Rh-Catalyzed Kinetic Resolution of Enynes and Highly Enantioselective Formation of 4-Alkenyl-2,3-disubstituted Tetrahydrofurans

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To obtain enantiomerically pure compounds has been a long journey begun hundreds years ago, and has been continually targeted by organic chemists.[1] The kinetic resolution has been established as a strategy for asymmetric synthesis to reach the enantiomerically pure compounds.[2] With extensive studies and developments in metal-catalyzed asymmetric reactions during the past 30 years, the metal-catalyzed kinetic resolution has been expanded and considered as a synthetically useful method.[3] If a process combines kinetic resolution and diastereoselectivity together, an enantiomeric product with multiple stereogenic centers can be obtained from racemic starting materials via single step. Obtaining this type of enantio-merically pure product along with enantiomerically pure unreacted starting materials through the process will be useful for organic syntheses. In this communication, we described a kinetic resolution process coupled with a high diastereoselectivity in Rh-catalyzed cycloisomerization of enynes, in which excellent stereoselectivity (over 99% ee for both products, which contain two adjacent stereogenic centers, and unreacted starting materials) was observed.

The transition metal-catalyzed cycloisomerization of enynes has been extensively studied as an elegant method to construct heterocyclic and carbocyclic compounds.[4] However, the asymmetric version of the reaction has not been fully developed. [5] Recently, we successfully achieved highly enantioselective Rh-catalyzed cycloisomerization of enynes.[6] To examine the reactivity of the substrates with substituents at the allylic position in the cyclo-isomerization, the reaction of racemic **1** was carried out in the presence of (*rac*)-BINAP, [Rh(COD)Cl]₂, and AgSbF₆ at room temperature for 2 min. The *trans*-(±)-**2** was obtained as the sole product. Exploration of the functional group tolerance revealed that the alkenyl ether substituted tetrahydrofuran *trans*-(±)-**4** can be prepared from readily available allylic ether **3** under the similar conditions. When the unprotected allylic alcohol **5** was used under the similar reaction condition, the tetrahydrofuran with an aldehyde side chain, *trans*-(±)-**6**, was formed in 92% yield. Further explora-tion of the substrates scope indicated that the tetrahydrofurans with a ketone functional group, *trans*-(±)-**8a** and *trans*-(±)-**8b,** can also be formed under the catalytic condition.[7]

A detailed analysis of these results in Scheme 1 reveals some very interesting phenomena. For example, the reaction of (±)-**3a** in the presence of (*rac*)-BINAP as the ligand yields *trans*-(±)-**4a** which is the mixture of (2*R*,3*S*)-**4a** and (2*S*,3*R*)-**4a.** However, the theoretical analysis of the reaction shown as Scheme 2, which contained the diastereoselectivity and competition between path A and path B, should generate four products, which are (2*R*,3*R*)-**4a,** (2*S*,3*S*)-**4a,** (2*R*,3*S*)-**4a,** and (2*S*,3*R*)-**4a**. Although it is easy to understand that the ratio of these products are closely related with the corresponding diastereoselectivity of each equation in Scheme 2, and the competition between path A and path B, only that (2*R*,3*S*)-**4a,** (2*S*,3*R*)-**4a** were selectively obtained is unusual. To explain the excellent selectivity under above reaction condition, we have to assume two prerequisites for the reaction. The first prerequisite is 100% selectivity between path A and path B in

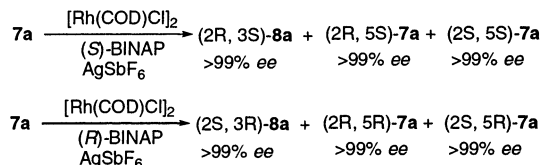**Scheme 1**
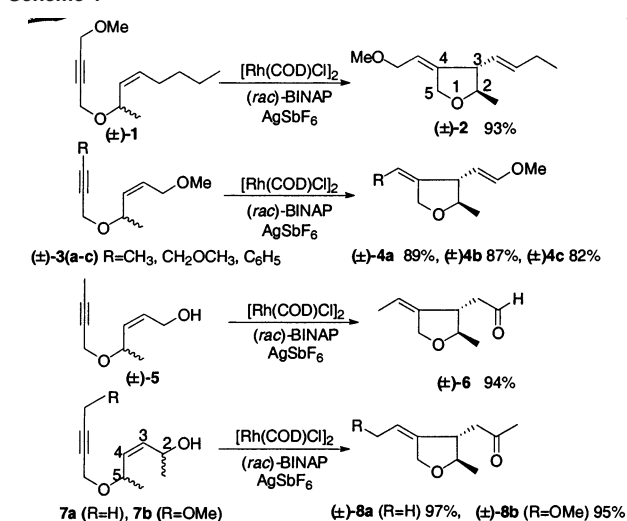
Scheme 2
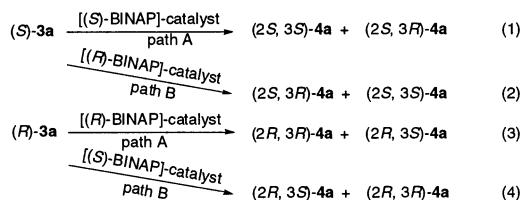
Scheme 2. The second prerequisite is 100% diastereoselectivity in each of the equations in Scheme 2.
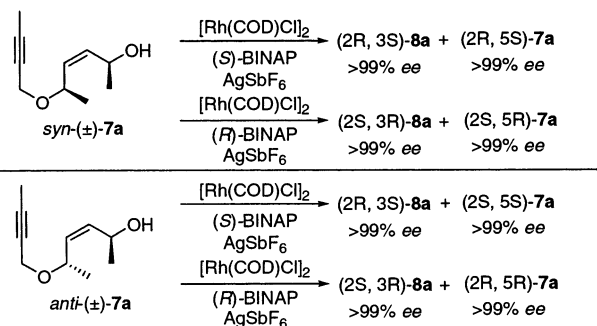
The selectivity between paths A and B is particularly interesting. It means that the reactants have excellent recognization of enan-tiomerically pure BINAP from (*rac*)-BINAP. Although we do not know which enantiomer of (*rac*)-BINAP will be matched by (*R*)- or (*S*)-reactants in this stage, we envision that the reaction path can be elucidated by using enantiomerically pure BINAP as the ligand. One enantiomer of the racemic starting materials will be converted into the corresponding product in excellent ee values, and the other enantiomer will be remained as the starting materials in highly enantiomeric purity because the corresponding enantiomerically pure BINAP matched with the substrate does not exist. Therefore, the whole process represents a perfect example of kinetic resolution!

The other interesting observation is the reactions of **7a** and **7b**. Although the starting materials **7** are mixtures of four enantiomers, the reactions yield only two enantiomers of a racemic compound as the products. The regiospecific β-hydride-elimination is the key for the transformation because it eliminates a stereogenic carbon center and simplifies the reaction. Thus, it will be possible to obtained enantiomerically pure compounds **7**, which contained two stereogenic carbon centers if the interesting proposal of kinetic resolution is applied for these types of substrates.

Scheme 3

$$7a \xrightarrow[\substack{(S)\text{-BINAP} \\ AgSbF_6}]{[Rh(COD)Cl]_2} (2R, 3S)\text{-}8a + (2R, 5S)\text{-}7a + (2S, 5S)\text{-}7a$$
$$\text{>99\% } ee \qquad \text{>99\% } ee \qquad \text{>99\% } ee$$

$$7a \xrightarrow[\substack{(R)\text{-BINAP} \\ AgSbF_6}]{[Rh(COD)Cl]_2} (2S, 3R)\text{-}8a + (2R, 5R)\text{-}7a + (2S, 5R)\text{-}7a$$
$$\text{>99\% } ee \qquad \text{>99\% } ee \qquad \text{>99\% } ee$$

Scheme 4

$$syn\text{-}(\pm)\text{-}7a \xrightarrow[\substack{(S)\text{-BINAP} \\ AgSbF_6}]{[Rh(COD)Cl]_2} (2R, 3S)\text{-}8a + (2R, 5S)\text{-}7a$$
$$\text{>99\% } ee \qquad \text{>99\% } ee$$

$$\xrightarrow[\substack{(R)\text{-BINAP} \\ AgSbF_6}]{[Rh(COD)Cl]_2} (2S, 3R)\text{-}8a + (2S, 5R)\text{-}7a$$
$$\text{>99\% } ee \qquad \text{>99\% } ee$$

$$anti\text{-}(\pm)\text{-}7a \xrightarrow[\substack{(S)\text{-BINAP} \\ AgSbF_6}]{[Rh(COD)Cl]_2} (2R, 3S)\text{-}8a + (2S, 5S)\text{-}7a$$
$$\text{>99\% } ee \qquad \text{>99\% } ee$$

$$\xrightarrow[\substack{(R)\text{-BINAP} \\ AgSbF_6}]{[Rh(COD)Cl]_2} (2S, 3R)\text{-}8a + (2R, 5R)\text{-}7a$$
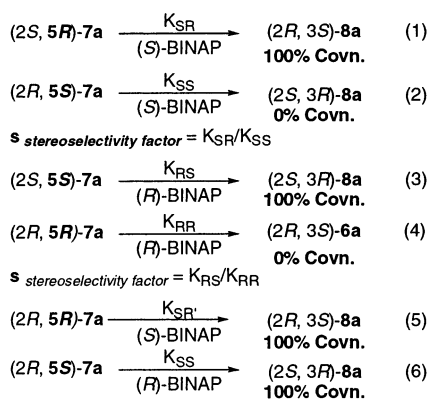$$\text{>99\% } ee \qquad \text{>99\% } ee$$

To examine the hypothesis, we carried out the reaction of **7a**, which is *syn*- and *anti*-mixtures, using enantiomerically pure BINAP (see Scheme 3). The high efficient kinetic resolution of **7a** was investigated in the presence of (*S*)-BINAP, [Rh(COD)Cl]$_2$, and AgSbF$_6$ at 15 °C for 2 min. The corresponding cycloisomerization product (2*R*,3*S*)-**8a**, which contained two of continual stereogenic carbon centers, was obtained in 49% yield and over 99% ee, while a mixture of (2*R*,5*S*)-**7a** (>99% ee) and (2*S*,5*S*)-**7a** (>99% ee) in 48% yields remained as the starting material. The other corresponding enantiomer (2*S*,3*R*)-**8a** was formed with a mixture of (2*S*,5*R*)-**7a** (>99% ee), and (2*R*,5*R*)-**7a** was obtained from the reaction of **7a** using (*R*)-BINAP as the ligand (see Scheme 4).[8]

To further clarify this reaction and obtain all of the enantiomerically pure enantiomers of **7a**, we prepared *syn*-(±)-**7a**, and *anti*-(±)-**7a**, respectively.[9] The reaction of *syn*-(±)-**7a** in the presence of 5 mol % (*S*)-BINAP, 2.5 mol % [Rh(COD)Cl]$_2$ and 10 mol % AgSbF$_6$ at 15 °C for 2 min provided the desired cycloisomerization product (2*R*,3*S*)-**8a** in 49% isolated yield and >99% ee along with (2*R*,5*S*)-**7a** in 48% isolated yield and >99% ee. When the reaction of *syn*-(±)-**7a** was carried out using (*R*)-BINAP as the ligand, the corresponding (2*S* 3*R*)-**8a** (>99% ee) and (2*S*,5*R*)-**7a** (>99% ee) were obtained in 47% and 49% yield, respectively. With (*S*)-BINAP as the ligand, the reaction of *anti*-(±)-**7a** under the same condition generates (2*R*,3*S*)-**8a** (>99% ee) in 48% isolated yield and (2*S*,5*S*)-**7a** (>99% ee) in 49% yield. With (*R*)-BINAP as the ligand, the reaction produced (2*S*,3*R*)-**8a** (>99% ee) and (2*R*,5*R*)-**7a** (>99% ee) in 49% and 49% yield, respectively.[10]

To understand the nature of the reaction, controlling reactions were examined as shown in Scheme 5. When (*S*)-BINAP was used

Scheme 5

$$(2S, 5R)\text{-}7a \xrightarrow[\substack{(S)\text{-BINAP}}]{K_{SR}} \substack{(2R, 3S)\text{-}8a \\ \textbf{100\% Covn.}} \quad (1)$$

$$(2R, 5S)\text{-}7a \xrightarrow[\substack{(S)\text{-BINAP}}]{K_{SS}} \substack{(2S, 3R)\text{-}8a \\ \textbf{0\% Covn.}} \quad (2)$$

s *stereoselectivity factor* = K_{SR}/K_{SS}

$$(2S, 5S)\text{-}7a \xrightarrow[\substack{(R)\text{-BINAP}}]{K_{RS}} \substack{(2S, 3R)\text{-}8a \\ \textbf{100\% Covn.}} \quad (3)$$

$$(2R, 5R)\text{-}7a \xrightarrow[\substack{(R)\text{-BINAP}}]{K_{RR}} \substack{(2R, 3S)\text{-}6a \\ \textbf{0\% Covn.}} \quad (4)$$

s *stereoselectivity factor* = K_{RS}/K_{RR}

$$(2R, 5R)\text{-}7a \xrightarrow[\substack{(S)\text{-BINAP}}]{K_{SR'}} \substack{(2R, 3S)\text{-}8a \\ \textbf{100\% Covn.}} \quad (5)$$

$$(2R, 5S)\text{-}7a \xrightarrow[\substack{(R)\text{-BINAP}}]{K_{SS}} \substack{(2S, 3R)\text{-}8a \\ \textbf{100\% Covn.}} \quad (6)$$

as the ligand, the reaction of (2*S*,5*R*)-**7a** provided the desired cycloisomerization product (2*R*,3*S*)-**8a** in 100% conversion and over 99% ee in 2 min. Reaction of (2*R*,5*S*)-**7a** did not occur under the same conditions. These results reveal that the stereoselectivity of the kinetic resolution is outstanding. In addition, the reactions confirm the excellent recognition between the ligand and substrates. On the basis of the results, we conclude that that the path B is preferred over path A in Scheme 2, which means (*R*)-reactants match (*S*)-BINAP.

$$9 \xrightarrow[\substack{(S)\text{-BINAP} \\ AgSbF_6}]{[Rh(COD)Cl]_2} 10 \qquad eq \ 1$$
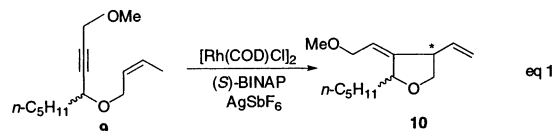
To distinguish the controlling factor of the excellent stereoselectivity, we examine the reaction of **9** under the similar reaction conditions. The kinetic resolution result is poor. A diastereoisomeric mixture was obtained, and both the ee values of the diastereoisomers are over 99%.

In summary, a highly stereoselective kinetic resolution of enynes and Rh(I)-catalyzed intramolecular cycloisomerization reaction were developed. Polyfunctionalized tetrahydrofurans with two adjacent stereogenic centers and high ee values of enynes were obtained in this process. Syntheses of more complex molecules are currently under investigation in our laboratory, and the results will be published in due course.

Supporting Information Available: Spectroscopic data, GC, HPLC spectra, and experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs. org.

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