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Rhodium-Catalyzed Asymmetric Reductive Cyclization of Heteroatom-Linked 5-Alkynals with Heteroatom-Substituted Acetaldehydes

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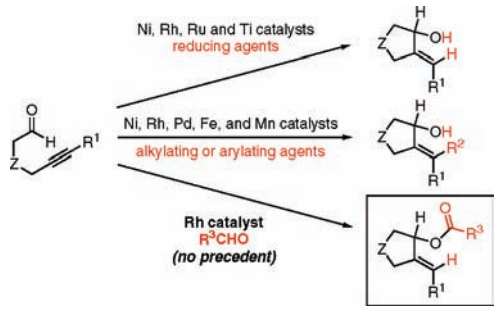
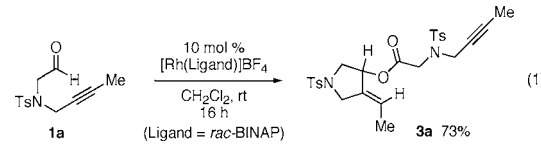
Transition-metal-catalyzed cyclizations of alkynals have been extensively studied for the stereoselective synthesis of cyclic allylic alcohols.[1] A number of efficient reductive cyclizations of alkynals leading to cyclic allylic alcohols with a trisubstituted alkene component have been reported that use nickel,[2] rhodium,[3] ruthenium,[4] or titanium[5] complexes as catalysts and organozincs,[2a] organosilanes,[2b−e,3a,b,5] hydrogen,[3c,d] or alcohols[4] as reducing agents (Scheme 1). Also, efficient alkylative or arylative cyclizations of alkynals leading to cyclic allylic alcohols with a tetrasubstituted alkene component have been reported that use nickel,[6] rhodium,[7] palladium,[8] iron,[9] or manganese[10] complexes as catalysts and organozincs,[6a] organozirconiums,[6b] organoborons,[6c,d] organoboronics,[7,8] organolithiums,[9] or organomagnesiums[10] as alkylating or arylating agents (Scheme 1). In this communication, we disclose an unprecedented mode of cyclization of alkynals that leads to cyclic allylic esters with a trisubstituted alkene component, namely, *asymmetric reductive cyclization of heteroatom-linked 5-alkynals with heteroatom-substituted acetaldehydes* using a cationic rhodium(I)/(*R*)-H$_8$-BINAP complex as a catalyst (Scheme 1).

Scheme 1



Our research group previously reported that a cationic rhodium(I)/*rac*-BINAP complex is able to catalyze the intramolecular hydroacylation of methylene-linked 5-alkynals **1** (Z = CH$_2$), leading to 2-alkylidenecyclopentanones **2** via acylrhodacycle **A** generated through aldehyde C−H bond activation followed by alkyne insertion (Scheme 2).[11] On the other hand, the rhodium-catalyzed reductive cyclization of heteroatom-linked 5-alkynals through oxarhodacyclopentenes had already been reported.[3] We anticipated that oxarhodacyclopentene **B** generated from heteroatom-linked 5-alkynals **1** (Z = NTs or O) and rhodium would react with the alkyne[12] or aldehyde component of **1** in the absence of reducing agents (Scheme 2).

Thus, the reaction of tosylamide-linked 5-alkynal **1a** in the presence of the cationic rhodium(I)/*rac*-BINAP complex (10 mol %) at room temperature was examined. We were pleased to find that an unprecedented reductive cyclization with aldehyde proceeded to yield cyclic allylic ester **3a** in 73% yield (eq 1):



The effect of the bisphosphine ligand in the reaction of **1a** was then examined (Table 1). The study revealed that biaryl bisphosphine ligands are effective for the reductive cyclization (entries 3−5), while nonbiaryl bisphosphine ligands are totally ineffective (entries 1 and 2).[13] (*R*)-H$_8$-BINAP was the best ligand, and the desired product **3a** was obtained in the highest yield with perfect enantioselectivity (entry 5).

Scheme 2

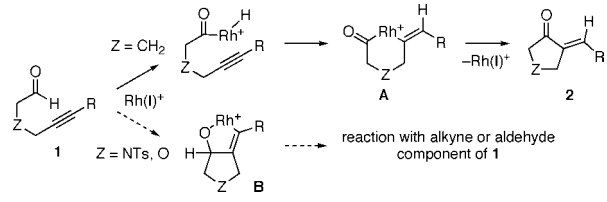
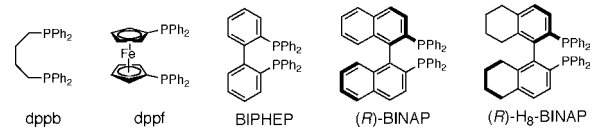


Table 1. Effect of the Ligand on Rh-Catalyzed Enantioselective Homo-Reductive Cyclization of **1a** Leading to **3a** (eq 1)[a]



entry	ligand	conv. (%)	yield (%)[b]	ee (%)
1	dppb	100	0	−
2	dppf	100	0	−
3	BIPHEP	88	33	−
4	(*R*)-BINAP	100	72	98 (+)
5	(*R*)-H$_8$-BINAP	100	78	>99 (+)

[a] [Rh(ligand)]BF$_4$ (0.010 mmol), **1a** (0.10 mmol), and CH$_2$Cl$_2$ (1.0 mL) were used. [b] Isolated yield.

The series of 5-alkynals **1a−f** were subjected to the above optimal reaction conditions (Table 2). Both alkyl- (**1a−d**, entries 1−4) and phenyl-substituted (**1e**, entry 5) tosylamide-linked 5-alkynals could participate in this reaction to yield the corresponding esters in high yields with outstanding ee values. Not only tosylamide-linked 5-alkynals but also ether-linked 5-alkynal **1f** could participate in this reaction (entry 6).

We subsequently investigated rhodium-catalyzed enantioselective cross-reductive cyclizations of 5-alkynals **1a−f** with heteroatom-substituted acetaldehydes **4a−c** (Table 3).[14] Commercially available benzyloxyacetaldehyde (**4a**) reacted with 5-alkynals **1a−f** to yield the corresponding esters in good yields with excellent ee values (entries 1−6). Not only **4a** but also phenoxyacetaldehyde (**4b**, entry

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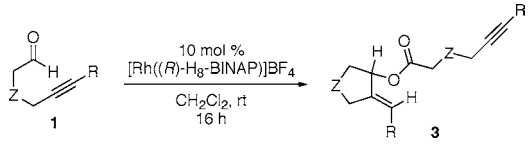
7) and a nitrogen-substituted acetaldehyde (**4c**, entry 8) could react with **1f** to yield the corresponding esters with excellent ee values. The absolute configuration of (+)-**5ca** was determined to be *S* by the anomalous dispersion method.

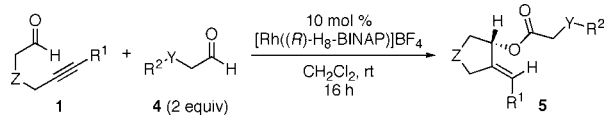
Table 2. Rh-Catalyzed Enantioselective Homo-Reductive Cyclizations of 5-Alkynals **1a**−**f**[a]



entry	**1** (Z, R)	**3**	% yield[b] (% ee)
1	**1a** (NTs, Me)	(+)-**3a**	78 (>99)
2	**1b** (NTs, *n*-Bu)	(+)-**3b**	72 (98)
3	**1c** (NTs, *n*-$C_{10}H_{21}$)	(+)-**3c**	82 (>99)
4	**1d** (NTs, Cy)	(+)-**3d**	81 (98)
5	**1e** (NTs, Ph)	(+)-**3e**	83 (>99)
6[c]	**1f** [O, $(CH_2)_3$Ph]	(−)-**3f**	75 (99)

[a] [Rh((*R*)-H_8-BINAP)]BF_4 (0.020 mmol), **1a**−**f** (0.20 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Isolated yield. [c] Using 4.0 mL of CH_2Cl_2.

Table 3. Rh-Catalyzed Enantioselective Cross-Reductive Cyclizations of 5-Alkynals **1a**−**f** with Aldehydes **4a**−**c**[a]

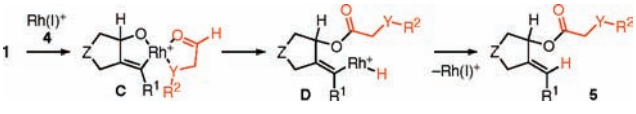


entry	**1** (Z, R^1)	**4** (Y, R^2)	**5**	% yield[b] (% ee)
1	**1a** (NTs, Me)	**4a** (O, Bn)	(+)-**5aa**	69 (>99)
2[c]	**1b** (NTs, *n*-Bu)	**4a** (O, Bn)	(+)-**5ba**	59 (>99)
3[c]	**1c** (NTs, *n*-$C_{10}H_{21}$)	**4a** (O, Bn)	(*S*)-(+)-**5ca**	57 (98)
4	**1d** (NTs, Cy)	**4a** (O, Bn)	(+)-**5da**	60 (99)
5	**1e** (NTs, Ph)	**4a** (O, Bn)	(−)-**5ea**	67 (>99)
6	**1f** [O, $(CH_2)_3$Ph]	**4a** (O, Bn)	(−)-**5fa**	55 (>99)
7	**1f** [O, $(CH_2)_3$Ph]	**4b** (O, Ph)	(−)-**5fb**	66 (>99)
8	**1f** [O, $(CH_2)_3$Ph]	**4c** (NTs, Bn)	(−)-**5fc**	49 (>99)

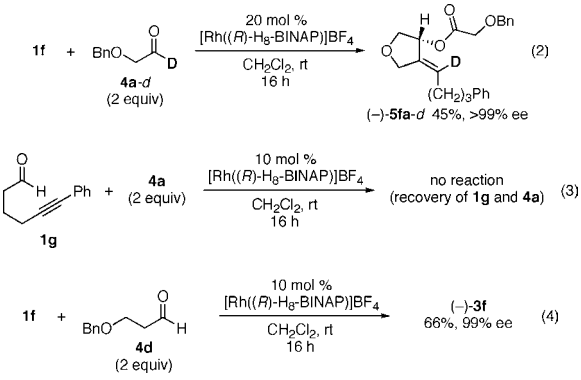
[a] [Rh((*R*)-H_8−BINAP)]BF_4 (0.020 mmol), **1a-f** (0.20 mmol), **4a-c** (0.40 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Isolated yield. [c] At 40 °C.

Scheme 3 depicts a possible mechanism for the present reductive cyclization. We believe that heteroatom-linked 5-alkynal **1** reacts with the rhodium(I) catalyst, affording oxarhodacyclopentene **C** with chelating heteroatom-substituted acetaldehyde **4**. σ-Bond methathesis[2c,3c] of the aldehyde C−H bond and the Rh−O bond would afford intermediate **D**, which would undergo reductive elimination to afford ester **5**.

Scheme 3



Consistent with the above pathway, the reaction of **1f** with deuterium-labeled aldehyde **4a**-*d* led to selective and quantitative incorporation of deuterium in the vinylic position of the product **5fa**-*d* (eq 2). Furthermore, starting materials were recovered unchanged in the reaction of methylene-linked 5-alkynal **1g** and benzyloxyacetaldehyde (**4a**) (eq 3), and ether-linked 5-alkynal **1f** failed to react with 3-benzyloxypropionaldehyde (**4d**) but reacted with **1f** to yield the homo-reductive cyclization product **3f** (eq 4). Therefore, the rapid oxarhodacyclopentene formation and the five-membered chelation of the heteroatom-substituted acetaldehyde to the cationic rhodium are essential in promoting the present reductive cyclization.



In conclusion, we have established that a cationic rhodium(I)/(*R*)-H_8-BINAP complex catalyzes the asymmetric reductive cyclization of heteroatom-linked 5-alkynals with heteroatom-substituted acetaldehydes. Future studies will focus on detailed mechanistic studies and expanding the reaction scope beyond heteroatom-substituted acetaldehydes.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Intramolecular hydroacylation products were generated in 20−50% yield, except for unidentified mixtures of byproducts in entries 1−3, although these hydroacylation products could not be isolated in pure forms.

(14) Homoreductive cyclization products **3** were generated in 5−30% yield, except for cross-reductive cyclization products **5**.

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