of (*E*)-**4he** was maintained at room temperature for a week under irradiation with visible light to give a blue $(CH_2Cl)_2$ solution of (*Z*)-**4he**.