SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RAD: 14-58169- -5 **FECHA**: 2015-03-27 12:16:57
DEP: 2020 DIRECCION DE NUEVAS CREACIONES **EVE:** 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II **FOLIOS**: 10
ACT: 476 TRASTITULARSOLI

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
JAIME EDUARDO DELGADO VILLEGAS

Asunto: Radicación: 14-58169- -5
Trámite: 11
Evento: 378
Actuación: 476
Oficio: 3282
Folios: 10

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/EP2012/069475				
Fecha de Presentación Internacional	02/10/2012				

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. **Documentos estudiados**

Descripción:	Radicado No. 14-058169-00000-0000	18/Marzo/2014
Reivindicaciones:	Radicado No. 14-058169-00000-0000	18/Marzo/2014
Prioridad:	EP 11382316.5	07/Octubre/2011
	US 61/561,645	18/Noviembre/2011

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la

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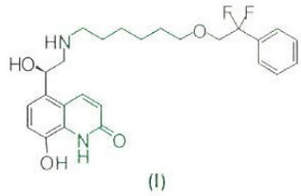
tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. En el presente caso se tiene en cuenta la totalidad del capítulo reivindicatorio.

Título de la solicitud: “Procedimiento para preparar 5-(2-{[6-(2,2-difluoro-2-feniletoxi)hexil]-amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona vía un nuevo intermedio”.

El problema planteado en esta solicitud consiste en la necesidad de proporcionar nuevos procedimientos sintéticos y productos intermedios adecuados para la producción de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo, que se puede producir fácilmente de un modo muy simple usando materiales de partida fácilmente obtenibles en la industria y evitando el uso de sustancias que no son inocuas para el medio ambiente.



El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D 215/26, A61K 31/4704, A61P 11/00.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 1 y 2 no son concisas, porque no establecen las posibilidades de grupos protectores P^1 y P^3, la descripción solo soporta procesos en los cuales el grupo protector de amino es bencilo o alilo, y el grupo protector de hidroxi es bencilo. Se sugiere hacer una generalización razonable de la materia que cuenta con soporte descriptivo.
Adicionalmente, las reivindicaciones 1 y 2 no son concisas porque no establecen claramente como se lleva a cabo la reducción del resto aminocetona, ya que solamente señalan que se realiza en presencia de un catalizador de rodio o rutenio, y la descripción solo soporta procesos en los cuales la reducción del resto aminocetona se efectúa usando un catalizador de rutenio como es el (R)-tol-BINAP $RuCl_2$ DAIPEN en isopropanol, en presencia de terc-butóxido de potasio y t-butanol. Por otro lado, la reivindicación 1 no establece como se desprotege el compuesto obtenido después de la rección del compuesto de fórmula (Ap). Se sugiere restringir la reivindicación a una generalización razonable de la materia que cuenta con soporte descriptivo.

Las reivindicaciones 1 y 2 presentan el mismo alcance por lo cual se sugiere eliminar una de ellas ya que la presencia de reivindicaciones que reclaman la misma materia no permite determinar claramente el alcance del capítulo reivindicatorio.

La reivindicación 1 no es clara porque de su redacción no es posible determinar si se efectúa primero la etapa de desprotección o la etapa de reducción. La descripción solo soporta procesos donde se efectúa primero la etapa de reducción del resto aminocetona y posteriormente se efectúa la etapa de desprotección. Se sugiere restringir el capítulo reivindicatorio a la materia que efectivamente cuenta con soporte descriptivo.

Las reivindicaciones 3 y 4 no cuentan con soporte descriptivo, porque no se encuentra

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en la misma ningún ejemplo en el cual se efectúe primero la desprotección del grupo hidroxi y del grupo amino y posteriormente se realice la reducción del resto aminocetona, por lo cual no es posible para una persona de nivel medio versada en la materia reproducir el proceso reclamado sin tener que efectuar nigún tipo de experimentación. Se sugiere restringir el capítulo reivindicatorio a la materia que efectivamente cuente con soporte descriptivo.
Adicionalmente, las reivindicaciones 3 y 4 presentan el mismo alcance, lo que resta claridad al capítulo reivindicatorio.

La reivindicación 5 no se encuentra enteramente soportada en la descripción porque la descripción solo soporta proceso en los cuales la reducción del grupo aminocetona se lleva a cabo en presencia de un catalizador de rutenio.

La reivindicación 8 no es concisa porque reclama rangos muy amplios de temperatura y de presión para la etapa de reducción del resto aminocetona, los ejemplos de la descripción se efectúan a 65°C y una presión de 25 bares. Se sugiere hacer una generalización razonable de la materia que efectivamente cuenta con soporte descriptivo.
Adicionalmente, la reivindicación 8 no es concisa porque no establece las posibilidades de base a usar en la etapa de reducción de acuerdo a lo soportado en la descripción. Se sugiere incorporar el contenido de las reivindicaciones dependientes 9 y 10 para dar concisión.

La reivindicación 12 no es clara, ni se encuentra totalmente soportada en la descripción, porque establece que los dos grupos protectores P^1 y P^3 representan el mismo grupo protector. Sin embargo, la descripción solo soporta procesos en los cuales cuando P1 y P3 representan el mismo grupo protector éste es bencilo, y no soporta procesos en los cuales los dos grupos protectores sean alilo. Se sugiere modificar la reivindicación de tal manera que no se presente confusión y que se encuentre totalmente soportada en la descripción.

La reivindicación 14 no es concisa porque no establece cuales son las posibilidades de grupo saliente L y de base. La descripción solo soporta procesos donde el grupo saliente L es Br y la base es trietilamina. Se sugiere incorporar a la reivindicación el contenido de las reivindicaciones dependientes 15 y 16.

La reivindicación 17 no se encuentra totalmente soportada en la descripción porque los ejemplos solo soportan la obtención de la sal napadisilato del compuesto de la fórmula (I). Se sugiere restringir el capítulo reivindicatorio a la materia que efectivamente cuenta con soporte descriptivo. Se sugiere eliminar la reivindicación 17 o combinarla con la reivindicación 18.

Las reivindicaciones 21 y 22 presentan una falsa dependencia al referirse al compuesto de la fórmula (A1) haciendo referencia a la reivindicación 20 o al compuesto de la fórmula (Ap) como el compuesto de las reivindicaciones 1, 11 o 12. Se sugiere eliminar dicha falsa dependencia con el fin de evitar confusiones a la hora de determinar el alcance del capítulo reivindicatorio. Adicionalmente, las reivindicaciones 21 y 22 no agregan materia a las reivindicaciones 5 a 10 o 4 o 13 de las cuales dependen, por lo cual se sugiere eliminarla del capítulo reivindicatorio pues el gran número de reivindicaciones con el mismo alcance puede generar confusión.

El capítulo reivindicatorio no es claro porque presenta un excesivo número de reivindicaciones. Se sugiere incorporar el contenido de las reivindicaciones 2 y 14 a la reivindicación independiente 1.

5. **Unidad de invención (Art 25 D 486)**

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La Solicitud no cumple con el Requisito de Unidad de Invención porque se refiere a 4 Grupos Inventivos.

Los Grupos Inventivos están definidos por las siguientes características **esenciales**:

1° Proceso de las reivindicaciones 1 y 2 para preparar el compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona de fórmula (I).
2° Proceso de las reivindicaciones 3 y 4 para preparar el compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona de fórmula (I).
3° Proceso de la reivindicación 14 para preparar el compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona de fórmula (I) que comprende las etapas (i) y (ii).
4° Compuesto A1 de la reivindicación 20 y su proceso de preparación de la reivindicación 22.

Se sugiere presentar las Solicitudes Divisionales que considere necesarias, ó limitar la solicitud inicial a una sola invención, eliminando de ella las otras invenciones.

No se encuentra concepto común entre los 4 grupos inventivos debido a que el compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona se divulgó previamente en los documentos WO2006122788 (Pág. 51, Ej. 5) y WO2010102831(Pág. 2 etapas c y d).

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: Octubre 7 de 2011 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	WO2008093188	Process for the preparation of 8-hydroxy-5-[(1R)-1-hydroxy-2[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]-ethyl]-2(1H)-quinolinone monohydrochloride	07/Agosto/2008
D2	WO2010102831	Process for manufacturing 5-(2-{[6-(2,2-difluoro-2-phenyiethoxy) hexyl]amino}-L-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one	16/Septiembre/2010

D1 http://worldwide.espacenet.com/publicationDetails/biblio?DB=worldwide.espacenet.com&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=20080807&CC=WO&NR=2008093188A1&KC=A1
divulga un proceso de obtención del compuesto clorhidrato de 8-hidroxi-5-[(1R)-1-hidroxi-2-{[(1R)-2(4-metoxi-fenil)-1-metiletil]amino}etil]-2(1H)-quinolina (I), el cual comprende las etapas de reducir el compuesto clorhidrato de 5-[[[(1R)-2-(4-metoxifenil)-1-metiletil]-(fenilmetil)amino]acetil]-8-(fenilmetoxi)-(1H)-quinolin-2-ona con un agente reductor tal como borohidruro de sodio y posteriormente retirar los grupos protectores preferiblemente de forma simultánea por medio de una desbencilación catalítica (Pág. 8, líns. 17 – 19 y Ejs. 1 – 3, Págs. 11 – 13).

D2 http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=20100916&CC=WO&NR=2010102831A1&KC=A1
divulga un proceso de obtención del compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona, en el cual se hace

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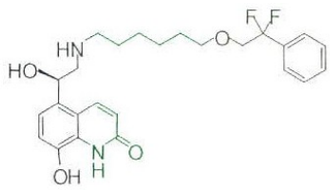
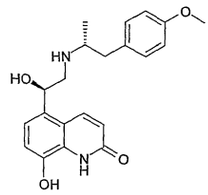
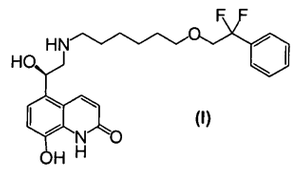
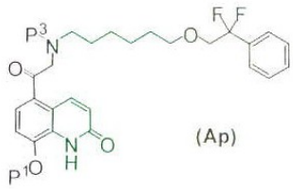
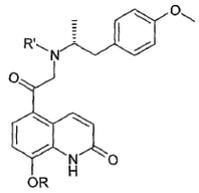
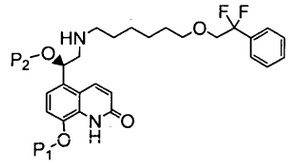
reaccionar un compuesto de fórmula (V) con un compuesto de fórmula (IV) para obtener un compuesto de fórmula (III) y posteriormente se retiran el grupo protector P2 y el grupo protector P1 en etapas independientes (Pág. 5, líns. 5 – 20; Pág. 6, líns. 1 – 12).

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un procedimiento para preparar un compuesto de 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona de fórmula (I) o una sal farmacéuticamente aceptable del mismo (…)

Comparación de las características técnicas **esenciales**, con las del estado de la técnica:

Características **esenciales**	**D1**	**D2**
Un procedimiento para preparar un compuesto  (I) o una sal farmacéuticamente aceptable del mismo que comprende:	Procedimiento para preparar un compuesto de fórmula (I):  (I) Que comprende:	Procedimiento para preparar un compuesto de fórmula (I):  (I) Que comprende:
Reducir y desproteger un compuesto de fórmula Ap o una sal farmacéuticamente aceptable del mismo  (Ap) Para dar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable, en donde: P^1 representa un grupo protector de hidroxi P^3 representa un grupo protector de amino El resto aminocetona se reduce en presencia de un catalizador a base de rodio o rutenio.	Reducir y desproteger un compuesto de fórmula (XIII)  (XIII) En donde: R es un grupo protector de hidroxilo R' es un grupo protector de amino (Pág. 6, esquema 1 y Pág. 7 a Pág. 8 lín. 19) El resto aminocetona se reduce en presencia de un agente reductor (Pág. 9, líns. 10 – 14).	Desproteger un compuesto de la fórmula:  (III) Para dar un compuesto de la fórmula (I) (Pág. 5, líns. 5 – 20 y Pág. 6, líns. 1 – 12).

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque:

El documento D1 divulga un proceso de obtención del compuesto clorhidrato de 8-hidroxi-5-[(1R)-1-hidroxi-2-{[(1R)-2(4-metoxi-fenil)-1-metiletil]amino}etil]-2(1H)-quinolina (I), el cual comprende las etapas de reducir el compuesto clorhidrato de 5-[[[(1R)-2-(4-metoxifenil)-1-metiletil]-(fenilmetil)amino]acetil]-8-(fenilmetoxi)-(1H)-quinolin-2-ona con un agente reductor tal como borohidruro de sodio y posteriormente retirar los grupos

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protectores preferiblemente de forma simultánea por medio de una desbencilación catalítica (Pág. 8, líns. 17 – 19 y Ejs. 1 – 3, Págs. 11 – 13).

La diferencia entre la invención, definida en la reivindicación 1 y el procedimiento divulgado en el documento D1 consiste en que en el procedimiento del documento D1 se obtiene un agonista Beta 2 adrenérgico diferente y en que la reducción del resto aminocetona no se realiza en presencia de un catalizador de rodio o rutenio.

El documento D2 divulga un proceso de obtención del compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona, en el cual se retira el grupo protector P2 y posteriormente se retira el grupo protector P1 en el compuesto de fórmula (III) (Pág. 6, líns. 1 – 12).

La diferencia entre la invención, definida en la reivindicación 1 y el procedimiento del documento D2 consiste en que en el proceso del documento D2 no se lleva a cabo una etapa de reducción usando un catalizador de rodio o rutenio.

No se encuentra un efecto superior o ventaja del procedimiento reclamado frente al divulgado previamente en el documento D2 porque de acuerdo a los resultados presentados en la descripción se encuentra que por medio de los dos procesos se obtienen resultados muy similares en cuanto a rendimiento y pureza del producto obtenido.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: “cómo modificar el procedimiento de obtención del compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona divulgado en el documento D2 para obtener un procedimiento alternativo”.

Sin embargo, el documento D1 divulga un proceso de obtención de un compuesto de estructura similar y el cual presenta la misma actividad como agonista Beta 2 adrenérgico, donde se lleva a cabo una etapa de reducción de un resto aminocetona con un agente reductor sin la presencia de un catalizador de rodio o rutenio. No obstante, dicha reacción de reducción de un resto aminocetona usando un catalizador de rutenio ya era ampliamente conocida por una persona de nivel medio versada en la materia[1].

En consecuencia, la persona del oficio normalmente versada en la materia, se vería motivada a usar un procedimiento de síntesis como el divulgado en el documento D1, usando un catalizador de rutenio durante la etapa de reducción como es de su conocimiento[2], con el fin de obtener un procedimiento alternativo al divulgado en el documento D2 en la obtención del compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona, con la expectativa razonable de éxito porque a pesar que el compuesto del documento D1 no es exactamente igual, si comprende los mismos grupos que participan en la reacción. Por lo cual el objeto de la reivindicación 1 se considera obvio.

Conclusión:
La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18), de la misma forma que sus reivindicaciones dependientes.

La reivindicación 14 consiste en un procedimiento para preparar un compuesto de 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona de

1 http://www.chiral.com/xumu_rev.pdf: New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. Chem. Rev. 2003, 103, 3029−3069 (Pág. 3054 último párr; Pág. 3055 y Pág. 3056 esquema 26).
2 Ibidem

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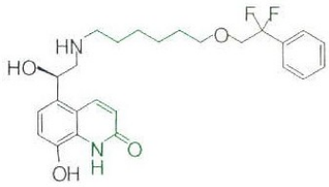
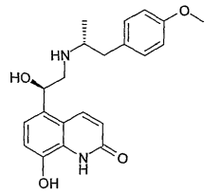
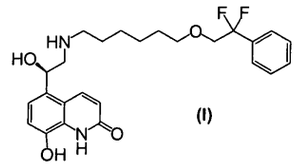
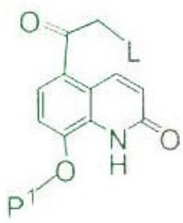
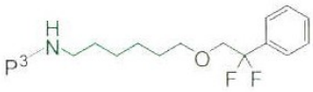
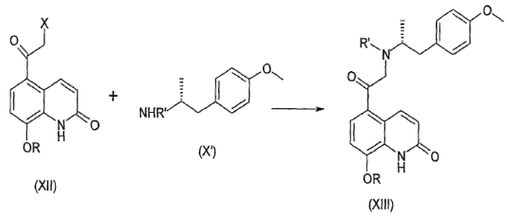
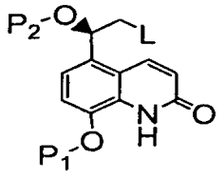
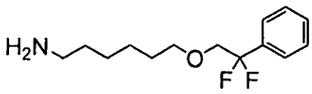
fórmula (I) o una sal farmacéuticamente aceptable del mismo (…)

Comparación de las características técnicas **esenciales**, con las del estado de la técnica:

Características **esenciales**	**D1**	**D2**
Un procedimiento para preparar un compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona de fórmula (I) o una sal farmacéuticamente aceptable  (I) que comprende:	Procedimiento para preparar un compuesto de fórmula (I):  (I) Que comprende:	Procedimiento para preparar un compuesto de fórmula (I):  (I) Que comprende:
(i) Preparar un compuesto de fórmula (Ap) como se define en cualquiera de las reivindicaciones 1, 11 o 12 o una sal farmacéuticamente aceptable del mismo mediante a) hacer reaccionar un intermedio de fórmula (VII):  (VII) En donde L es un grupo saliente, con un derivado de 6-(2,2-difluoro-2-feniletoxi)hexan-1-amina de fórmula (X),  (X) En presencia de una base, en donde P1 y P3 son como se definen en una cualquiera de las reivindicaciones 1, 11 o 12,	Preparar un compuesto de fórmula (XIII) mediante la siguiente reacción:  Donde R es un grupo protector de hidroxilo, y X es un átomo de halógeno.	Preparar un compuesto de fórmula (III) mediante: a) La reacción de un compuesto de fórmula (V)  **(V)** Donde P1 y P2 representan grupos protectores de hidroxi y L es un grupo saliente, Con un compuesto de la fórmula (IV)  **(IV)**
Y después, (ii) reducir y desproteger un compuesto de fórmula Ap o una sal farmacéuticamente aceptable del mismo	Reducir y desproteger un compuesto de fórmula (XIII)	b) Desproteger un compuesto de la fórmula:

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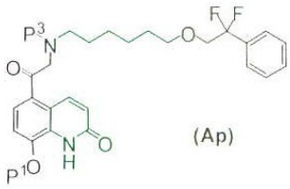
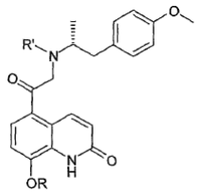
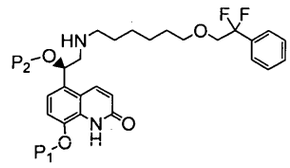
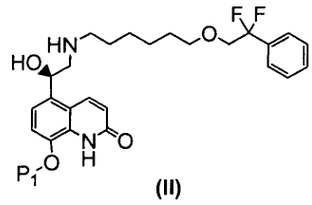
Características **esenciales**	**D1**	**D2**
 (Ap) Para dar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable, en donde: P^1 representa un grupo protector de hidroxi P^3 representa un grupo protector de amino El resto aminocetona se reduce en presencia de un catalizador a base de rodio o rutenio.	 (XIII) En donde: R es un grupo protector de hidroxilo R' es un grupo protector de amino (Pág. 6, esquema 1 y Pág. 7 a Pág. 8 lín. 19). El resto aminocetona se reduce en presencia de un agente reductor (Pág. 9, líns. 10 – 14).	 **(III)** Para dar un compuesto de la fórmula (II)  **(II)** c) Desproteger el compuesto de fórmula (II) para dar el compuesto de fórmula (I) (Pág. 5, líns. 5 – 20 y Pág. 6, líns. 1 – 12).

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 14 porque divulgan:

El documento D1 divulga un proceso de obtención del compuesto clorhidrato de 8-hidroxi-5-[(1R)-1-hidroxi-2-{[(1R)-2(4-metoxi-fenil)-1-metiletil]amino}etil]-2(1H)-quinolina (I), el cual comprende las etapas de hacer reaccionar el compuesto 5-(alfa-bromo)acetil-8-benciloxi-2(1H)-quinolina (XII) con el compuesto (R)-4-metoxi-α-metil-N-(bencil)-bencenetanamina (X') para obtener el compuesto clorhidrato de 5-[[[(1R)-2-(4-metoxifenil)-1-metiletil]-(fenilmetil)amino]acetil]-8-(fenilmetoxi)-(1H)-quinolin-2-ona, reducir el compuesto clorhidrato de 5-[[[(1R)-2-(4-metoxifenil)-1-metiletil]-(fenilmetil)amino]acetil]-8-(fenilmetoxi)-(1H)-quinolin-2-ona con un agente reductor tal como borohidruro de sodio, y posteriormente retirar los grupos protectores preferiblemente de forma simultánea por medio de una desbencilación catalítica (Pág. 6, lín. 16; Pág. 7, líns. 1 – 10; Pág. 8, líns. 17 – 19 y Ejs. 1 – 3, Págs. 11 – 13).

La diferencia entre la invención, definida en la reivindicación 14 y el procedimiento divulgado en el documento D1 consiste en que en el procedimiento del documento D1 se obtiene un agonista Beta 2 adrenérgico diferente, en consecuencia, se usan intermediarios diferentes. Adicionalmente, la reducción del resto aminocetona no se realiza en presencia de un catalizador de rodio o rutenio.

El documento D2 divulga un proceso de obtención del compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona, en el cual se hace reaccionar un compuesto de fórmula (V) con un compuesto de fórmula (IV) para obtener un compuesto de fórmula (III) y posteriormente se retiran el grupo protector P2 y el grupo protector P1 en etapas independientes (Pág. 5, líns. 5 – 20; Pág. 6, líns. 1 – 12).

La diferencia entre la invención, definida en la reivindicación 1 y el procedimiento del documento D2 consiste en que el proceso de la anterioridad comprende reacciones e intermediarios diferentes.

No se encuentra un efecto superior o ventaja del procedimiento reclamado frente al divulgado previamente en el documento D2 porque de acuerdo a los resultados

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presentados en la descripción se encuentra que por medio de cualquiera de los dos procesos se obtienen resultados muy similares en cuanto a rendimiento y pureza del producto obtenido.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar el procedimiento de obtención del compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona divulgado en el documento D2 para obtener un procedimiento alternativo".

Sin embargo, el documento D1 divulga un proceso de obtención de un compuesto de estructura similar y el cual presenta la misma actividad como agonista Beta 2 adrenérgico, donde se llevan a cabo el mismo tipo de reacciones del proceso de la presente solicitud, entre ellas una etapa de reducción de un resto aminocetona con un agente reductor sin la presencia de un catalizador de rodio o rutenio. No obstante, dicha reacción de reducción de un resto aminocetona usando un catalizador de rutenio ya era ampliamente conocida por una persona de nivel medio versada en la materia[3].

En consecuencia, la persona del oficio normalmente versada en la materia, se vería motivada a usar un procedimiento de síntesis como el divulgado en el documento D1, usando un catalizador de rutenio durante la etapa de reducción como es de su conocimiento[4], con el fin de obtener un procedimiento alternativo al divulgado en el documento D2 para la obtención del compuesto 5-(2-{[6-(2,2-difluoro-2-feniletoxihexil]amino}-1(R)-hidroxietil)-8-hidroxiquinolin-2(1H)-ona, con la expectativa razonable de éxito porque a pesar que el compuesto del documento D1 no es exactamente igual, si comprende los mismos grupos que participan en la reacción. Por lo cual el objeto de la reivindicación 14 se considera obvio.

Conclusión:
La reivindicación 14 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18), de la misma forma que sus reivindicaciones dependientes.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2008093188	1 – 22	Nivel Inventivo
D2	WO2010102831	1 – 22	Nivel Inventivo

3 http://www.chiral.com/xumu_rev.pdf: New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. Chem. Rev. 2003, 103, 3029−3069 (Pág. 3054 último párr; Pág. 3055 y Pág. 3056 esquema 26).
4 Ibidem

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En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2015-03-31

Elaboró: Juanita Catalina Rico Valbuena
Revisó: Gloria Jacqueline Alfonso Rozo

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New Chiral Phosphorus Ligands for Enantioselective Hydrogenation

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Received January 29, 2003

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* Corresponding author.

1. Introduction

The increasing demand to produce enantiomerically pure pharmaceuticals, agrochemicals, flavors, and other fine chemicals has advanced the field of asymmetric catalytic technologies.[1,2] Among all asymmetric catalytic methods, asymmetric hydrogenation utilizing molecular hydrogen to reduce prochiral olefins, ketones, and imines, have become one of the most efficient methods for constructing chiral compounds.[3]

The development of homogeneous asymmetric hydrogenation was initiated by Knowles[4a] and Horner[4b] in the late 1960s, after the discovery of Wilkinson's homogeneous hydrogenation catalyst $[RhCl(PPh_3)_3]$.[5] By replacing triphenylphosphine of the Wilkinson's catalyst with resolved chiral monophosphines,[6] Knowles and Horner reported the earliest examples of enantioselective hydrogenation, albeit with poor enantioselectivity. Further exploration by Knowles with an improved monophosphine CAMP provided 88% ee in hydrogenation of dehydroamino acids.[7] Later, two breakthroughs were made in asymmetric hydrogenation by Kagan and Knowles, respectively. Kagan reported the first bisphosphine ligand, DIOP, for Rh-catalyzed asymmetric hydrogenation.[8] The successful application of DIOP resulted in several significant directions for ligand design in asymmetric hydrogenation. Chelating bisphosphorus ligands could lead to superior enantioselectivity compared to monodentate phosphines. Additionally, P-chiral phosphorus ligands were not necessary for achieving high enantioselectivity, and ligands with backbone chirality could also provide excellent ee's in asymmetric hydrogenation. Furthermore, C_2 symmetry was an important structural feature for developing new efficient chiral ligands. Kagan's seminal work immediately led to the rapid development of chiral bisphosphorus ligands. Knowles made his significant discovery of a C_2-symmetric chelating bisphosphine ligand, DIPAMP.[9] Due to its high catalytic efficiency in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, DIPAMP was quickly employed in the industrial production of L-DOPA.[10] The success of practical synthesis of L-DOPA via asymmetric hydrogenation constituted a milestone work and for this work Knowles was awarded the Nobel Prize in 2001.[3k] This work has enlightened chemists to realize

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Wenjun Tang was born in 1974 in Zhejiang Province, China. He received his B.Eng. degree in Chemical Engineering from East China University of Sciences and Technology in 1995. Subsequently, he joined Professor Dawei Ma's research group at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, where he received his M.S. degree in Chemistry in 1998. Presently, he is pursuing his Ph.D. degree in Chemistry at The Pennsylvania State University under the guidance of Professor Xumu Zhang. His research interests are in the area of asymmetric synthesis and catalysis, particularly the development of efficient chiral ligands and catalysts.

Xumu Zhang was born in 1961 in Hubei Province, China. He received his B.S. degree in chemistry (1982) from Wuhan University, China, and M.S. in chemistry (1985) from the Chinese Science Academy, Fuzhou, China, under the supervision of Professor Jiaxi Lu. After a short stay in UC San Diego, he received his Ph.D. in chemistry in 1992 from Stanford University under the guidance of Professor James P. Collman. He then carried out postdoctoral work at Stanford for two years. In 1994, he joined the department of chemistry at The Penn State University as an Assistant Professor of chemistry. In 1999, he was promoted to an Associate Professor of chemistry. His research interests include the development of chiral phosphine ligands for asymmetric catalysis, the investigation of asymmetric hydrogenation and carbon–carbon bond-forming reactions, the synthesis of biologically active compounds, and the discovery of new synthetic methods.

the power of asymmetric hydrogenation for the synthesis of chiral compounds.

Following significant contributions by Knowles and Kagan came the development of thousands of chiral phosphorus ligands for asymmetric hydrogenation. The mechanistic study of Rh-catalyzed asymmetric hydrogenation mainly by Halpern[11] and Brown[12] provides a deep insight into the reaction. However, the development in the early 1980s was mainly focused on chiral Rh catalysts, and the substrate scope was limited to α-dehydroamino acids. Noyori's research on BINAP-Ru catalysts for asymmetric hydrogenation opened up opportunities for efficient hydrogenations of a variety of substrates.[13] The initial application of Noyori's BINAP-Ru system was associated with olefin reduction, but soon afterward the system was found to be useful for hydrogenation of ketones as well. Thus a wide variety of prochiral olefin and ketone substrates were hydrogenated with excellent enantioselectivity. For this beautiful work, Noyori was awarded the Nobel Prize in 2001. In the 1990s, significant progress was also achieved in Rh-catalyzed asymmetric hydrogenation with the introduction of some efficient chiral bisphosphorus ligands such as DuPhos and BPE developed by Burk et al.[14] Excellent ee's were achieved in the hydrogenation of various functionalized olefins, so the scope of asymmetric hydrogenation expanded significantly.

Today, thousands of efficient chiral phosphorus ligands with diverse structures have been developed, and their applications in asymmetric hydrogenation have been extensively utilized in both academic research and industry. The development of many efficient chiral phosphorus ligands also allows the discovery of new mechanistic information of Rh- or Ru-catalyzed asymmetric hydrogenation.[15] The catalysts are not restricted on those with Rh or Ru metals; complexes of other transition metals such as Ir, Pt, Ti, Zr, and Pd are also effective. Numerous unsaturated compounds can be hydrogenated in excellent ee's using a metal catalyst associated with an appropriate chiral ligand.

Although some homogeneous hydrogenation catalysts do not contain chiral phosphorus ligands[16] (e.g., catalysts with chiral cyclopentadienyl ligands[17,18,19] or N-heterocyclic carbene ligands[20]), transition metal complexes associated with chiral phosphorus ligands are the dominant choice of catalysts for asymmetric hydrogenation. An overview of efficient chiral phosphorus ligands not only helps readers to track the development of asymmetric hydrogenation but also encourages chemists to develop new efficient chiral phosphorus ligands. This review summarizes efficient chiral phosphorus ligands, particularly those newly developed in the past 10 years, as well as their representative applications in asymmetric hydrogenation. It is inevitable that some excellent phosphorus ligands and their applications are still missed in this discussion since there has been a vast amount of literature on asymmetric hydrogenation covering them. Fortunately, many previous reviews and books on this field may alleviate this problem.[3] Asymmetric transfer hydrogenation and heterogeneous asymmetric hydrogenation will not be discussed.

2. Chiral Phosphorus Ligands: A Historical Overview

The development of efficient chiral phosphorus ligands has played an important role in the development of asymmetric hydrogenation. A historical overview of efficient chiral phosphorus ligands may also to some extent represent the development of asymmetric hydrogenation. In fact, the exploration of chiral phosphorus ligands for asymmetric hydrogenation is a continuous effort which started in the

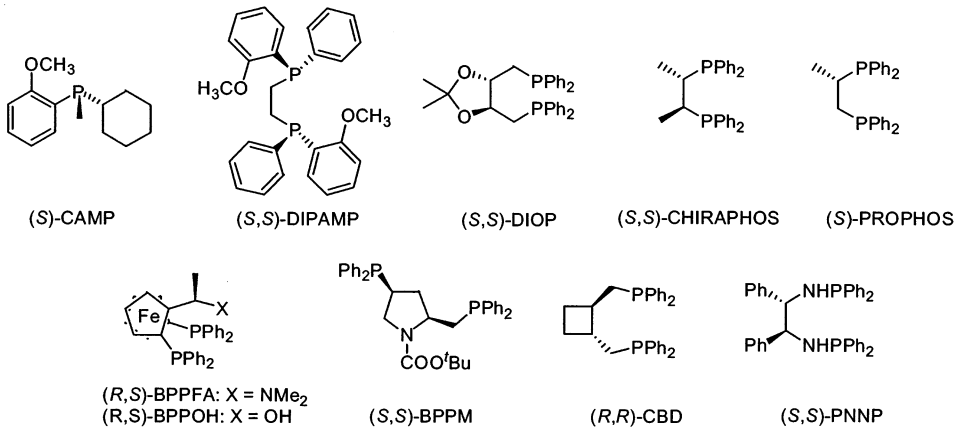


Figure 1.

late 1960s. The authors have arbitrarily divided the whole development period into three stages mainly for the purpose of discussion.

2.1. Chiral Phosphorus Ligands from 1970 to 1980

During the period of 1970−1980, asymmetric hydrogenation was in its early stage of development. Applications were mostly limited in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids. In addition to Knowles's P-chiral phosphines CAMP[7] and DIPAMP[9] and Kagan's DIOP ligand,[8] several successful chiral phosphorus ligands were subsequently discovered during this period (Figure 1). Those include Bosnich's CHIRAPHOS[21] and PROPHOS,[22] Kumada's ferrecene ligand BPPFA[23] and BPPFOH,[24] Achiwa's BPPM,[25] Rhone Poulenc's CBD,[26] and Giongo's bis(aminophosphine) ligand PNNP.[27]

2.2. Chiral Phosphorus Ligands from 1980 to 1992

In 1980, Noyori and Takaya reported an atropisomeric C_2-symmetric bisphosphine ligand BINAP.[28] This ligand was first used in Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids, and high selectivities were reported for some substrates.[29] However, the significant impact of BINAP in asymmetric hydrogenation did not gain two much attention until it was applied in Ru chemistry. In 1986, a major breakthrough was made in BINAP-Ru chemistry when Noyori and Takaya et al. prepared a BINAP-Ru dicarboxylate complex for asymmetric hydrogenation of various functionalized olefins.[30] Subsequently, they discovered that the halogen-containing BINAP-Ru complexes were also efficient catalysts for asymmetric hydrogenation of a range of functionalized ketones.[31] In the middle 1990s, another breakthrough was made on BINAP-Ru chemistry when Noyori discovered that the Ru-BINAP/diamine complexes are efficient catalysts for asymmetric hydrogenation of some unfunctionalized ketones.[32] This advance addressed a long-standing and challenging problem in asymmetric hydrogenation. Importantly, this catalytic system can selectively reduce ketones in the presence of carbon−carbon double bonds.[33] Inspired by Noyori's work on the BINAP chemistry, other research groups developed many excellent atropisomeric biaryl bisphosphine ligands. For example, Miyashima reported on a BICHEP ligand, which was successfully applied in both Rh- and Ru-catalyzed asymmetric hydrogenation.[34] Schmid et al. reported on the BIPHEMP[35] and MeO-BIPHEP[36] ligands, both of which were successfully applied in many Ru-catalyzed hydrogenations. Achiwa also developed several atropisomeric ligands such as BIMOP,[37] FUPMOP,[38] and MOC-BIMOP.[39] In addition, Achiwa successfully developed several modified DIOP ligands by varying the electronic and steric properties of DIOP. MOD-DIOP was applied in asymmetric hydrogenation of itaconic acid derivatives and up to 96% ee's were obtained.[40] A series of modified BPPM ligands such as BCPM and MOD-BCPM were also developed by Achiwa.[41] Some excellent chiral 1,2-bisphosphane ligands such as NORPHOS,[42] PYRPHOS (DEGPHOS),[43] and DPCP[44] for Rh-catalyzed asymmetric hydrogenation were also developed during this period. A few 1, 3-bisphosphorus ligands such as BDPP (SKEWPHOS)[45] and PPCP[46] were prepared. An (aminoalkyl)-ferrocenylphosphine ligand **2** developed by Hayashi and Ito was successfully applied in the Rh-catalyzed hydrogenation of trisubstituted acrylic acids.[47] In the early 1990s, Burk introduced the new series of efficient chiral bisphospholane ligands BPE and DuPhos (Figure 2).[48] The invention of these ligands has expanded the substrate scope of Rh-catalyzed enantioselective hydrogenation. For example, with Rh-DuPhos or Rh-BPE as catalysts, extremely high efficiencies have been observed in asymmetric hydrogenation of α-(acylamino)acrylic acids, enamides, enol acetates, β-keto esters, unsaturated carboxylic acids, and itaconic acids.[14b]

2.3. Chiral Phosphorus Ligands from 1992 to Present

Encouraged by the excellent results of many chiral ligands such as BINAP and DuPhos developed in 1980s and in the early 1990s, many research groups have devoted their efforts toward the design and discovery of new efficient chiral phosphorus ligands. Structural variations of known excellent ligand mo-

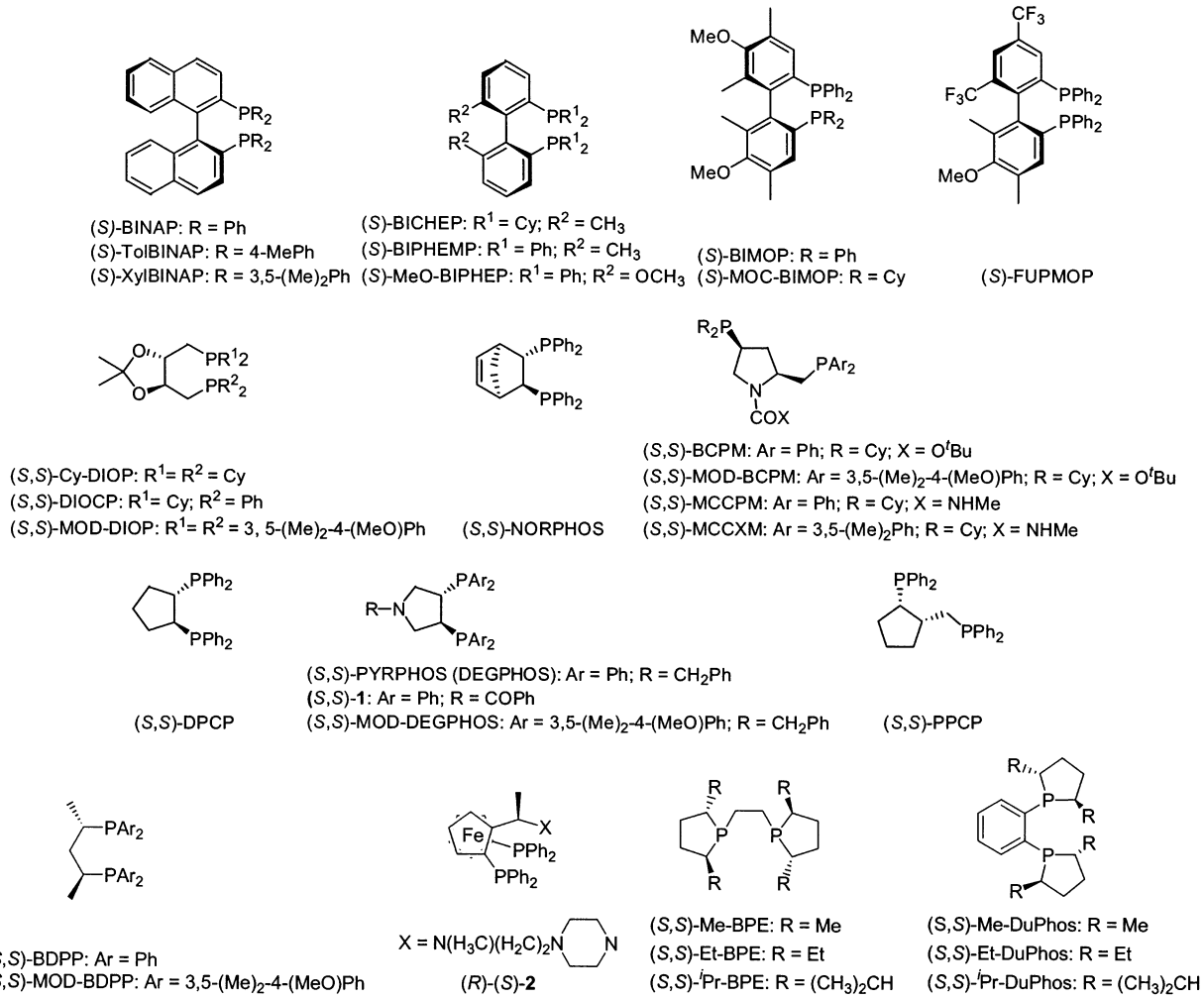


Figure 2.

tifs have often resulted in new efficient chiral ligands with improved efficiency. It has also helped to understand the impact of structural, electronic, and steric properties of ligands in asymmetric hydrogenation. Although a number of new chiral ligands have been developed with significant structural diversities, most of these ligands can be divided into several different categories.

2.3.1. Atropisomeric Biaryl Bisphosphine Ligands

Modification of the electronic and steric properties of BINAP, BIPHEMP, and MeO-BIPHEP can lead to the development of new, efficient atropisomeric ligands (Figure 3). In fact, Takaya has found that a modified BINAP ligand, H_8-BINAP, provides better enantioselectivity than BINAP in Ru-catalyzed hydrogenation of unsaturated carboxylic acids.[49] Mohr has developed a bis-steroidal bisphosphine **3**, which has shown similar catalytic results to BINAP in the Ru-catalyzed asymmetric hydrogenation.[50] Hiemstra has developed a dibenzofuran-based bisphosphine BIFAP, which has shown excellent enantioselectivity in Ru-catalyzed hydrogenation of methyl acetoacetate.[51] The dihedral angle of the biaryl backbone is expected to have strong influence on enantioselectivity. A chiral biaryl bisphosphine ligand SEGPHOS, developed by Takasago international corporation, possesses a narrower dihedral angle than BINAP. The ligand has provided greater enantioselectivities than BINAP in Ru-catalyzed hydrogenation of a wide variety of carbonyl compounds.[52] Chan has reported a closely related ligand BisbenzodioxanPhos.[53] To systematically investigate the influence of dihedral angle of biaryl ligands on enantioselectivity of reactions, Zhang has developed a series of TunaPhos ligands with tunable dihedral angles. When the TunaPhos ligands are applied in Ru-catalyzed asymmetric hydrogenation of β-keto esters, the obtained ee's fluctuate according to the different dihedral angles of the TunaPhos ligands.[54] C4-TunaPhos shows comparable or superior enantioselectivity to BINAP in Ru-catalyzed hydrogenation of β-keto esters. Further applications of the TunaPhos ligands have shown that different asymmetric catalytic reactions may require a different TunaPhos ligand with a different dihedral angle. When TunaPhos ligands are applied in the Ru-catalyzed hydrogenation of enol acetates, C2-TunaPhos is the best ligand in terms of enantioselectivity.[55] Genêt and Marinetti have developed a non-C_2 symmetric biaryl bisphosphine, MeO-NAPhePHOS, which has shown comparable results to C_2-symmetric biaryl bisphosphine in Ru-catalyzed hydrogenation.[56]

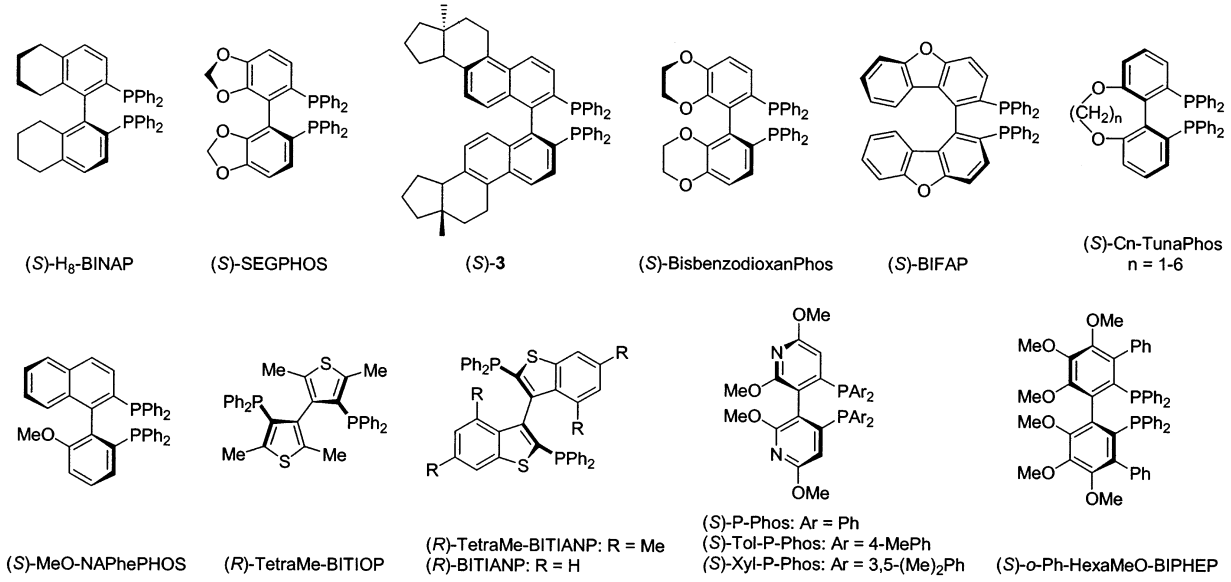


Figure 3.

Structural variations of BINAP or MeO-BIPHEP can also be made on the aromatic rings of the biaryl backbone. For example, the aromatic rings can be replaced by five- or six- membered heteroaromatic rings. Sannicolò et al. have discovered a series of biheteroaryl bisphosphines such as BITIANP, TetraMe-BITIANP,[57] and TetraMe-BITIOP.[58] These ligands have shown comparably good results to BINAP in Ru-catalyzed asymmetric hydrogenation. Chan has reported a dipyridylphosphine ligand P-Phos for Ru-catalyzed asymmetric hydrogenation and high enantioselectivities and reactivities have been obtained for hydrogenation of β-keto esters and α-arylacrylic acids.[59]

An ortho-substituted BIPHEP ligand, *o*-Ph-HexaMeO-BIPHEP, has been developed by Zhang recently.[60] With two phenyl groups at ortho positions of two diphenylphosphino groups, *o*-Ph-HexaMeO-BIPHEP is specially designed to restrict the rotation of the P-phenyl groups, which is considered a detriment for some enantioselective reactions. The design is effective when *o*-Ph-HexaMeO-BIPHEP is employed in the Rh-catalyzed asymmetric hydrogenation of cyclic enamides. While chiral ligands without ortho substituents such as BINAP, BIPHEP, and HexaMeO-BIPHEP provide very poor selectivities, *o*-Ph-HexaMeO-BIPHEP shows excellent enantioselectivity for hydrogenation of a series of cyclic enamides.

Some derivatives have also been made from BINAP or BIPHEP ligands in order to make catalysts water-soluble or recyclable (Figure 4). The literature on homogeneous-supported catalysts in the field of asymmetric hydrogenation using BINAP derivatives have been recently reviewed.[61] Davis et al. have reported a sulfonated BINAP ligand, BINAP-4-SO_3-Na, and found that its water-soluble Ru complex has comparable catalytic properties to the unmodified BINAP-Ru catalyst for hydrogenation of 2-acetamidoacrylic acid.[62] Schmid et al. have developed a water soluble MeO-BIPHEP type ligand, MeOBIPHEP-S. The ligand has the attachments of the sulfonato group at the para position of each P-phenyl groups to minimize the possible steric interactions of the sulfonato groups with the inner ligand sphere of a coordinated metal, and thus retains the high enantioselectivity of the nonsulfonated catalyst. Indeed, MeOBIPHEP-S has shown similarly high enantioselectivity and reacitivity to MeO-BIPHEP for Ru-catalyzed hydrogenation of unsaturated carboxylic acids.[63] By tethering BINAP with guanidine and PEG groups, Genêt has recently reported some recyclable BINAP ligands such as *Digm*-BINAP and PEG-*Am*-BINAP. The Ru catalysts of these ligands maintained high enantioselectivity after three or four times of recycling.[64] Many polymer-supported BINAP ligands have been developed. For instance, Bayston incorporated the BINAP framework onto an insoluble polymer (polystyrene). The resulting polymer-bound BINAP, after treatment with $[Ru(cod)(2\text{-methylallyl})_2]_2$ and HBr, provides high ee's in hydrogenation of β-keto esters and acrylic acids.[65] The polymer can be recycled as the catalyst for several times while high ee's are maintained. Noyori used the same polymer-bound BINAP to make a polymer-bound BINAP/diamine Ru catalyst, which has shown high ee's and turnover numbers for hydrogenation of simple ketones.[66] Chan has developed a highly effective polyester-supported BINAP ligand through copolymerization of chiral 5,5′-diaminoBINAP, chiral pentanediol, and terephthaloyl chloride.[67] The ligand has been successfully applied in Ru-catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2-naphthyl)acrylic acid. A dendrimer-supported BINAP ligand has also been reported.[68] Pu has developed several polymer-based chiral ligands such as poly(BINAP) and BINOL-BINAP. These ligands have successfully been applied in Rh-catalyzed hydrogenation of (*Z*)-methyl α-(benzamido)cinnamate and Ru-catalyzed hydrogenation of simple ketones.[69] Lemaire et al. have reported a polyNAP Ru complex, which provides 99% ee in hydrogenation of methyl acetoacetate even after four recycles of the catalyst.[70]

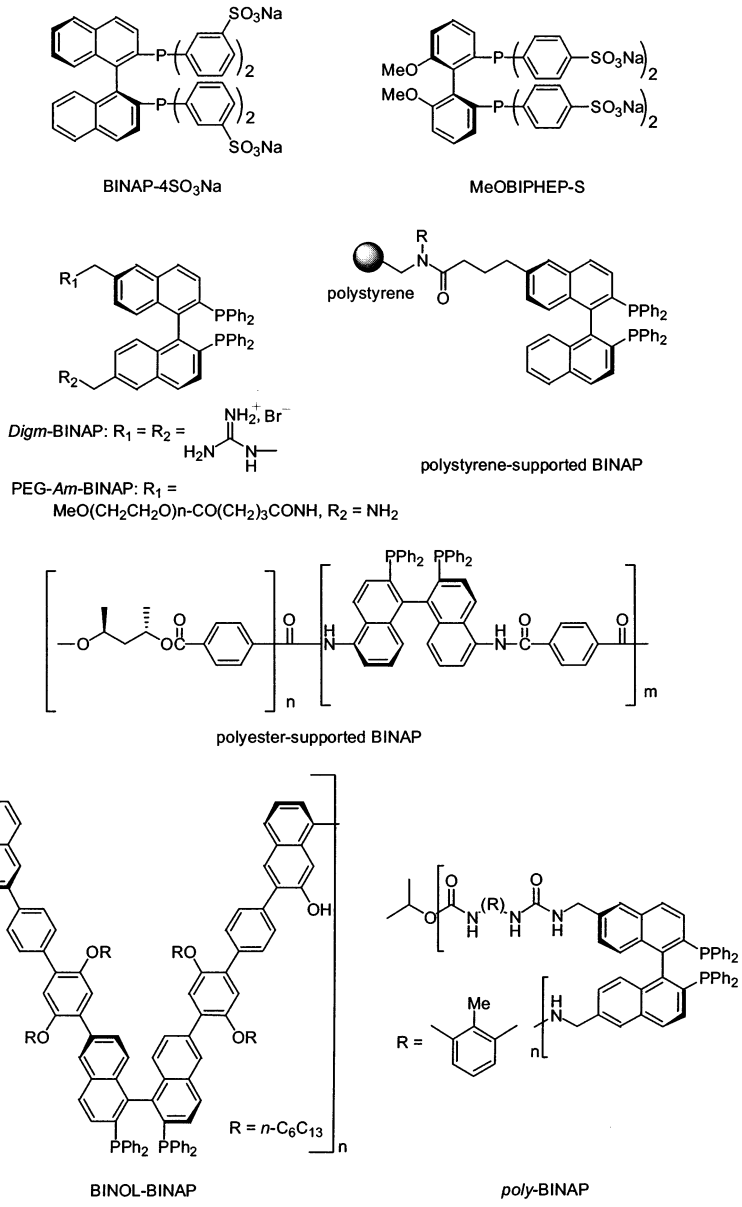


Figure 4.

2.3.2. Chiral Bisphosphane Ligands on the Modification of DuPhos and BPE

Since Burk reported excellent results of DuPhos and BPE ligands in asymmetric hydrogenation of functionalized olefins and ketones, many bisphosphanes have been developed based on the structural variations of DuPhos and BPE ligands (Figure 5). Börner,[71] Zhang,[72] and RajanBabu[73] have independently reported a series of modified DuPhos and BPE ligands with ether, ketal, or hydroxyl groups at the 3 and 4 positions of the phospholanes. These types of ligands maintain the high efficiency of DuPhos or BPE in Rh-catalyzed hydrogenation. One major advantage of these ligands is their ease of preparation from D-mannitol. The ligand with four hydroxy groups **7** also enabled the hydrogenation to be conducted in aqueous solution and high enantioselectivities are maintained. Another four hydroxyl water-soluble ligand BASPHOS (**11**) developed by Holz and Börner also exhibits high efficiency for asymmetric hydrogenation in water.[74] Structrual variations can also be made on the backbone of DuPhos and BPE. Holz and Börner have recently reported a bisphospholane ligand bearing a maleic anhydride backbone, MalPHOS, which has provided good enantioselectivities in hydrogenation of (β-acylamino)acrylates.[75]

Marinetti reported a series of bisphosphetane ligands such as CnrPHOS and BPE-4 ligands.[76] Compared with their bisphospholane analogues DuPhos and BPE, CnrPHOS and BPE-4 provide only moderate enantioselectivity in Rh-catalyzed hydrogenation of dehydroamino acid derivatives. However, these bisphosphetane ligands have shown excellent enantioselectivities in Ru-catalyzed hydrogenation. Helmchen has developed a bisoxaphosphinane ligand **17** for Rh-catalyzed hydrogenation of dehydroamino and itaconic acid derivatives, and up to 97% ee's have been obtained.[77] Zhang has reported two bisdinaphthophosphepine analogues, BINAPHANE and **18**, which have been applied in Rh-catalyzed hydrogenation of enamides.[78] These two ligands, with axial

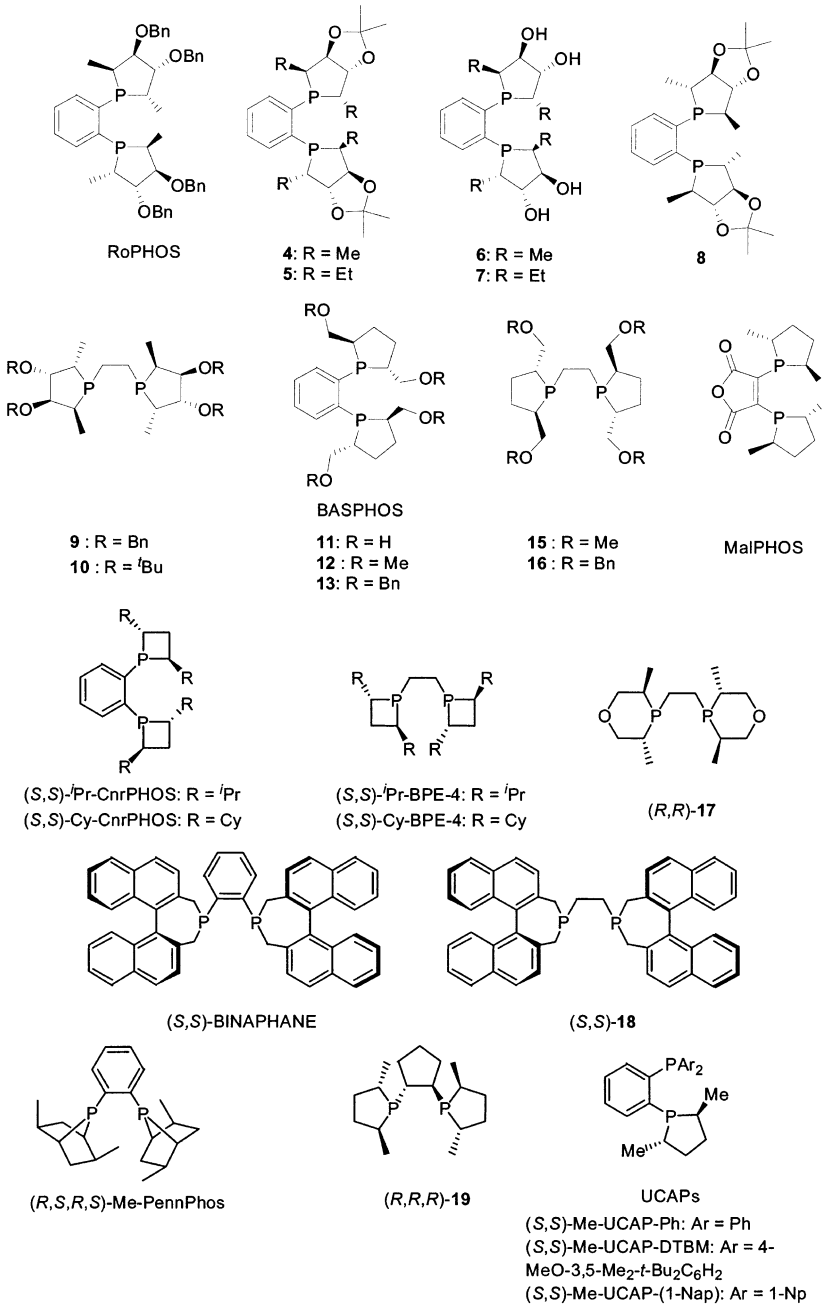


Figure 5.

chirality, provide excellent enantioselectivities (up to 99% ee) for hydrogenation of *E*/*Z* isomeric mixtures of β-substituted arylenamides. A sterically bulky and conformationally rigid bisphosphane PennPhos developed by Zhang has different hydrogenation properties compared to other DuPhos-type ligands.[79] With 2,6-lutidine and KBr as the additives, PennPhos has shown excellent enantioselectivities for Rh-catalyzed hydrogenation of both aryl and alkyl methyl ketones. The PennPhos ligand has also shown high efficiency in Rh-catalyzed hydrogenation of cyclic enamides and cyclic enol acetates, which are difficult substrates for most DuPhos-type ligands.[80] An improved BPE analogue has been developed by incorporating two additional chiral carbon centers on the backbone. The matched (*R*,*R*,*R*)-1,2-bis(phospholano)cyclopentane (**19**) provides better enantioselectivity than BPE in hydrogenation of dehydroamino acids.[81] By replacing one phospholane ring of Me-DuPhos with a disubstituted phosphino group, Saito et al. have developed a series of non-C_2-symmetric phosphine-phospholane ligands, UCAPs, for Rh-catalyzed hydrogenation of enamides and good enantioselectivities are obtained.[82]

2.3.3. Chiral Bisphosphane Ligands on the Modification of DIOP

Kagan's pioneering work on the development of DIOP had a significant impact in the design of new, efficient chiral ligands for asymmetric hydrogenation.[8] However, DIOP itself only provides moderate to good enantioselectivities in asymmetric hydrogenation of dehydroamino acid derivatives, and its applications in highly enantioselective asymmetric

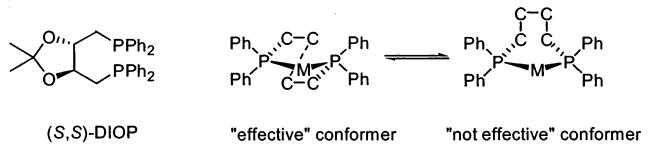


Figure 6.

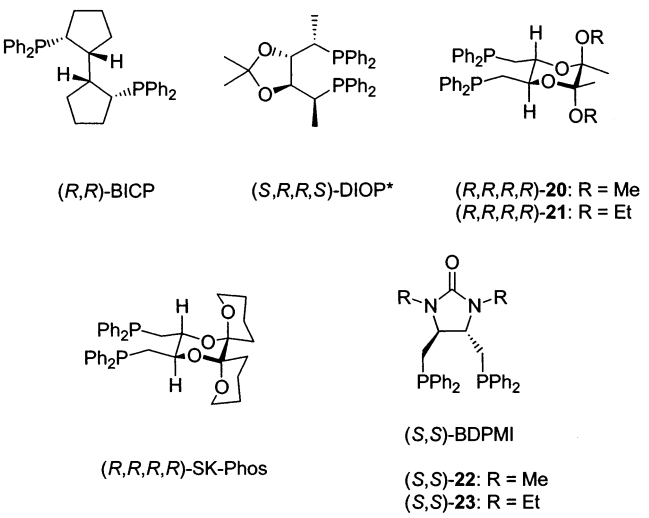


Figure 7.

hydrogenation have rarely been disclosed. A possible reason is that the seven-membered chelate ring of DIOP metal complex is conformationally flexible. The conformational ambiguities in DIOP metal complexes depicted in Figure 6 may be responsible for its low efficiency.

To rigidify the conformational flexibility of DIOP ligand, Zhang[83] has introduced a rigid 1,4-diphosphane ligand BICP with two five-membered carbon rings on its backbone (Figure 7). BICP has found to be efficient for hydrogenation of α-dehydroamino acids, β-dehydroamino acids, arylenamides, and MOM-protected β-hydroxy enamides. Several rigidified DIOP-type ligands have been developed. Zhang[84] and RajanBabu[85] have independently reported the development of DIOP* by introducing two alkyl substituents at α positions of the diphenylphosphine groups. It is found that the (*S*,*R*,*R*,*S*)-DIOP* provides excellent enantioselectivity in Rh-catalyzed hydrogenation of arylenamides. However, its isomeric ligand (*S*,*S*,*S*,*S*)-DIOP*, which was first synthesized by Kagan,[86] provides much lower enantioselectivity. It is believed that the two methyl groups of (*S*,*R*,*R*,*S*)-DIOP* are oriented at pseudoequatorial positions in the "effective" conformer of the DIOP* metal complex, therefore stabilizing the "effective" conformer to promote high enantioselectivity. On the other hand, its isomeric ligand (*S*,*S*,*S*,*S*)-DIOP* has two methyl groups at pseudoaxial positions which destabilize the "effective" conformer and lead to diminished ee's. Lee has developed a type of 1,4-diphosphane ligands BDPMI with an imidazolidin-2-one backbone.[87] The gauche steric interaction between the *N*-substituents and phosphanylmethyl group of the ligands may restrict the conformational flexibility of the seven-membered metal chelate ring. The BDPMI ligands have successfully applied in Rh-catalyzed hydrogenation of arylenamides, and up to 99% ee's have been obtained. A series of 1,4-diphosphane ligands with a conformationally rigid 1,4-dioxane backbone such as ligand **20**, **21**, and SK-Phos have been developed by Zhang and found to be efficient (up to 99% ee) in asymmetric hydrogenation of arylenamides and MOM-protected β-hydroxyl enamides.[88]

2.3.4. Chiral Ferrocene-Based Bisphosphane Ligands

Many excellent chiral ferrocene-based bisphosphane ligands with great structural variations have been developed recently (Figure 8). Ito has successfully developed a series of *trans*-chelating bisphosphane ligands TRAPs, which have shown great capabilities for asymmetric hydrogenation.[89] EtTRAP and BuTRAP have shown excellent reactivity for Rh-catalyzed hydrogenation of β,β-disubstituted α-acetamidoacrylates and up to 88% ee's have been obtained.[89b] The TRAP ligands have also been applied for hydrogenation of β-oxy-α-acetamidoacrylates, and PrTRAP has been proved to be the best ligand in terms of enantioselectivity.[89e] In the presence of 10 mol % of Et_3N or $CsCO_3$, a PhTRAP-Rh complex is able to hydrogenate *N*-acetyl-2-substituted indoline in high ee's.[89g]

Togni and Spindler have reported a class of non-C_2-symmetrical ferrocene-based bisphosphanes: the Josiphos-type ligands.[90] Josiphos has been found to be effective for Rh-catalyzed hydrogenation of α-acetamidocinnamate, dimethyl itaconate, and β-keto esters. Some excellent industrial applications have been realized with the Josiphos type ligands. For example, PPF-tBu_2, a Josiphos type ligand with di(*tert*-butyl)phosphino group, has been applied as the ligand in asymmetric hydrogenation for commercial synthesis of (+)-biotin.[91] Another notable example is the application of XyliPhos in Ir-catalyzed hydrogenation of an imine for the synthesis of the herbicide (*S*)-metolachlor.[92] Weissensteiner and Spindler have also reported a class of rigidified Josiphos type ligands by incorporating a mono- or heteroannular bridge in the structure.[93] However, their applications in asymmetric hydrogenation are less efficient than the original Josiphos-type ligands.

A C_2-symmetric bisphosphane FerroPhos has been developed by Kang and is found to be efficient for Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives.[94] Knochel has independently reported a class of FERRIPHOS (MandyPhos) with similar structural features.[95] All these ligands have provided excellent enantioselectivities in asymmetric hydrogenation of α-dehydroamino acids.

A class of non-C_2-symmetrical ferrocene-based 1,5-diphosphane ligands (TaniaPhos) has also been developed by Knochel.[96] These ligands have been effectively used in Rh- or Ru-catalyzed asymmetric hydrogenations. The ligand **33**, which has a MeO group at the chiral carbon center, has shown excellent applications in hydrogenation of several olefin and ketone substrates.[97] Weissensteiner and Spindler have reported a series of structurally different ferrocene-based 1,5-diphosphane ligands Walphos, which have shown good results in some Ru-catalyzed hydrogenations.[98]

Mezzetti[99a] and van Leeuwen/Widhalm[99b] have independently reported P-chiral ferrocenyl bisphos-

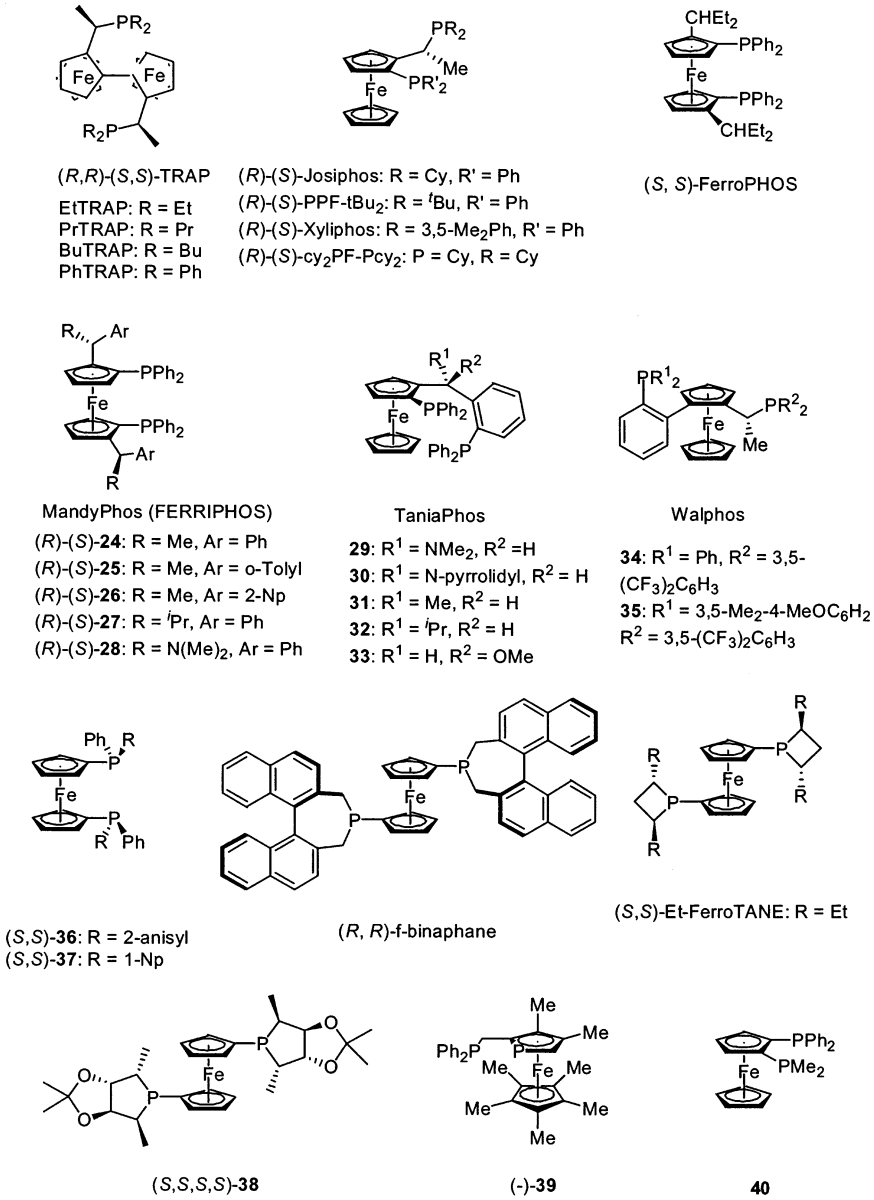


Figure 8.

phines **36** and **37**. These two ligands have shown excellent enantioselectivities (up to 99% ee) for asymmetric hydrogenation of α-dehydroamino acid derivatives.

The synthesis of chiral 1,1′-bis(phosphetano)ferrocenes (FerroTANE) has been independently reported by Marinetti[100] and Burk.[101] Et-FerroTANE has been successfully applied by Burk in Rh-catalyzed hydrogenation of itaconates. It has also been successfully employed in hydrogenation of (*E*)-(β-acylamino)acrylates.[102] Zhang has reported a 1,1′-bis(phospholanyl)ferrocene ligand **38** with ketal substituents at the 3 and 4 positions.[103] The ligand has shown excellent enantioselectivities in hydrogenation of α-dehydroamino acid derivatives. The ketal groups of the ligand are important for achieving the high enantioselectivity, since the corresponding ligand without ketal groups only provides moderate ee's.[104] Zhang has also developed a 1,1′-bis(dinaphthophosphepinyl)ferrocene ligand, f-binaphane, which has been successfully applied in Ir-catalyzed hydrogenation of acyclic arylimines.[105]

Fu has reported a plane-chiral bisphosphorus ligand **39** with a phosphaferrocene backbone. The ligand has provided up to 96% ee's in hydrogenation of α-dehydroamino acid derivatives.[106] Another plane-chiral ferrocene-based bisphosphorus ligand **40** has been reported by Kagan recently, and up to 95% ee's have been obtained in reduction of dimethyl itaconate.[107]

2.3.5. P-Chiral Bisphosphane Ligands

Although the first P-chiral bisphosphane-DIPAMP was developed by Knowles over 20 years ago and has already been proven to be a very efficient hydrogenation ligand, the discovery of new, efficient P-chiral bisphosphanes has been slow partly because of the difficulties in ligand, synthesis. It was not until Imamoto[108] discovered a series of efficient P-chiral ligands such as BisP* that the development of P-chiral phosphorus ligands regained much attention (Figure 9). The BisP* ligands have shown significant activities and enantioselectivities in hydrogenation

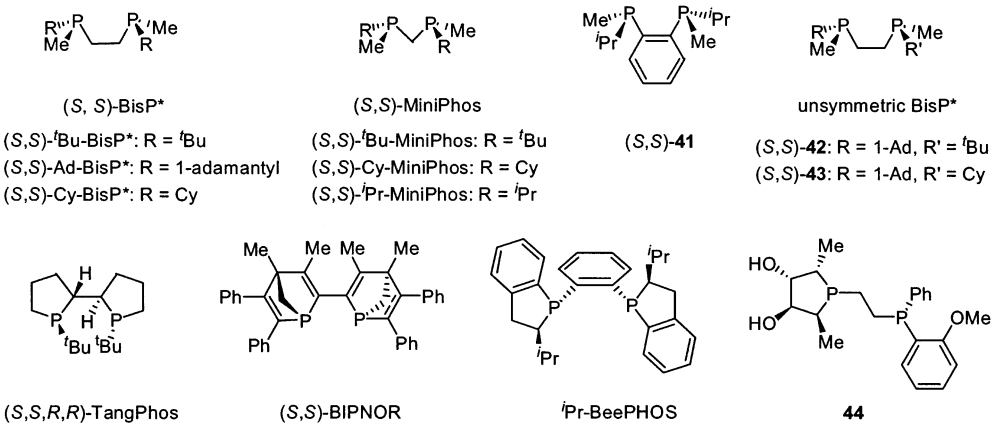


Figure 9.

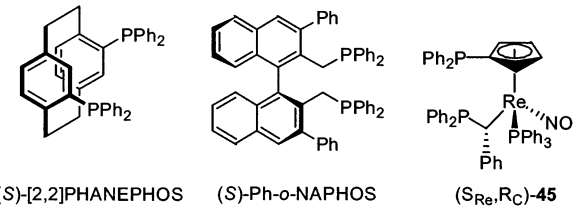


Figure 10.

of α-dehydroamino acids, enamides,[109] (*E*)-*β*-(acylamino)-acrylates[110] and α,*β*-unsaturated-α-acyloxyphosphonates.[111] Mechanistic studies on asymmetric hydrogenation with ^{t}Bu-BisP* as the ligand by Gridnev and Imamoto illustrate that the Rh-catalyzed hydrogenation can proceed in a different mechanism with an electron-rich phosphorus ligand. A dihydride pathway[112] is suggested, which is different from the classic unsaturated pathway[11,12] proposed by Halpern and Brown. In addition to Bisp*, several other P-chiral bisphosphanes such as MiniPhos,[113] 1,2-bis-(isopropylmethylphosphino)benzene (**41**),[114] and unsymmetrical P-chiral BisP* (such as **42** and **43**)[115] have also been developed by Imamoto. Zhang has recently reported a rigid P-chiral bisphospholane ligand, TangPhos, for asymmetric hydrogenation.[116] This ligand has two chiral carbon centers and two chiral phosphorus centers in its structure and has been found to be very efficient in Rh-catalyzed hydrogenation of a variety of functionalized olefins such as α-dehydroamino acids, α-arylenamides, *β*-(acylamino)acrylates,[117] itaconic acids, and enol acetates.[118] Mathey has reported a bisphosphane ligand BIPNOR which contains two chiral bridgehead phosphorus centers.[119] BIPNOR has shown high enantioselectivities in hydrogenation of α-(acetomido)-cinnamic acids and itaconic acids. Saito has reported a P-chiral bisphospholane ligand ^{i}Pr-BeePHOS, which has provided high enantioselectivity in hydrogenation of an enamide.[120] A hybrid P-chiral bisphosphane **44** reported by Brown[121] has shown high selectivity for asymmetric hydrogenation of itaconic acids (up to 95% ee).

2.3.6. Other Bisphosphane Ligands

Some other efficient chiral bisphosphane ligands have been listed in Figure 10. Pye and Rossen have developed a planar chiral bisphosphine ligand, [2.2]-PHANEPHOS, based on a paracyclophane backbone.[122] The ligand has shown excellent enantioselectivity in Rh- or Ru-catalyzed hydrogenations. An *ortho*-phenyl substituted NAPHOS ligand, Ph-*o*-NAPHOS, has been applied successfully in Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives.[123] Compared to NAPHOS, Ph-*o*-NAPHOS has a more rigid structure and provides higher enantioselectivities. A chiral bisphosphine **45** bearing a rhenium stereocenter in the backbone has recently reported by Gladysz, and the ligand has provided good selectivity in Rh-catalyzed hydrogenation of dehydroamino acid derivatives.[124]

2.3.7. Bisphosphinite, Bisphosphonite, and Bisphosphite Ligands

Compared to the rapid development of chiral bisphosphane ligands, the discovery of highly efficient bisphosphinites, bisphosphonites, or bisphosphites for asymmetric hydrogenation has been relatively slow due to their greater conformational flexibility and instability. Nevertheless, some efficient ligands have been discovered with rigid backbones (Figure 11). Selke[125] and RajanBabu[126] have developed a series of bisphosphinites based on sugar backbones. The phosphinite ligands derived from D-glucose have shown excellent enantioselectivities in hydrogenation of α-dehydroamino acid derivatives. A major electronic effect has been identified in this system.[126] High enantioselectivities are obtained with electron-rich bisphosphinites, while electron-deficient bisphosphinites provide much lower selectivities. Chan and Jiang have reported a rigid spirocyclic bisphosphinite ligand spirOP, which has been applied in hydrogenation of α-dehydroamino acid derivatives.[127] A bisphosphinite ligand DIMOP derived from D-mannitol has also been developed by Chan and up to 97% ee's has been obtained in hydrogenation of α-dehydroamino acids.[128] A water-soluble Rh complex associated with a bisphosphinite ligand **49** derived from a *β*,*β*-trehalose backbone is effective for hydrogenation of α-dehydroamino acid derivatives in water or an aqueous/organic biphasic medium (up to 99.9% ee).[129] To rigidify the flexible structure of BINAPO, Zhang has recently reported a series of *o*-BINAPO ligands with substituents at the 3 and 3′ positions of the binaphthyl group. The ligand Ph-*o*-BINAPO, with phenyl groups at the 3 and 3′ positions, is an efficient

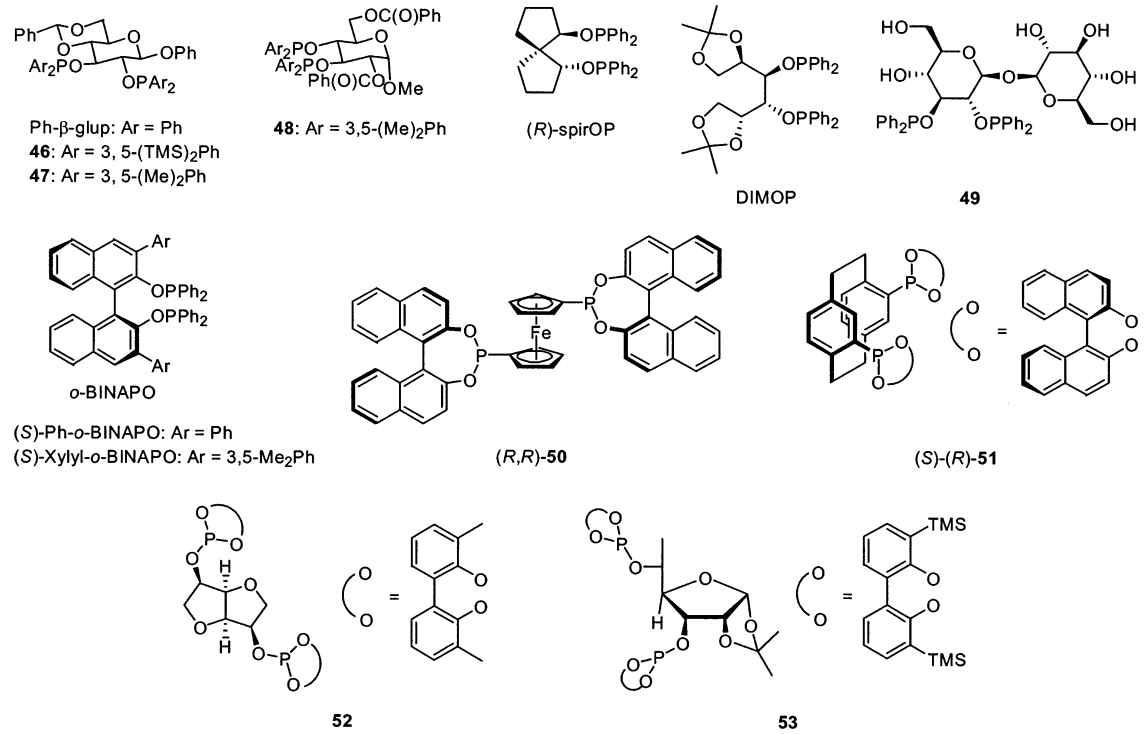


Figure 11.

ligand for hydrogenation of α-dehydroamino acid derivatives.[123] The *o*-BINAPO ligands have also been applied in Ru-catalyzed hydrogenation of *β*-aryl-*β*-(acylamino)acrylates and up to 99% ee's have been obtained.[130]

Some excellent bisphosphonite ligands have also been developed. For example, Reetz has developed a binaphthol-derived ferrocene-based bisphosphonite ligand **50**, which has shown excellent reactivities and enantioselectivities in Rh-catalyzed hydrogenation of itaconates and α-dehydroamino acid derivatives.[131] Zanotti-Gerosa developed a bisphosphonite ligand **51** on the basis of a paracyclophane backbone. The ligand has been successfully applied in asymmetric hydrogenation of α-dehydroamino acid derivatives, and up to 99% ee's have been obtained.[132]

A few efficient bisphosphite ligands have been used for asymmetric hydrogenation of itaconates or α-dehydroamino acid derivatives. Reetz has developed a series of C_2-symmetric bisphosphite ligands such as **52** on the basis of the structure of 1,4:3,6-dianhydro-D-mannitol.[133] The ligands have shown excellent enantioselectivities and reactivities in asymmetric hydrogenation of itaconates. A series of non-C_2-symmetric bisphosphite ligands derived from D-glucose have been reported by Diéguez.[134] Ligand **53** has provided high enantioselectivities for asymmetric hydrogenation of α-dehydroamino acid derivatives.

2.3.8. Chelating Aminophosphine, Amidophosphine, and Phosphoramidites

Several efficient amidophosphine- and aminophosphine-phosphinite ligands have been reported by Agbossou and Carpentier (Figure 12).[135] Amidophosphine-phosphinite ligands (*S*)-Cy,Cy-oxoProNOP and (*S*)-Cp,Cp-oxoProNOP have been demonstrated to be efficient ligands for Rh-catalyzed hydrogenation of dihydro-4,4-dimethyl-2,3-furandione, and up to 98% ee's have been obtained. Aminophosphine-phosphinite ligands (*S*)-Cp,Cp-IndoNOP and (*S*,2*S*)-Cr(CO)$_3$-Cp,Cp-IndoNOP are also effective for this substrate. The two ligands have also provided high enantioselectivity for hydrogenation of *N*-benzoylformamide and 2-(*N*,*N*-dimethyl)aminoacetophenone. An aminophosphine-phosphinite ligand PINDOPHOS derived from Pindolol has been applied for asymmetric hydrogenation of α-dehydroamino acid derivatives and up to 95% ee is obtained.[136] Another aminophosphine-phosphinite DPAMPP has been reported by Jiang and Mi recently,[137] and the ligand has shown excellent enantioselectivities for hydrogenation of a series of α-dehydroamino acid derivatives. Some bisaminophosphine ligands such as H8-BDPAB and BDPAB have been reported by Chan and have been successfully applied for hydrogenation of arylenamides.[138] Xyl-BDPAB is also found to be an efficient ligand for asymmetric hydrogenation of α-dehydroamino acid derivatives.[139] A series of mixed phosphine-phosphoramidite ligands QUINAPHOS developed by Leitner work well for Rh-catalyzed hydrogenation of itaconic acid and α-dehydroamino acid derivatives.[140] A phosphite-phosphoroamidite ligand **54** developed by Diéguez is also useful for asymmetric hydrogenation of α-dehydroamino acid derivatives.[141] Boaz has developed a family of ferrocene-based phosphine-aminophosphine ligands, BoPhoz.[142] These air-stable ligands have shown excellent reactivities and selectivities for hydrogenation of α-dehydroamino acid derivatives and itaconic acids.

2.3.9. Chiral Monophosphorus Ligands

While more and more efficient chelating bisphosphorus ligands have been discovered, the development of monophosphorus ligands for asymmetric

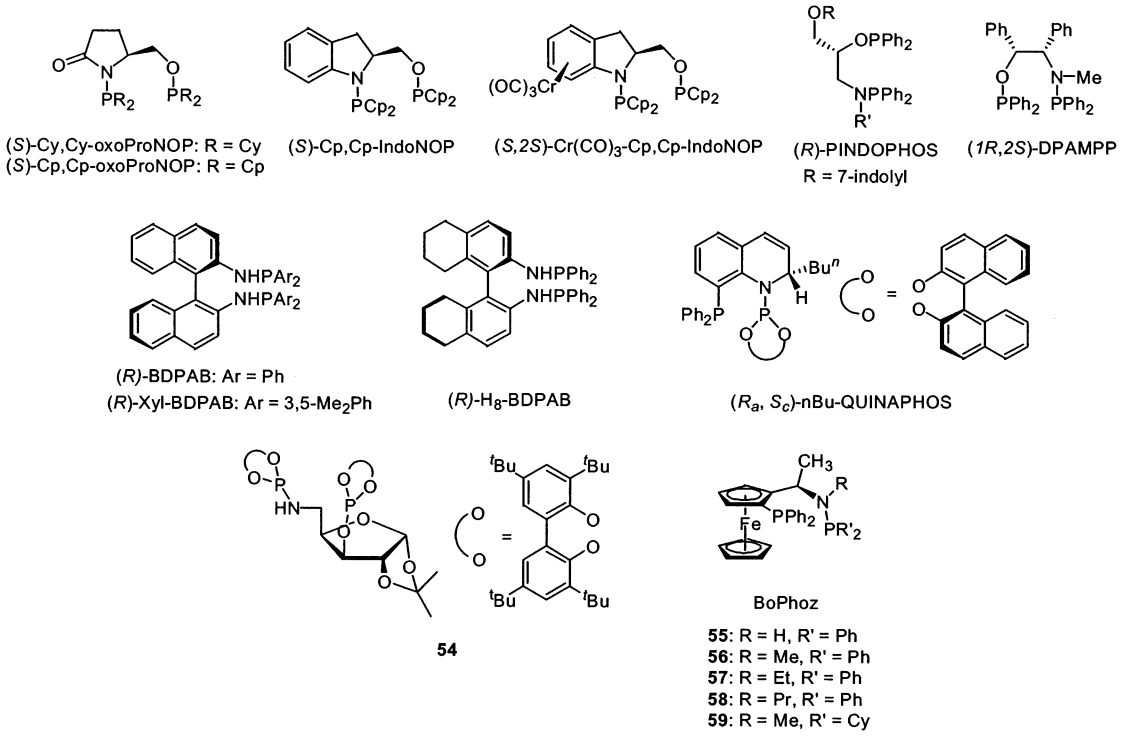


Figure 12.

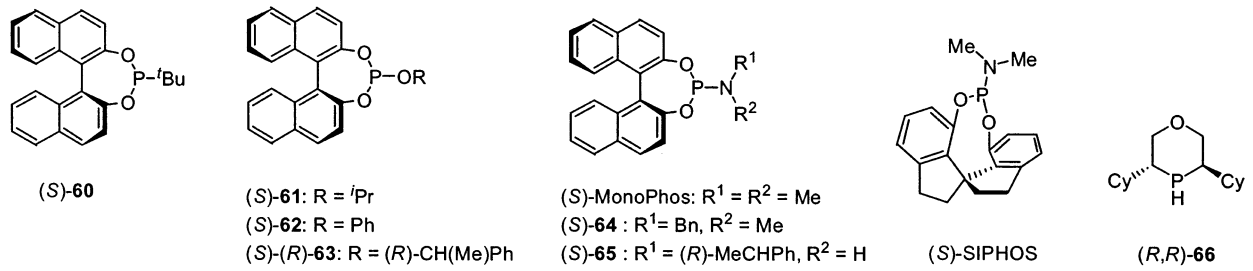


Figure 13.

hydrogenation is slow.[143] However, this does not mean that monophosphorus ligands cannot be as effective as chelating bisphosphorus ligands for asymmetric hydrogenation. Recently, some monophosphorus ligands have been found to be very efficient for Rh-catalyzed asymmetric hydrogenation (Figure 13).[144] Orpen and Pringle have reported a series of biarylphosphonite ligands such as **60** achieving up to 92% ee's for asymmetric hydrogenation of methyl (2-acetamide)acrylate.[145] Reetz has developed a series of monophosphite ligands such as **61**, **62**, and **63**, which have shown excellent reactivities and enantioselectivities for dimethyl itaconate.[146] De Vries and Feringa developed a phosphoramidite ligand named as MonoPhos, which has provided up to 99% ee's for asymmetric hydrogenation of dehydroamino acid derivatives;[147] the ligand is also effective for asymmetric hydrogenation of arylenamides.[148] Two similar phosphoramidite ligands **64** and **65** have shown excellent enantiselecitivities in Rh-catalyzed hydrogenation of (β-acylamino)acrylates.[149] Zhou reported a monophosphoramidite ligand SIPHOS on the basis of a chiral 1,1′-spirobiindane-7,7′-diol. Up to 99% ee's have been obtained in asymmetric hydrogenation of α-dehydroamino acids, arylenamides, and itaconates.[150] Helmchen has reported a secondary monodentate phosphane **66**, which is also very effective for hydrogenation of itaconates.[77]

2.3.10. Chiral N, P Ligands

Although the Ir complex $[Ir(COD)(Py)PCy_3]^+PF_6^-$ was reported by Crabtree[151] as a highly active nonchiral catalyst for hydrogenation of tri- and tetrasubstituted olefins over 20 years ago, the development of efficient chiral N, P ligands for Ir-catalyzed asymmetric hydrogenation was relatively slow until a set of Phox[152] ligands was applied by Pfaltz for Ir-catalyzed hydrogenation of simple olefins (Figure 14).[153] The successful applications of Phox-Ir complexes in asymmetric hydrogenation of unfunctionalized olefins has driven Pfaltz and co-workers[3m] to develop several efficient N, P ligands such as phosphite-oxazoline,[154] PyrPHOX,[155] phosphino-imidazolines (PHIM ligands),[156] phosphinite-oxazolines,[157] and threonine-derived phosphinite-oxazolines.[158] Burgess has also reported a series of JM-Phos[159] and imidazolylidine-oxazolines[20a] for asymmetric hydrogenation of unfunctionalized olefins. A set of phospholane-oxazoline ligands have been recently developed by Zhang, and the ligands have provided

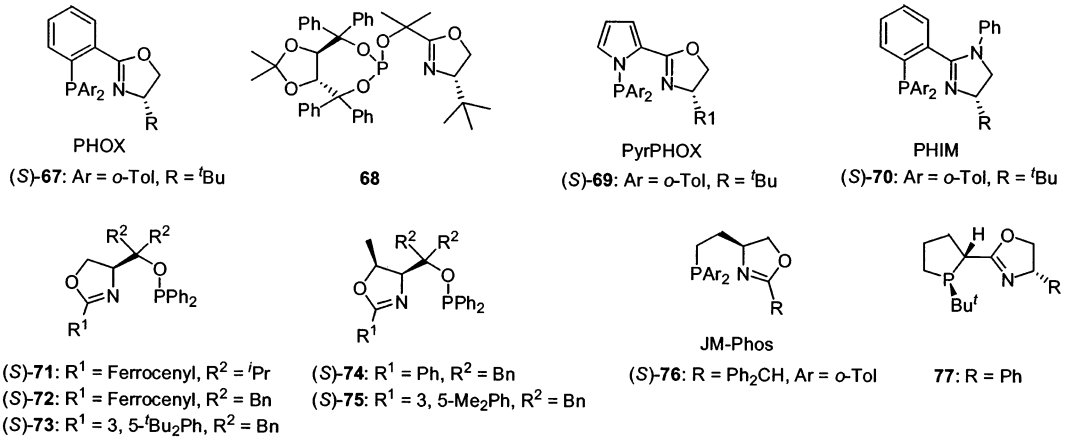


Figure 14.

excellent ee's in hydrogenation of unfuctionalized olefins and unsaturated esters.[160]

3. Applications of Chiral Phosphorus Ligands in Asymmetric Hydrogenation

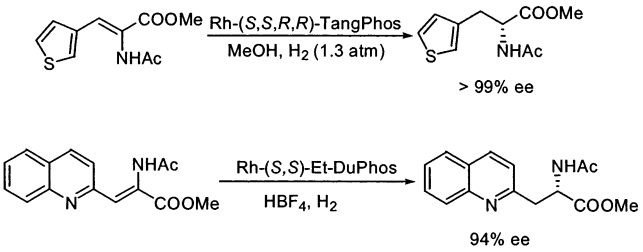
3.1. Hydrogenation of Olefins

3.1.1. Hydrogenation of α-Dehydroamino Acid Derivatives

Hydrogenation of α-dehydroamino acid derivatives has been a typical reaction to test the efficiency of new chiral phosphorus ligands. Indeed, a number of chiral phosphorus ligands with great structural diversity are found to be effective for Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives. Since (*Z*)-2-(acetamido)cinnamic acid, 2-(acetamido) acrylic acid, and their methyl esters are the most frequently applied substrates, Table 1 lists some efficient examples (>95% ee) of hydrogenation of these substrates with different chiral ligands. Generally, cationic Rh complexes and low hydrogenation pressure are applied for the hydrogenation reactions.

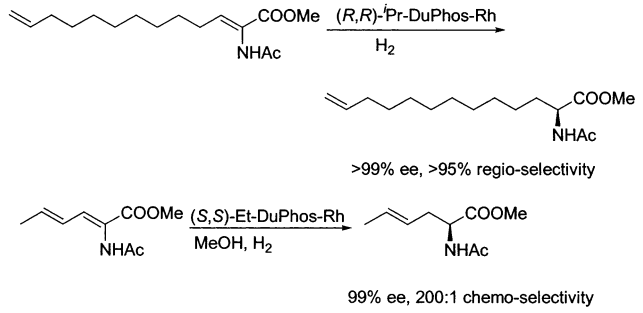
Several chiral ligands such as PYRPHOS,[43b] Et-DuPhos,[161] **38**,[103] TangPhos,[116] DPAMPP,[137] and Bo-Phoz (**56**)[142] have been demonstrated to be very efficient ligands for hydrogenation of α-dehydroamino acid derivatives in terms of both high enantioselectivity and reactivity; the substrate-to-catalyst ratio as high as 50000:1 have been used. DuPhos-type ligands, such as Me-DuPhos, Et-DuPhos, **6**, and **7**, are very efficient ligands for hydrogenation of a wide variety of β-substituted α-dehydroamino acid derivatives. Various chiral α-amino acids containing alkyl and substituted aryl groups can be produced in over 95% ee's, even in supercritical CO_2.[162] With a Tang-Phos-Rh complex as the catalyst, over 99% ee's have been observed in hydrogenation of a series of β-aryl substituted α-dehydroamino acid derivatives.[116] An α-amino acid containing a thiophenyl group is also obtained in over 99% ee (Scheme 1). Hydrogenation of α-dehydroamino acid derivatives with strongly coordinating heteroaryl groups such as pyridyl are difficult since the heteroaryl groups may potentially inhibit catalyst activity by coordinating with metal. This problem can be partially solved by converting the substrate into a protonated derivative with the addition of tetrafluoroboric acid.[163] For example, in the presence of tetrafluoroboric acid, 2-quinolylalanine is obtained in 94% ee via asymmetric hydrogenation with a Et-DuPhos-Rh catalyst.[164] However, 2-pyridyl or 3-isoquinolylalanine cannot be obtained through a similar protocol.

Scheme 1



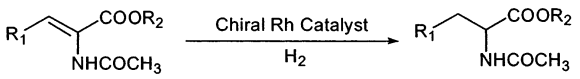
The Et-DuPhos-Rh system has shown good regioselectivity in hydrogenation of substrates possessing two or more different alkene groups.[161] Since enamides are known to chelate to a cationic Rh-bisphosphine catalyst through the alkene and the carbonyl oxygen of the N-acyl group, this chelation directs the hydrogenation to occur preferentially at the enamide alkenes (Scheme 2). Indeed, over 98% regioselectivities have been observed in hydrogenation of α,γ-dienamides with an Et-DuPhos-Rh catalyst and a variety of chiral γ,δ-unsaturated amino acids can be generated.[165]

Scheme 2



In contrast to the high enantioselectivity achieved for the *Z* isomeric substrates, hydrogenation of the *E* isomeric substrates usually proceeds in a much lower rate and gives poor enantioselectivities.[166] With the Rh-BINAP system as the catalyst and THF as

Table 1.



A: R_1 = H, R_2 = H
B: R_1 = H, R_2 = CH_3
C: R_1 = Ph, R_2 = H
D: R_1 = Ph, R_2 = CH_3

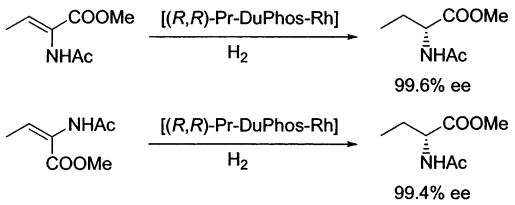
ligand	substrate	S/C ratio	reaction conditions	% ee of product (confign)	ref
(*R*,*R*)-DIPAMP	D	900	MeOH, 50 °C, 3 atm H_2	96 (*S*)	9a
(*R*,*R*)-NORPHOS	C	95	MeOH, rt, 1.1 atm H_2	96 (*R*)	42
(*R*,*R*)-PYRPHOS	D	50000	MeOH, rt, 61 atm H_2	96.5 (*S*)	43b
(*S*)-BINAP	D[a]	100	EtOH, rt, 3 atm H_2	100 (*S*)	28
(*R*)-BICHEP	D[b]	1000	EtOH, rt, 1 atm H_2	95 (*S*)	34c
(*S*,*S*)-Et-DuPhos	B	50440	MeOH, rt, 2 atm H_2	>99 (*S*)	161
(*R*,*R*)-BICP	A	100	THF, Et_3N, rt, 1 atm H_2	97.5 (*S*)	83a
ROPHOS	D	100	MeOH, rt, 1 atm H_2	98.4 (*S*)	71a
7	C	100	MeOH, rt, 3 atm H_2	>99 (*S*)	72b
11	A	100	H_2O, rt, 3.3 atm H_2	>99 (*S*)	74a
(*R*,*R*)-**17**	A	1000	MeOH, 20 °C, 1.1 atm H_2	97.4 (*R*)	77
(*R*,*R*,*R*)-**19**	D	1000	MeOH, 25 °C, 2 atm H_2	98 (*R*)	81
(*R*,*R*)-(*S*,*S*)-EtTRAP	B	100	CH_2Cl_2, 60 °C, 0.5 atm H_2	96 (*R*)	89b
(*R*)-(*S*)-JosiPhos	D	100	MeOH, 35 °C, 1atm H_2	96 (*S*)	90
(*S*,*S*)-FerroPhos	C	100	EtOH, rt, 2 atm H_2	98.9 (*R*)	94a
(*R*)-(*S*)-**24**	D	100	MeOH, rt, 1 atm H_2	98.0 (*S*)	95a
32	D	100	MeOH/toluene, 1 atm H_2	96.6 (*R*)	96a
33	D	100	MeOH/toluene, 1 atm H_2	99 (*S*)	97
(*S*,*S*)-**37**	C	100	MeOH, 25 °C, 2 atm H_2	98.2 (*R*)	99
(*S*,*S*,*S*,*S*)-**38**	B	10000	THF, rt, 3 atm H_2	100 (*S*)	103
(*S*,*S*)-^{t}Bu-BisP*	D	500	MeOH, rt, 2 atm H_2	99.9 (*R*)	108a
(*S*,*S*)-^{t}Bu-MiniPhos	B	500	MeOH, rt, 2 atm H_2	99.9 (*R*)	113
(*S*,*S*)-**41**	B	500	0 °C, 2 atm H_2	97 (*S*)	114
(*S*,*S*)-**42**	D	500	MeOH, rt, 2 atm H_2	99.2 (*R*)	115a
(*S*,*S*,*R*,*R*)-TangPhos	D	10000	MeOH, rt, 1.3 atm H_2	99.8 (*S*)	116
(−)-BIPNOR	C	100	EtOH, rt, 3 atm H_2	>98 (*S*)	119a
^{i}Pr-BeePHOS	D	200	MeOH, 30 °C, 4 atm H_2	98 (*R*)	120
(*R*)-PHANEPHOS	B	100	MeOH, rt, 1atm H_2	99.6 (*R*)	122a
(*S*)-Ph-o-NAPHOS	B	100	MeOH, rt, 3 atm H_2	98.7 (*S*)	123
(S_{Re},R_C)-**45**	D	500	THF, 30 °C, 1 atm H_2	97 (*R*)	124
47	C	1000	THF, rt, 2 atm H_2	99.0 (*S*)	126a
(*R*)-spirOP	C	100	MeOH, rt, 1atm H_2	97.9 (*R*)	127a
DIMOP	A	500	acetone, rt, 33 atm H_2	96.7 (*R*)	128
49	D	100	H_2O, rt, 5 atm H_2[c]	99.9 (*S*)	129
(*S*)-Ph-*o*-BINAPO	B	100	MeOH, rt, 3 atm H_2	99.9 (*S*)	123
(*R*,*R*)-**50**	B	1000	CH_2Cl_2, rt, 1.3 atm H_2	99.5 (*S*)	131
(*S*)-(*R*)-**51**	B	5000	MeOH, rt, 3.5 atm H_2	98.5 (*S*)	132
53	D	100	CH_2Cl_2, 25 °C, 5 atm H_2	98 (*S*)	134
(1*R*,2*S*)-DPAMPP	D	10000	MeOH, rt, 50 atm H_2	97 (*R*)	137b
(*S*)-Xyl-BDPAB	D	500	MeOH, rt, 3.3 atm H_2	98 (*S*)	139
(*R*a,*R*c)-^{n}Bu-QUINAPHOS	B	1000	CH_2Cl_2, rt, 30 atm H_2	97.8 (*S*)	140
54	B	100	CH_2Cl_2, 5 °C, 30 atm H_2	>99 (*S*)	141
56	D	10000	THF, rt, 0.7 atm H_2	99.4 (*S*)	142
(*S*)-MonoPhos	B	20	EtOAc, rt, 1 atm H_2	99.6 (*R*)	147a
(*S*)-SIPHOS	D	200	CH_2Cl_2, rt, 1atm H_2	96.4 (*S*)	150b

[a] Benzoyl derivative. [b] Ethyl ester. [c] Sodium dodecyl sulfate (10 mol %) is added.

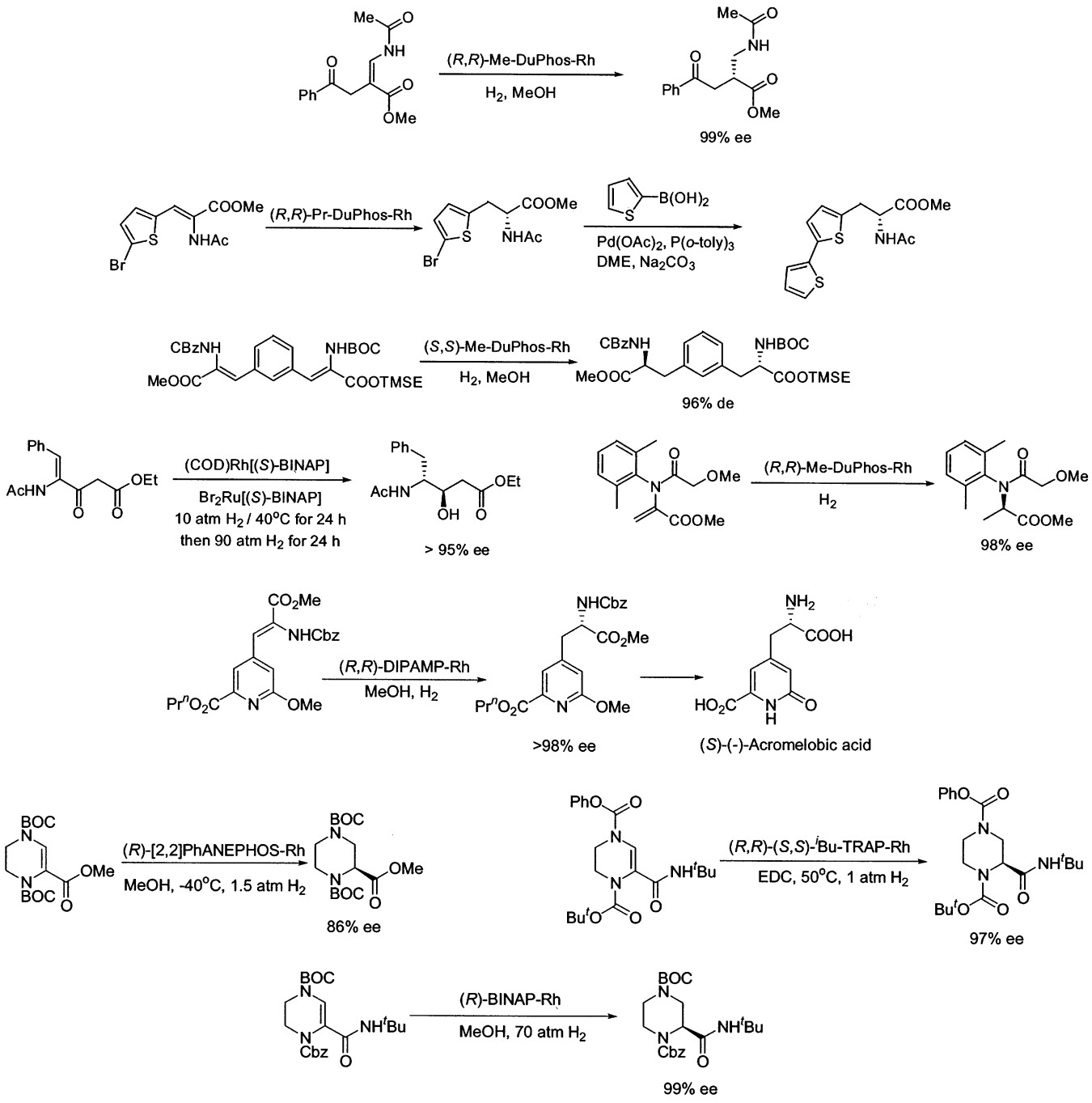
the solvent, hydrogenation of the *Z* and *E* isomeric substrates generates products with different configurations.[29] Remarkably, the DuPhos-Rh system provides excellent enantioselectivities for both *Z* and *E* isomeric substrates, and the hydrogenation products are formed with the same configuration (Scheme 3). This result is particularly important for hydrogenation of alkyl dehydroamino acid derivatives, which are difficult to prepare in geometrically pure form.

Many synthetic utilities of Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives have been recently explored (Scheme 4). For example, chiral α,β-diaminopropanoates can be efficiently synthesized via asymmetric hydrogenation of α,β-diamidopropenoates with a Et-DuPhos-Rh catalyst.[167] A tandem catalytic process involving asymmetric hydrogenation of dehydroamino acid derivatives fol-

Scheme 3

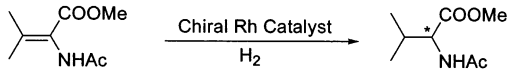


Scheme 4



lowed by a Suzuki coupling can provide a wide range of diverse α-amino acids, which have been used for the rapid synthesis of analogous peptides.[168] A bis-dehydroamino acid derivative has been hydrogenated with a (*S*,*S*)-Me-DuPhos-Rh catalyst to yield an α,ω-diamino dicarboxylate with a 98:2 diastereomeric ratio. The product has been used for the synthesis of a peptidomimetic of the turn in the helix−turn−helix DNA-binding protein motif.[169] Takahashi has reported a one-pot sequential asymmetric hydrogenation utilizing a BINAP-Rh and a BINAP-Ru catalyst to synthesize 4-amino-3-hydroxy-5-phenylpentanoic acids in over 95% ee. The process involves a step of hydrogenation of a dehydroamino acid with the BINAP-Rh catalyst, followed by a step of hydrogenation of a β-keto ester with the BINAP-Ru catalyst.[170] (*R*)-Metalaxyl, a highly active fungicide, has also been produced via asymmetric hydrogenation with a DuPhos-Rh catalyst.[171] A hindered pyridine-substituted α-dehydroamino acid derivative has been hydrogenated by a DIPAMP-Rh complex to give the corresponding chiral α-amino acid derivative in over 98% ee. The chiral product has been used for the synthesis of (*S*)-(−)-acromelobic acid.[172] Hydrogenation of a tetrahydropyrazine derivative catalyzed by a PHANEPHOS-Rh complex at −40 °C gives an intermediate for the synthesis of Crixiran in 86% ee.[122a] An (*R*,*R*)-(*S*,*S*)-^{i}Bu-TRAP-Rh catalyst provides 97% ee for hydrogenation of a tetrahydropyrazine carboxamide derivative;[173] interestingly, a related (*R*,*R*)-(*S*,*S*)-Me-TRAP-Rh catalyst provides the hydrogenation product with a different configuration. Hydrogenation

Table 2.



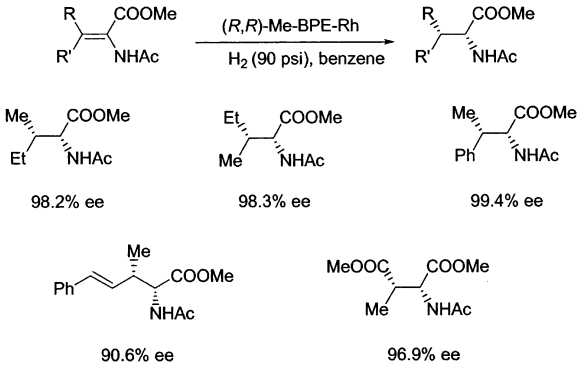
ligand	S/C ratio	conditions	% ee of product (confign)	ref
(*R*,*R*)-(*S*,*S*)-BuTRAP	100	^{i}PrOH, 15 °C, 1 atm H_2	88 (*S*)	89b
(*S*,*S*)-Me-DuPhos	500	benzene, 25 °C, 6 atm H_2	96.0 (*S*)	175
(*R*,*R*)-Me-BPE	500	benzene, 25 °C, 6 atm H_2	98.2 (*R*)	175
(*S*,*S*,*S*,*S*)-**38**	100	THF, rt, 1 atm H_2	87.3 (*S*)	103
(*S*,*S*)-Cy-BisP*	500	MeOH, rt, 6 atm H_2	90.9 (*R*)	108a
(*S*,*S*)-^{t}Bu-MiniPhos	500	MeOH, rt, 6 atm H_2	87 (*R*)	113
(*S*,*S*)-**41**	500	rt, 6 atm H_2	87 (*S*)	114
(*S*,*S*)-**43**	100	MeOH, rt, 20 atm H_2	96.1 (*R*)	115b

of another tetrahydropyrazine carboxamide derivative catalyzed by an (*R*)-BINAP-Rh catalyst leads to the chiral product in 99% ee.[174]

Hydrogenation of β,β-disubstituted α-dehydroamino acids remains a relatively challenging problem. Remarkably, the less bulky DuPhos- or BPE-type ligands, such as Me-DuPhos and Me-BPE, provide excellent enantioselectivity for a variety of this type of substrates.[175] The Rh complexes of chiral ligands, such as BuTRAP,[89b] **38**,[103] Cy-BisP*,[108a] MiniPhos,[113] and unsymmetrical BisP* **43**,[115b] have also shown high efficiencies for some β,β-disubstituted α-dehydroamino acid substrates. Table 2 lists some efficient examples of hydrogenation of β,β-dimethyl α-dehydroamino acid esters with different chiral phosphorus ligands.

When dissimilar groups occupy the two β-positions, two stereogenic centers are simultaneously established in the hydrogenation. The Me-DuPhos-Rh or Me-BPE-Rh systems allow a series of both *Z* and *E* isomeric β,β-disubstituted α-dehydroamino acid derivatives to be hydrogenated with excellent enantioselectivities (Scheme 5).[175] Good chemoselectivity is

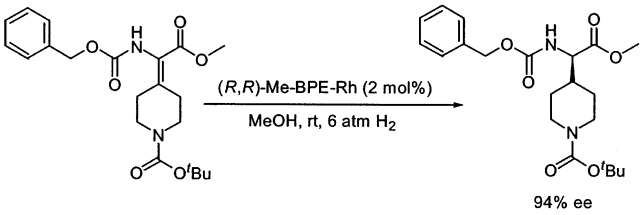
Scheme 5



observed in hydrogenation of substrates containing other olefin functionalities.[176] Thus, hydrogenation of β-substituted α,β,γ,δ-unsaturated amino acids with a Me-DuPhos-Rh or Me-BPE-Rh catalyst provides a series of β-substituted γ,δ-unsaturated amino acids in high ee's.

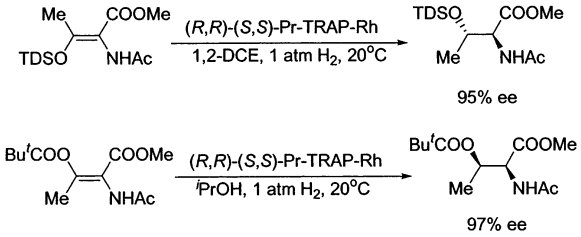
Hydrogenation of a (*Z*)-dehydro-β-methyl tryptophan derivative with a (*R*,*R*)-Me-DuPhos-Rh catalyst provides β-(2*R*,3*S*)-methyl tryptophan in 97% ee.[177] A tetrasubstituted enamide containing a piperidine component is hydrogenated with a (*R*,*R*)-Me-BPE-Rh catalyst to give (*R*)-4-piperidinylglycine in 94% ee (Scheme 6).[178] The Pr-TRAP-Rh system

Scheme 6



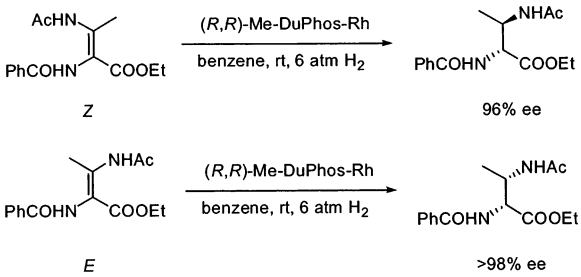
provides excellent ee's in hydrogenation of (*Z*)-β-siloxy-α-(acetamido) acrylates and (*E*)-β-pivaloyloxy-α-(acetamido)acrylates (Scheme 7).[89e] By hydrogena-

Scheme 7



tion of both *Z* and *E* isomeric substrates of β-(acetylamino)-β-methyl-α-dehydroamino acid derivatives with Me-DuPhos-Rh catalysts, four isomers of the *N*,*N*-protected 2,3-diaminobutanoic acid can be efficiently obtained with excellent ee's (Scheme 8).[179]

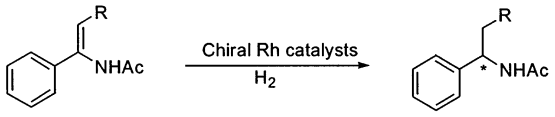
Scheme 8



A Pr-TRAP-Rh catalyst is also applied for hydrogenation of a series of (*E*)-β-(acylamino)-β-alkyl-α-dehydroamino acid derivatives, and up to 82% ee's have resulted.[89d]

Compared to the further advance achieved in Rh-catalyzed asymmetric hydrogenation, Ru-catalyzed asymmetric hydrogenation of α-dehydroamino acid

Table 3.



A: R = H
B: R = CH_3 (*Z*/*E*)

ligand	substrate	S/C ratio	reaction conditions	% ee of product (config)	ref
(*R*, *R*)-Me-BPE	A	500	MeOH, 22 °C, 0.4 atm H_2	95.2 (*R*)	181
	B	500	MeOH, 22 °C, 0.4 atm H_2	95.4 (*R*)	181
7	A	100	MeOH, rt, 10 atm H_2	96 (*S*)	72b
(*S*,*S*)-BINAPHANE	B	100	CH_2Cl_2, rt, 1.3 atm H_2	99.1 (*S*)	78a
(*S*,*S*)-Me-UCAP-(1-Nap)	B	500	MeOH, 30 °C, 4 atm H_2	95 (*S*)	82
(*R*,*R*)-BICP	B	100	toluene, rt, 2.7 atm H_2	95.0 (*R*)	83b
(*R*,*S*,*S*,*R*)-DIOP*	A	50	MeOH, rt, 10 atm H_2	98.8 (*R*)	84
	B	50	MeOH, rt, 10 atm H_2	97.3 (*R*)	84
(*R*,*R*,*R*,*R*)-**20**	B	100	MeOH, rt, 3 atm H_2	98 (*S*)	88
(*R*,*R*,*R*,*R*)-SK-Phos	B	100	MeOH, rt, 3 atm H_2	97 (*S*)	88
(*S*,*S*)-**22**	A	100	CH_2Cl_2, rt, 1 atm H_2	98.5 (*R*)	87a
	B	100	CH_2Cl_2, rt, 1 atm H_2	>99 (*R*)	87a
33	A	100	MeOH/toluene, rt, 1 atm H_2	96 (*S*)	97
(*S*,*S*)-^{t}Bu-BisP*	A	100	MeOH, rt, 3 atm H_2	98 (*R*)	109
(*S*,*S*,*R*,*R*)-TangPhos	A	10000	MeOH, rt, 1.3 atm H_2	99.3 (*R*)	116
	B	100	MeOH, rt, 1.3 atm H_2	98 (*R*)	116
(*R*)-H_8-BDPAB	A	200	THF, 5 °C, 1 atm H_2	96.8 (*R*)	138a
(*S*)-MonoPhos	A	100	CH_2Cl_2, −20 °C, 20 atm H_2	95 (*S*)	148
(*S*)-SIPHOS	A	200	toluene, 5 °C, 10 atm H_2	98.7 (*S*)	150a

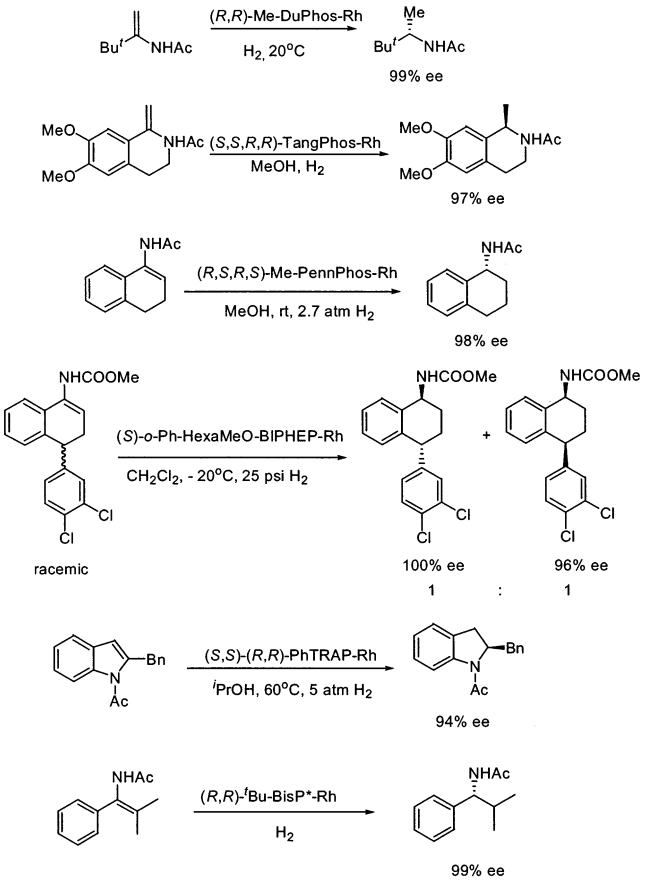
derivatives undergoes a different mechanistic pathway,[180] and little progress has been made.

3.1.2. Hydrogenation of Enamides

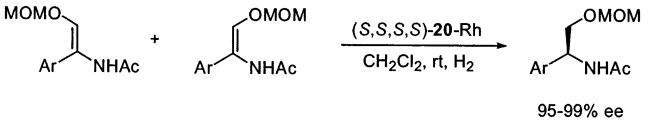
Rh-catalyzed hydrogenation of simple enamides has attracted much attention recently. With the development of more and more efficient chiral phosphorus ligands, extremely high ee's can be obtained in the Rh-catalyzed hydrogenation of α-aryl enamides. *E*/*Z* isomeric mixtures of *β*-substituted enamides can also be hydrogenated in excellent ee's. Table 3 lists some efficient examples (>95% ee) of hydrogenation of α-phenylenamide and *E*/*Z* isomeric mixture of *β*-methyl-α-phenylenamide. The P-chiral ligand TangPhos has been demonstrated to be an efficient ligand for Rh-catalyzed hydrogenation of enamides in terms of both enantioselectivity and reactivity; up to 10 000 turnover numbers have been achieved.[116]

Some alkyl enamides such as *tert*-butylenamide or 1-admantylenamide can also be hydrogenated with a ^{t}Bu-BisP*-Rh catalyst[109] or a Me-DuPhos-Rh catalyst[182] in 99% ee. Notably, the configurations of the hydrogenation products of these bulky alkyl enamides are opposite to those of aryl enamides. Mechanistic study[183] by Gridnev and Imamoto[109] using NMR technique indicates that the hydrogenations of bulky alkyl enamides and aryl enamides involve different coordination pathways. Hydrogenation of *N*-acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroquinoline can be catalyzed by a (*S*,*S*,*R*,*R*)-TangPhos-Rh complex to yield (*R*)-(−)-*N*-acetylsalsolidine in 97% ee.[116] PennPhos,[80a] *o*-Ph-HexaMeO-BIPHEP,[60] and Me-BPE[182] have shown high efficiencies in Rh-catalyzed hydrogenation of cyclic enamides. Additionally, racemic cyclic enecarbamate has been hydrogenated with an *o*-Ph-HexaMeO-BIPHEP-Rh catalyst to yield the cis chiral carbamate in 96% ee.[60] The chiral product can be directly used for the synthesis of sertraline, an anti-depressant agent. A set of 2-substituted *N*-acetylindoles can be efficiently

Scheme 9



Scheme 10



hydrogenated by the Ph-TRAP-Rh system with excellent enantioselecitivities.[89g] Hydrogenation of some tetra-substituted enamides has also been reported. ^{t}Bu-BisP* and ^{t}Bu-MiniPhos have provided excellent ee's for hydrogenation of a β,β- dimethyl-α-phenyl enamide derivatives (Scheme 9).[109] Using a Penn-Phos-Rh catalyst[80a] or an *o*-Ph-BIPHEP-Rh catalyst,[60] the tetra-substituted enamides derived from 1-indanone and 1-tetralone have been hydrogenated in excellent enantioselectivities.

Hydrogenation of a series of *E*/*Z* isomeric mixtures of α-arylenamides with a MOM-protected β-hydroxyl group catalyzed by a BICP-Rh complex or a Me-DuPhos complex leads to chiral β-amino alcohol derivatives in excellent ee's.[83c] A 1,4-diphosphane **20** with a rigid 1,4-dioxane backbone is also very effective for this transformation (Scheme 10).[88]

Other than Rh chemistry, the Ru-BINAP system has shown excellent enantioselectivity in hydrogenation of (*Z*)-*N*-acyl-1-alkylidenetetrahydroisoquindines. Thus, a series of chiral isoquinoline products can be efficiently synthesized.[30a,b,184] A cyclic enamide derived from 6-bromo-tetralone is hydrogenated with a Ru-BINAP catalyst to give the corresponding chiral amide product in 97% ee.[185] Hydrogenation of a series of tetrasubstituted enamides derived from 1-substituted-2-tetralones catalyzed by a Ru complex generated in situ from (COD)Ru(methallyl)$_2$, Me-DuPhos, and HBF_4 provides chiral amide products in up to 72% ee's (Scheme 11). [186]

3.1.3. Hydrogenation of (β-Acylamino) Acrylates

Asymmetric hydrogenation of (β-acylamino) acrylates has gained much attention recently because the resulting β-amino acid derivatives are important building blocks for making chiral drugs.[187] Since both (*Z*)- and (*E*)-(β-acylamino) acrylates are generally formed simultaneously through most synthetic methods, to obtain high enantioselectivities for hydrogenation of both *Z* and *E* isomeric substrates is important for practical synthesis of β-amino acid derivatives. Many Rh and Ru complexes with chiral phosphorus ligands such as BINAP,[188] DuPhos,[189] BICP,[83e] BDPMI,[87b] *o*-Ph-HexaMeO-BIPHEP,[60] ^{t}Bu-BisP*,[110] TangPhos,[117] phosphoramidite **64**,[149] Et-FerroTANE,[102] Xyl-P-Phos,[59c] and MalPHOS[75] are found to be effective for hydrogenation of (*E*)-β-alkyl (β-acylamino)acrylates. However, only a few chiral ligands, such as BDPMI,[87b] TangPhos,[117] and monophoramidite **65**,[149] can provide over 95% ee's for hydrogenation of (*Z*)-β-alkyl (β-acylamino)acrylates (Table 4). With a TangPhos-Rh catalyst, an *E*/*Z* (1:1) isomeric mixture of methyl 3-acetamido-2-butenoate was hydrogenated in THF to give (*R*)-methyl 3-acetamidobutanoate in 99.5% ee. Mechanistic study of hydrogenation of β-alkyl (β-acylamino)acrylates with a Rh-BisP* complex as the catalyst has shown that the reaction proceeds via a β-carbon-bound Rh monohydride species.[110] Few efficient ligands have been reported for hydrogenation of β-aryl (β-acylamino)acrylates. An Et-FerroTANE-Rh catalyst has provided up to 99% ee's for hydrogenation of a series of (*E*)-β-aryl (β-acylamino)-acrylates,[102] while a Xylyl-BINAPO-Ru catalyst[130] and a TangPhos-Rh catalyst[117] are found to be effective for a variety of (*Z*)-β-aryl (β-acylamino)-acrylates.

3.1.4. Hydrogenation of Enol Esters

Enol esters have similar structures to enamides. However, in contrast to many highly enantioselective examples on asymmetric hydrogenation of enamides, only a few successful examples have been reported for hydrogenation of enol esters. One possible reason is that the acyl group of an enol ester has a weaker coordinating ability to the metal catalyst than that of the corresponding enamide substrate. Some Rh

Scheme 11

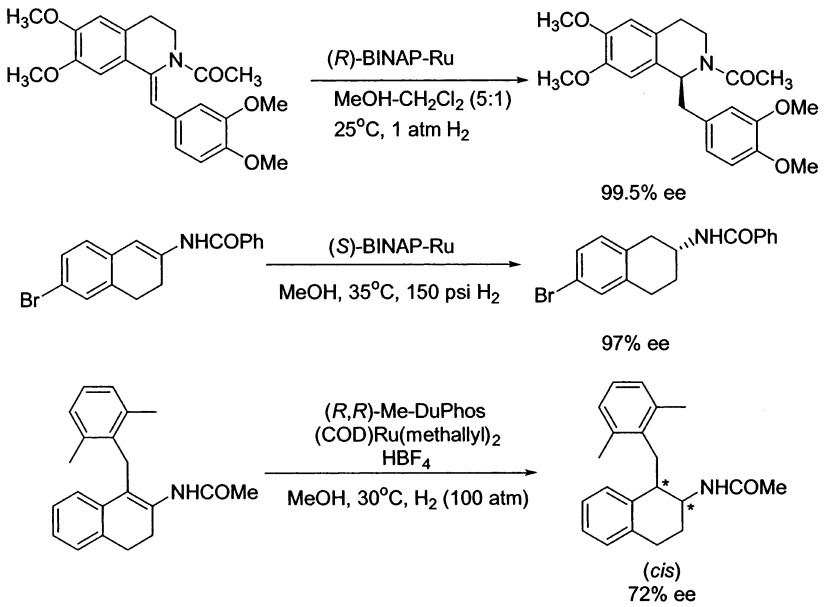
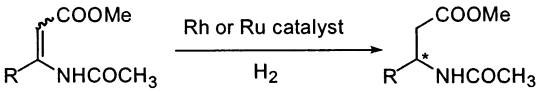


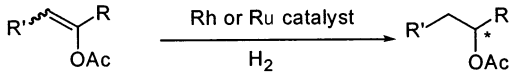
Table 4.



catalyst	R	geometry	reaction conditions	% ee of product (confign)	ref
(*R*)-BINAP-Ru	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	96 (*S*)	188
(*R*)-Xyl-P-Phos-Ru	CH_3	*E*	MeOH, 0 °C, 8 atm H_2	98.1 (*S*)	59c
(*S*,*S*)-Me-DuPhos-Rh	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	98.2 (*S*)	189
(*R*,*R*)-BICP-Rh	CH_3	*E*	toluene, rt, 2.7 atm H_2	96.1 (*R*)	83e
(*S*,*S*)-**22**-Rh	CH_3[a]	*E*	CH_2Cl_2, rt, 1 atm H_2	94.6 (*R*)	87b
(*S*,*S*)-^{t}Bu-BisP*-Rh	CH_3	*E*	THF, rt, 3 atm H_2	98.7 (*R*)	110
(*S*,*S*)-MiniPhos-Rh	CH_3	*E*	THF, rt, 3 atm H_2	96.4 (*R*)	110
(*S*,*S*,*R*,*R*)-TangPhos-Rh	CH_3	*E*	THF, rt, 1.3 atm H_2	99.6 (*R*)	116
(*S*)-**64**-Rh	CH_3	*E*	CH_2Cl_2, rt, 10 atm H_2	99 (*R*)	149
(*R*,*R*)-MalPHOS-Rh	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	97.8 (*R*)	75
(*R*,*R*)-Et-FerroTANE-Rh	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	99 (*R*)	102
(*S*,*S*)-Me-DuPhos-Rh	CH_3	*Z*	MeOH, 25 °C, 1 atm H_2	87.8 (*S*)	189
(*S*,*S*)-**22**-Rh	CH_3[a]	*Z*	CH_2Cl_2, rt, 6.7 atm H_2	95 (*R*)	87b
(*S*,*S*,*R*,*R*)-TangPhos-Rh	CH_3	*Z*	THF, rt, 1.3 atm H_2	98.5 (*R*)	116
(*S*)-**65**-Rh	CH_3	*Z*	^{i}PrOH, rt, 10 atm H_2	95 (*R*)	149
(*S*,*S*,*R*,*R*)-TangPhos-Rh	CH_3	*E*/*Z*[b]	THF, rt, 1.3 atm H_2	99.5 (*R*)	116
(*R*,*R*)-Et-FerroTANE-Rh	Ph	*E*	MeOH, 25 °C, 1 atm H_2	>99 (*R*)	102
(*S*)-**65**-Rh	Ph[a]	*Z*	^{i}PrOH, rt, 10 atm H_2	92 (*S*)	149
(*S*)-Xylyl-*o*-BINAPO-Ru	Ph	*Z*	EtOH, 50 °C, 5.3 atm H_2	99 (*S*)	130
(*S*)-Xylyl-*o*-BINAPO-Ru	*p*-F-Ph	*Z*	EtOH, 50 °C, 5.3 atm H_2	99 (*S*)	130
(*S*)-Xylyl-*o*-BINAPO-Ru	*p*-MeO-Ph	*Z*	EtOH, 50 °C, 5.3 atm H_2	99 (*S*)	130
(*S*,*S*,*R*,*R*)-TangPhos-Rh	Ph	*Z*	THF, rt, 1.3 atm H_2	93.8 (*S*)	116
(*S*,*S*,*R*,*R*)-TangPhos-Rh	*p*-F-Ph	*Z*	THF, rt, 1.3 atm H_2	95.0 (*S*)	116
(*S*,*S*,*R*,*R*)-TangPhos-Rh	*p*-MeO-Ph	*Z*	THF, rt, 1.3 atm H_2	98.5 (*S*)	116

[a] Ethyl ester. [b] *E*/*Z* = 1:1.

Table 5.

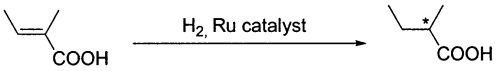


catalyst	R	R′	geometry	reaction conditions	% ee of product (confign)	ref
(*R*,*R*)-Et-DuPhos-Rh	COOEt	H	N/A	MeOH, rt, 2 atm H_2	>99 (*R*)	194
(*R*)-(*S*)-**27**-Rh	COOMe	H	N/A	acetone, rt, 1 atm H_2	94.9 (*S*)	95c
(*R*)-(*S*)-**33**-Rh	COOMe	H	N/A	MeOH, rt, 1 atm H_2	98 (*S*)	97
(*R*,*R*)-DIPAMP-Rh	COOEt	^{i}Pr	*E*/*Z*[a]	MeOH, rt, 3 atm H_2	92 (*S*)	191
(*R*,*R*)-Et-DuPhos-Rh	COOEt	^{i}Pr	*E*/*Z*[b]	MeOH, rt, 6 atm H_2	96.1 (*R*)	192
(*R*)-BINAP-Ru	COOEt	^{i}Pr	*E*/*Z*[a]	MeOH, 50 °C, 50 atm H_2	98 (*S*)	191
(*R*,*R*)-DIPAMP-Rh	COOEt	Ph	*Z*	MeOH, rt, 3 atm H_2	88 (*S*)	191
(*R*,*R*)-Et-DuPhos-Rh	COOEt	Ph	*E*/*Z*[c]	MeOH, rt, 3 atm H_2	95.6 (*R*)	192
(*S*,*S*)-Me-DuPhos-Rh	Ph	H	N/A	MeOH, rt, 3 atm H_2	89 (*S*)	194
(*S*,*S*,*R*,*R*)-TangPhos-Rh	Ph	H	N/A	EtOAc, rt, 1.3 atm H_2	96 (*R*)	118
(*S*,*S*)-Me-DuPhos-Rh	1-Np	H	N/A	MeOH, rt, 3 atm H_2	93 (*S*)	194
7-Rh	1-Np	H	N/A	MeOH, rt, 3 atm H_2	95 (*S*)	72b
(*S*,*S*,*R*,*R*)-TangPhos-Rh	1-Np	H	N/A	EtOAc, rt, 1.3 atm H_2	97 (*R*)	118
(*S*)-C2-TunaPhos-Ru	1-Np	H	N/A	EtOH/CH_2Cl_2, rt, 3 atm H_2	97.7 (*S*)	55
(*R*,*R*)-Me-DuPhos-Rh	PhCH=CH (*E*)	H	N/A	THF, rt, 2 atm H_2	94 (*R*)	196
(*R*,*R*)-Et-BPE-Rh	CF_3	H	N/A	MeOH, rt, 2 atm H_2	>95 (*R*)	194

[a] *E*/*Z* = 70:30. [b] *E*/*Z* = 6:1. [c] *E*/*Z* = 9:1.

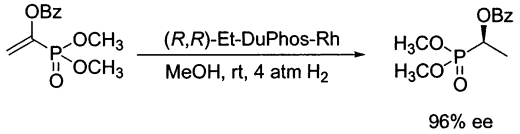
and Ru complexes associated with chiral phosphorus ligands such as DIPAMP,[190,191] DuPhos,[192,194] BINAP,[191] FERRIPHOS **27**,[95c] and TaniaPhos **33**[97] are effective for asymmetric hydrogenation of α-(acyloxy) acrylates (Table 5). A wide range of α-(acyloxy) acrylates have been hydrogenated with an Et-DuPhos-Rh catalyst in excellent ee's.[192] High selectivities are also obtained on hydrogenation of the *E*/*Z* isomeric mixtures of *β*-substituted substrates. The products can be easily converted to α-hydroxy esters and 1,2-diols. Asymmetric hydrogenation of a series of enol phosphates with a DuPhos-Rh or a BPE-Rh catalyst provides moderate to excellent ee's (Scheme 12).[193] Some Rh or Ru catalysts with chiral phosphorus ligands, such as DuPhos,[194] **7**,[72b] TangPhos,[118] BINAP,[195] and TunaPhos,[55] have been used for asymmetric hydrogenation of aryl enol acetates without other functionalities (Table 5). A TangPhos-Rh catalyst provides enantioselectivities ranging from 92% to 99% ee's for a diverse set of aryl enol acetates;[118]

Table 6.



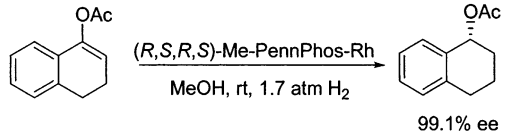
catalyst	S/C ratio	reaction conditions	% ee of product (confign)	ref
$Ru(OAc)_2[(R)\text{-BINAP}]$	100	MeOH, 15−30 °C, 4 atm H_2	91 (*R*)	30d
$Ru[(R)\text{-BINAP}](2\text{-methallyl})_2$	100	MeOH, 20 °C, 4 atm H_2	90 (*R*)	201
$Ru(OAc)_2[(S)\text{-H8-BINAP}]$	200	MeOH, 10−25 °C, 1.5 atm H_2	97 (*S*)	200
$[(R)\text{-MeO-BIPHEP}]RuBr_2$	100	MeOH, 20 °C, 1.4 atm H_2	92 (*R*)	201
$[NH_2Et_2][\{RuCl[(S)\text{-BIPHEMP}]\}_2(\mu\text{-Cl})_3]$	100	MeOH, 20 °C, 4 atm H_2	98 (*S*)	201
$Ru(p\text{-cymene})[(-)\text{-TetraMe-BITIANP}]I_2$	500	MeOH, 25 °C, 10 atm H_2	92 (*S*)	57b
$Ru[(-)\text{-TetraMe-BITIOP}](2\text{-methally})_2$	3000	MeOH, 25 °C, 10 atm H_2	94 (*R*)	58

Scheme 12



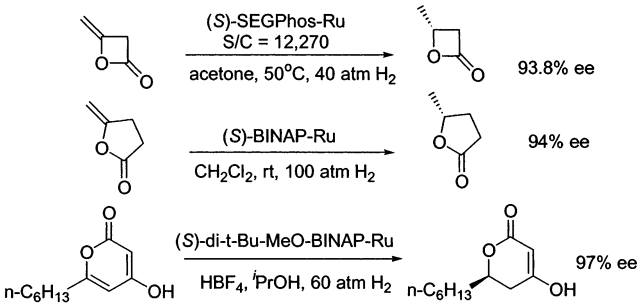
a C_2-TunaPhos-Ru catalyst is found to be equally effective for this transformation.[55] Hydrogenation of cyclic enol acetates, in contrast, is a challenging problem. Me-PennPhos is found to be efficient for Rh-catalyzed hydrogenation of five- or six-membered-ring cyclic enol acetates (Scheme 13).[80b] Hydrogenation of acyclic enol acetates is also possible. Vinylic, acetylenic,[196] and trifluoromethyl[197] enol acetates have been hydrogenated with a DuPhos-Rh or BPE-Rh catalyst in excellent ee's (Table 5).

Scheme 13



Although high hydrogen pressure is required, BINAP and its analogous ligands have provided superior results in Ru-catalyzed hydrogenation of four- and five-membered cyclic lactones or carbonates bearing an exocyclic methylene group (Scheme 14).[195]

Scheme 14



A (*S*)-SEGPHOS-Ru catalyst provides 93.8% ee in hydrogenation of a diketene with high turnover numbers.[198] With a (*S*)-BINAP-Ru catalyst, 94% ee is obtained in hydrogenation of 4-methylene-γ-butyrolactone.[195] In the presence of a small amount of HBF_4, a di-t-Bu-MeOBIPHEP-Ru catalyst allows the hydrogenation of a 2-pyrone substrate, yielding 97% ee.[199]

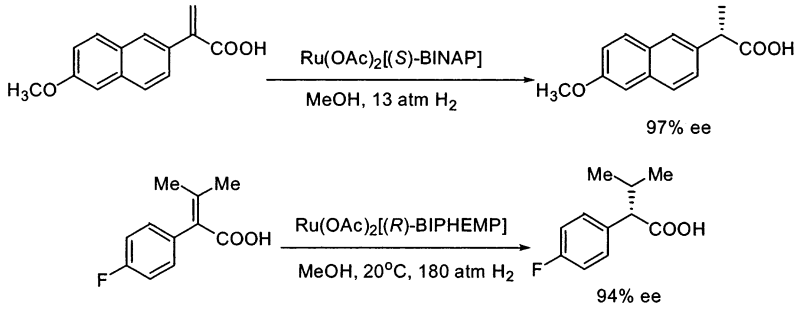
3.1.5. Hydrogenation of Unsaturated Acids and Esters

3.1.5.1. α,β-Unsaturated Carboxylic Acids. Significant progress has been achieved in asymmetric hydrogenation of α,β-unsaturated carboxylic acids with chiral Ru catalysts. The Ru-BINAP-dicarboxylate complex produces excellent enantioselectivities in hydrogenation of some α,β-unsaturated carboxylic acids, despite the fact that the catalytic efficiencies are still highly sensitive to the substrates, reaction temperature, and hydrogen pressure.[30d] Other atropisomeric ligands, such as H_8-BINAP,[200] MeO-BIPHEP,[201] BIPHEMP,[201] P-Phos,[59] TetraMe-BITIANP,[57b] and TetraMe-BITIOP,[58] are also effective for this transformation. Ru complexes prepared in different forms may exhibit slightly different efficiencies. Table 6 lists examples of hydrogenation of tiglic acid with different metal−ligand complexes. The H_8-BINAP ligand with a larger dihedral angle gives superior results compared to the BINAP ligand.

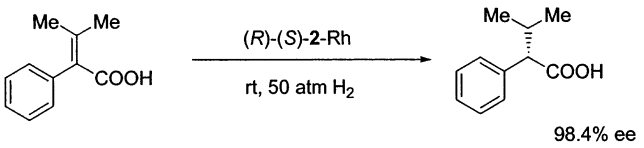
With a BINAP-Ru,[30d,202] H_8-BINAP-Ru,[200] or P-Phos-Ru[59a] catalyst, the antiinflammatory drug (*S*)-ibuprofen and (*S*)-naproxen can be efficiently synthesized via asymmetric hydrogenation (Scheme 15). In the case of hydrogenation of α-arylpropionic acids, high hydrogenation pressure and low temperature are required to achieve good enantioselectivity. With an (*R*)-BIPHEMP-Ru catalyst, (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid, a key intermediate for the synthesis of calcium antagonist Mibefradil, can be produced in 94% ee.[203]

In contrast to successful results obtained with Ru catalysts, few systems have been reported on Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acids. The (aminoalkyl)ferrocenylphosphine ligand **2** provides excellent reactivities and enantioselectivities in Rh-catalyzed hydrogenation of trisubstituted acrylic acids (Scheme 16).[47] The aminoalkyl side chain of the ligand is important to maintain the high reactivity and enantioselectivity. It is believed that the amino group of the ligand interacts with the carboxylic acid functionality of the substrate, therefore facilitating olefin coordination to the Rh center. When substrates with two different substituents at β positions are employed, the hydrogenation products with two chiral centers can be efficiently obtained. A (*R*)-(*S*)-**2**-Rh complex has also been employed for the synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid, and 98% ee is obtained.[204] An ^{i}Pr-DuPhos-Rh complex is also efficient for hydrogenation of some α,β-unsaturated carboxylic acids such as tiglic acid.[14a,b]

Scheme 15

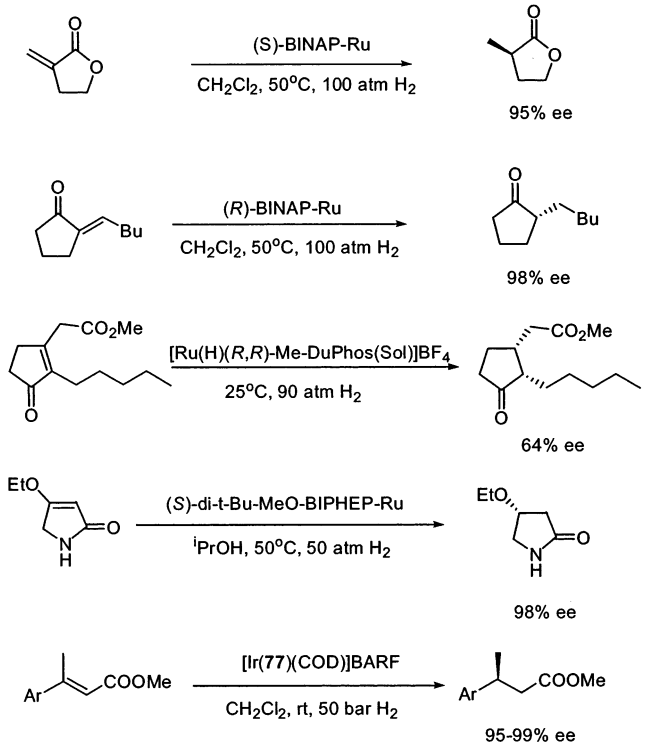


Scheme 16



3.1.5.2. α,β-Unsaturated Esters, Amides, Lactones, and Ketones. Limited advances, however, have been achieved in asymmetric hydrogenation of α,β-unsaturated carboxylic acid esters, amides, lactones, and ketones (Scheme 17). The Ru-BINAP

Scheme 17



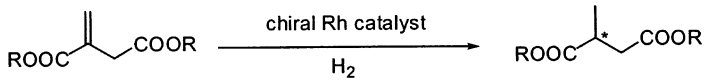
system is efficient for hydrogenation of 2-methylene-γ-butyrolactone, and 2-methylene-cyclopentanone.[195,204] By using a cationic (*R*,*R*)-Me-DuPhos-Ru hydride complex as the catalyst, hydrogenation of a vinylogous β-oxoester with a tetrasubstituted C=C bond provides (+)-cis-methyl dihydrojasmonate in 64% ee.[205] With a dicationic (*S*)-di-t-Bu-MeOBIPHEP-Ru complex under high hydrogen pressure, 3-ethoxy pyrrolidinone is hydrogenated in 2-propanol to give (*R*)-4-ethoxy-γ-lactam in 98% ee.[63] Recent development of Ir−N,P ligand systems has enabled the hydrogenation of β-methyl cinnamates with high enantioselectivities. Hydrogenation of ethyl β-methyl cinnamate with a cationic (*S*)-**75**-Ir complex as the catalyst provides the corresponding chiral ester in 94% ee.[158] A chiral phospholane-oxazoline ligand **77** is even more effective.[160] Its cationic Ir complex has allowed the synthesis of a set of chiral aryl 2-methyl butyric acid esters with ee's ranging from 95% to 99%.

3.1.5.3. Itaconic Acids and Their Derivatives. Many chiral phosphorus ligands have shown excellent reactivities and enantioselectivities in Rh-catalyzed hydrogenation of itaconic acids or esters. Table 7 lists successful examples (over 95% ee) of hydrogenation of itaconic acid or dimethyl ester with different chiral phosphorus ligands. High reactivity is observed with electron-rich phosphane ligands such as BICHEP,[34c] Et-DuPhos,[206] and TangPhos,[118] as well as electron-deficient phosphonite or phosphite ligands such as **50**[131] and **52**.[133] Some mono-phosphorus ligands such as MonoPhos[148] and **63**[146a] are as equally efficient as bisphosphorus chelating ligands. A secondary phosphane **66**[77] is also effective. A bisphospholane ligand **7** with four hydroxyl groups allows the hydrogenation to proceed in aqueous solution.[72b]

In contrast to the many successful examples for hydrogenation of the parent itaconic acid or its dimethyl ester, only a few ligands have been reported to be efficient for hydrogenation of β-substituted itaconic acid derivatives. Rh complexes with chiral ligands such as MOD-DIOP,[40] BPPM, Et-DuPhos, and TangPhos are efficient for hydrogenation of several β-substituted itaconic acid derivatives; some examples are shown in Table 8. In the presence of a base such as sodium methoxide or a tertiary amine, an Et-DuPhos-Rh complex has shown excellent enantioselectivities and reactivities in hydrogenation of a series of β-aryl or alkyl itaconic acid monomethyl esters.[206] The *E*/*Z* isomeric mixtures of substrates can be directly used. High enantioselectivities have also been obtained with a TangPhos-Rh catalyst in hydrogenation of a variety of β-aryl or alkyl substituted itaconic acid substrates.[118]

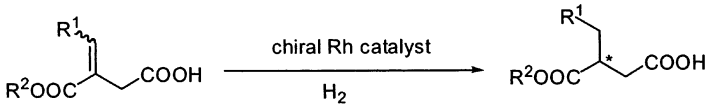
A chiral 1,1′-diphosphetanylferrocene ligand, Et-FerroTANE, is very efficient for hydrogenation of a series of β-aryl or alkyl substituted monoamido itaconates (Scheme 18).[101] For example, in the presence of 0.005 mol % Et-FerroTANE-Rh catalyst, a β-phenyl monoamido itaconate is hydrogenated completely to give the chiral monoamido succinate in 98% ee. A PYRPHOS ligand is also found to be effective

Table 7.



ligand	R	S/C	reaction condition	% ee of product (config)	ref
(*R*)-BICHEP-Rh	H	1000	EtOH, 25 °C, 1 atm H_2	96 (*R*)	34c
(*R*,*R*)-Et-DuPhos	Me	10000	MeOH, 25 °C, 5 atm H_2	98 (*R*)	206
7	H	100	MeOH/H_2O(3:97), rt, 10 atm H_2	>99 (*R*)	72b
10	Me	100	MeOH, rt, 1 atm H_2	99.1 (*R*)	71a
12	Me	100	MeOH, rt, 1 atm H_2	97.9 (*R*)	74b
(*R*,*R*)-(*S*,*S*)-Et-TRAP	Me	200	CH_2Cl_2, reflux, 1atm H_2	96 (*S*)	89c
(*R*)-(*S*)-Josiphos	Me	100	MeOH, rt, 1 atm H_2	98−99 (S)	90
32	Me	100	MeOH, rt, 1 atm H_2	98 (*S*)	96a
33	Me	100	MeOH, rt, 1 atm H_2	98 (*R*)	97
(*S*,*S*)-Et-FerroTANE	Me	200	MeOH, rt, 5.5 atm H_2	98 (*R*)	101
(*S*,*S*,*S*,*S*)-**38**	H	100	MeOH, rt, 5.3 atm H_2	99.5 (*R*)	103
40	Me	100	MeOH, rt, 1atm H_2	95 (*R*)	107
(*S*,*S*)-Ad-BisP*	Me	500	MeOH, rt, 1.6 atm H_2	99.6	108b
(*S*,*S*,*R*,*R*)-TangPhos	Me	5000	THF, rt, 1.3 atm H_2	99 (*S*)	118
(*R*,*R*)-**50**	Me	5380	CH_2Cl_2, rt, 1.3 atm H_2	>99.5 (*R*)	131
52	Me	1000	CH_2Cl_2, −10 °C, 0.3 atm H_2	98.7 (*R*)	133
56	H	100	MeOH, rt, 20 atm H_2	97.4 (*R*)	142
(*S*)-MonoPhos	H	20	CH_2Cl_2, 25 °C, 1 atm H_2	96.6 (*S*)	148
(*S*)-(*R*)-**63**	Me	5000	CH_2Cl_2, 20 °C, 1.3 atm H_2	97.4 (*S*)	146a
(*R*,*R*)-**66**	H	100	^{i}PrOH, 20 °C, 1.1 atm H_2	96.0 (*S*)	77

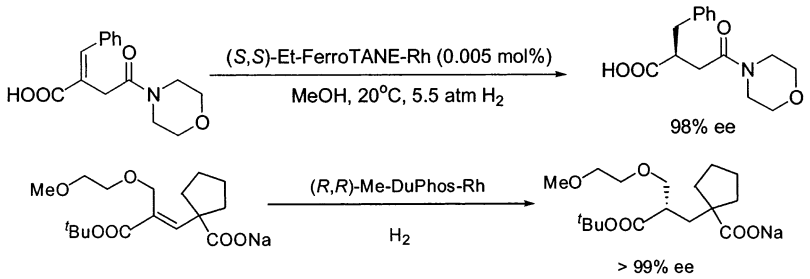
Table 8.



ligand	R^1	R^2	geometry, S/C ratio	reaction conditions	% ee of product (confign)	ref
(*R*,*R*)-MOD-DIOP	Ph	Me	*E*, 500	MeOH, NEt_3, 30 °C, 1 atm H_2	96 (*S*)	40c
(*R*,*R*)-BPPM	Ph	H	*E*, 200	MeOH, NEt_3, 25 °C, 1 atm H_2	94 (*R*)	207
(*S*,*S*)-Et-DuPhos	Ph	Me	*E*/*Z*, 3000	MeOH, rt, 5.5 atm H_2[a]	97 (*S*)	206
(*S*,*S*,*R*,*R*)-TangPhos	Ph	Me	*E*/*Z*, 200	THF, rt, 1.3 atm H_2	95 (*S*)	118
(*S*,*S*)-Et-DuPhos	^{i}Pr	Me	*E*/Z, 3000	MeOH, rt, 5.5 atm H_2[a]	99 (*R*)	206
(*S*,*S*,*R*,*R*)-TangPhos	^{i}Pr	Me	*E*/*Z*, 200	THF, rt, 1.3 atm H_2	96 (*S*)	118

[a] 10 mol % of NaOMe is added.

Scheme 18

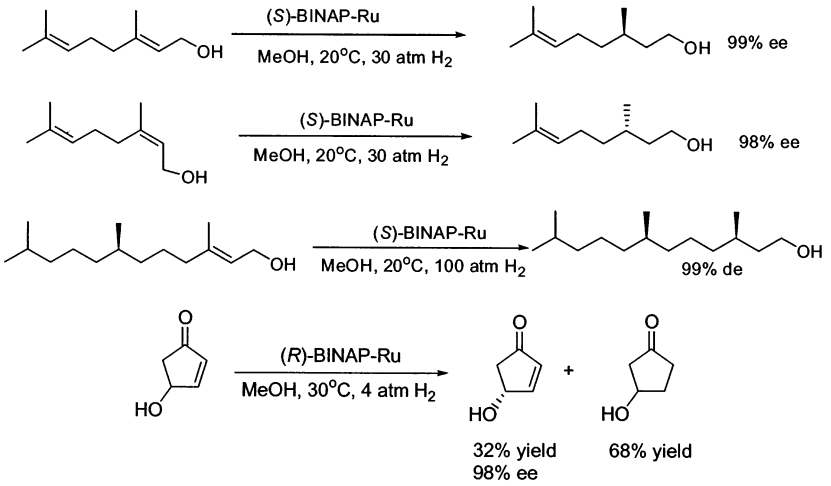


for hydrogenation of a β-aryl monoamido itaconate.[207] With an Et-DuPhos-Rh catalyst, a unique olefin substrate is hydrogenated to afford an important intermediate for the drug candoxatril in over 99% ee.[208] A MeO-BIPHEP-Ru catalyst is also found to be very effective for this process when a mixed solvent (THF/H_2O) is used.[209]

3.1.6. Hydrogenation of Unsaturated Alcohols

Asymmetric hydrogenation of unsaturated alcohols such as allylic and homoallylic alcohols was not very efficient until the discovery of the BINAP-Ru catalyst. With Ru(BINAP)$(OAc)_2$ as the catalyst, geraniol and nerol are successfully hydrogenated to give (*S*)- or (*R*)-citronellol in nearly quantitative yield with 96−99% ee's.[30c] The substrate-to-catalyst ratio up to 48 500 can be applied, and the other double bond at the C6 and C7 positions of the substrate is not reduced. High hydrogen pressure is required for the high enantioselectivity in the hydrogenation of geraniol. Low hydrogen pressure facilitates the isomerization of geraniol to γ-geraniol, which leads to the

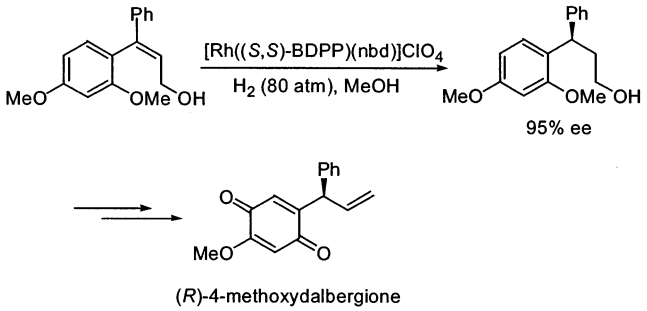
Scheme 19



hydrogenation product with opposite configuration and therefore yielding a decreased ee.[210] In addition to BINAP, other chiral atropisomeric ligands, such as MeO-BIPHEP,[36] TetraMe-BITIANP,[57b] and TetraMe-BITIOP,[58] are also effective for this transformation. The catalytic efficiency of the BINAP-Ru catalyst is highly sensitive to the substitution patterns of the allylic alcohols. Homoallylic alcohols can also be hydrogenated in high ee's with the BINAP-Ru catalyst. Its application in the synthesis of (3*R*,7*R*)-3,7,11-trimethyldodecarol, an intermediate for the synthesis of α-tocopherol, has been shown in Scheme 19. When racemic allylic alcohols are subjected for asymmetric hydrogenation, highly efficient kinetic resolutions are achieved with a BINAP-Ru complex as the catalyst.[31c] A racemic 4-hydroxy-2-cyclopentenone is hydrogenated with a (*S*)-BINAP-Ru catalyst to leave unreacted starting material in 98% ee at 68% conversion. The chiral starting material serves as an important building block for three-component-coupling prostaglandin synthesis.

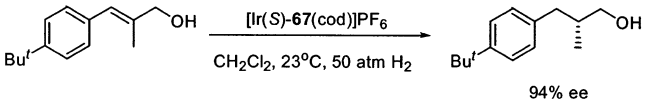
A chiral BDPP-Rh complex is an efficient catalyst for hydrogenation of 3-(2′,4′-dimethoxyphenyl)-3-phenyl-2-propenol. The chiral alcohol product, with enantiomeric excess up to 95%, has been used for the synthesis of chiral 4-methoxydalbergione (Scheme 20).[211]

Scheme 20



The development of Ir-chiral N,P ligand systems opens another promising way for hydrogenation of allylic alcohol and its derivatives. For example, a cationic Phox-Ir complex catalyzes the hydrogenation of (*E*)-2-methyl-3-phenyl-9-propen-1-ol in highly enantioselective fashion.[153a] With 1 mol % (*S*)-**67**−Ir catalyst, the hydrogenation proceeds completely to provide the chiral alcohol product in 96% ee. Under the same conditions, a *para*-^{t}Bu-substituted chiral alcohol derivative is obtained in 94% ee for the synthesis of lilial (Scheme 21).

Scheme 21

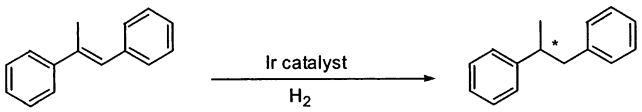


3.1.7. Hydrogenation of Unfunctionalized Olefins

Asymmetric hydrogenation of unfunctionalized olefins remains a challenging area and only limited success has been achieved. Some chiral metallocene catalysts such as chiral titanocene[212] or zirconocene[213] have been found to be efficient for hydrogenation of tri- or tetra-substituted unfunctionalized olefins. With (EBTHI)TiH or (EBTHI)ZrH as the catalyst, a series of tri- or tetra-substituted aryl alkenes have been hydrogenated with excellent enantioselectivity. Chiral cyclolanthanide complexes are also effective in hydrogenation of 2-phenyl-1-butene at low reaction temperature.[19] Some Ru and Rh complexes with chiral bisphosphorus ligands have been tried with few successful results.[214] A Me-DuPhos-Ru complex in the presence of ^{t}BuOK has been applied for hydrogenation of 3-phenylbutenes and up to 89% ee is obtained.[215] Cationic Ir-chiral N and P ligand complexes have recently shown promising results in enantioselective hydrogenation of unfunctionalized olefins.[3m] Several chiral N and P ligands have been developed and have provided excellent ee's in asymmetric hydrogenation of 2-methyl stilbene, as shown in Table 9.

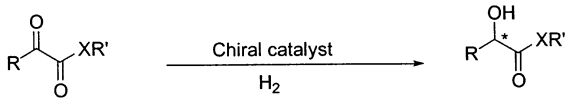
A series of para-substituted (*E*)-methylstilbenes have been hydrogenated with a Phox-Ir catalyst in excellent enantioselectivities.[153] In addition, threonine-derived phosphinite-oxazoline ligand (*S*)-**75** has provided high enantioselectivities for hydrogenation of both (*E*)- and (*Z*)-2-(4-methoxyphenyl)-2-butene, although the configurations of the products are opposite (Scheme 22).[158] A terminal olefin 2-arylbutene is hydrogenated at 0 °C under 1 atm hydrogen pressure to give the chiral product in 89% ee.

Table 9.



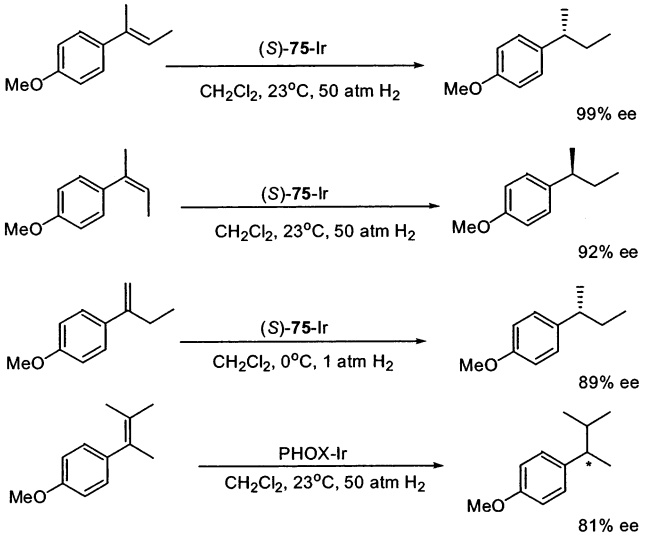
ligand	S/C ratio	reaction conditions	% ee of product (confign)	ref
(*S*)-**67** (PHOX)	1000	CH_2Cl_2, 23 °C, 50 atm H_2	97 (*R*)	153a
(*S*)-**68** (PyrPHOX)	100	CH_2Cl_2, rt, 50 atm H_2	99 (*R*)	155
(*S*)-**70** (PHIM)	100	CH_2Cl_2, 25 °C, 50 atm H_2	94 (*R*)	156
(*S*)-**73**	250	CH_2Cl_2, 23 °C, 50 atm H_2	98 (*R*)	157
(*S*)-**74**	5000	CH_2Cl_2, rt, 50 atm H_2	99 (*R*)	158
(*S*)-**76** (JM-Phos)	500	CH_2Cl_2, 25 °C, 50 atm H_2	95 (*R*)	159
77	100	CH_2Cl_2, rt, 50 atm H_2	95 (*R*)	160

Table 10.



catalyst	R	XR′	S/C ratio	reaction conditions	% ee of product (confign)	ref
(*S*,*S*)-MCCPM-Rh	Me	OMe	2000	THF, 20 °C, 20 atm H_2	87 (*R*)	216
(−)-TetraMe-BITIANP-Ru	Me	OMe	600	MeOH, 25 °C, 100 atm H_2	88 (*S*)	57b
(*S*)-Cy,Cy-oxoProNOP-Rh	Me	OEt	200	toluene, 20 °C, 50 atm H_2	95 (*R*)	135f
59-Rh	$Ph(CH_2)_2$	OEt	100	THF, rt, 20 atm H_2	92.4 (*R*)	152
(+)-TetraMe-BITIOP-Ru	$Ph(CH_2)_2$	OEt	462	EtOH, H_2O, 50 °C, 100 atm H_2, HBF_4	91 (*S*)	58
(*R*)-SEGPHOS-Ru	^{t}Bu	OEt	1000	EtOH, 70 °C, 50 atm H_2	98.5 (*R*)	52
(*R*)-BICHEP-Ru	Ph	OMe	100	EtOH, 25 °C, 5 atm H_2	>99 (*S*)	34d
(*S*)-MeO-BIPHEP-Ru	Ph	OMe		MeOH, 50 °C, 20 atm H_2	86 (*S*)	201
(*S*)-BINAP-Ru	4-MePh	OMe	150	MeOH, 30 °C, 100 atm H_2, HBF_4	93 (*S*)	217
(*S*)-Cp,Cp-IndoNOP-Rh	Ph	NHBn	200	toluene, 20 °C, 1 atm H_2	91 (*S*)	135g
(*S*,2*S*)-$Cr(CO)_3$-Cp,Cp-IndoNOP-Rh	Ph	NHBn	200	toluene, 20 °C, 1 atm H_2	97 (*S*)	135g
(*R*)-BICHEP-Ru	Ph	NHBn	100	MeOH, 25 °C, 40 atm H_2	96 (*R*)	34d

Scheme 22



Hydrogenation of a tetra-substituted olefin is catalyzed by a PHOX-Ir complex to give product in 81% ee with complete conversion.[153]

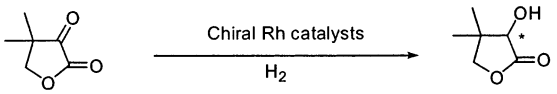
3.2. Hydrogenation of Ketones

3.2.1. Hydrogenation of Functionalized Ketones

3.2.1.1. α-Keto Esters. Asymmetric hydrogenation of α-keto esters has been studied with some Rh and Ru catalysts. Several neutral Rh catalysts with chiral ligands such as MCCPM,[41b,216] Cy,Cy-oxoProNOP,[135c,d,f] Cp,Cp-IndoNOP,[135g] and $Cr(CO)_3$-Cp,Cp-IndoNOP[135g] have shown excellent reactivities and enantioselectivities in hydrogenation of some α-keto esters or amides. A cationic BoPhoz (**59**)-Rh complex is also effective for this transformation.[142] Some Ru catalysts associated with chiral atropisomeric ligands such as BINAP,[217] BICHEP,[34d] MeOBIPHEP, TetraMe-BITIOP,[58] TetraMe-BITIANP[57b] are also applicable (Table 10). A cyclic α-keto ester, dihydro-4,4-dimethyl-2,3-furandione, has been efficiently hydrogenated by several Rh catalysts with high turnover numbers (Table 11). The (*R*)-pantolactone product is a key intermediate in the syntheses of vitamin B and of co-enzyme A.

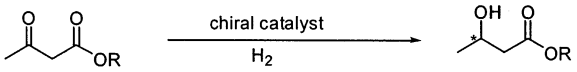
3.2.1.2. β-Keto Esters. Asymmetric hydrogenation of β-keto esters have been very successful using chiral Ru catalysts and a detailed review has been written on this subject.[220] With a BINAP-Ru catalyst, a variety of β-keto esters have been hydrogenated to give chiral β-hydroxyl esters in high enantioselectivities.[31a] Several different Ru-BINAP complexes have been employed and similarly high enantionselectivities observed.[221] In addition to BINAP, many other chiral atropisomeric biaryl ligands are also very efficient for this transformation. Some other C_2-symmetric ligands, such as BPE,[222] BisP*,[223] and PHANEPHOS,[122b] are also effective. A Josiphos-Rh

Table 11.



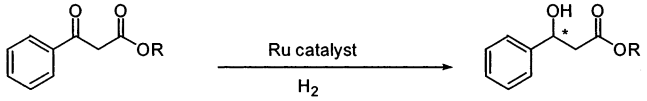
ligand	S/C ratio	reaction conditions	% ee of product (confign)	ref
(*S*,*S*)-BCPM	1000	THF, 50 °C, 50 atm H_2	90.5 (*R*)	218
(*S*,*S*)-m-MePOPPM	150000	toluene, 40 °C, 12 atm H_2	95 (*R*)	219
(*S*)-Cp,Cp-oxoProNOP	70000	toluene, 40 °C, 40 atm H_2	96 (*R*)	135d
(*S*)-Cp,Cp-IndoNOP	200	toluene, 20 °C, 1 atm H_2	>99 (*R*)	135g
(*S*,2*S*)-Cr(CO)$_3$-Cp,Cp-IndoNOP	200	toluene, 20 °C, 1 atm H_2	>99 (*R*)	135g
59 (BoPhoz)	100	THF, rt, 20 atm H_2	97.2 (*R*)	142

Table 12.



catalyst	R	S/C ratio	reaction conditions	% ee of product (confign)	ref
$RuCl_2$[(*R*)-BINAP]	Me	2000	MeOH, 23 °C, 100 atm H_2	>99 (*R*)	31a
$RuCl_2$[(*S*)-**3**)] $(DMF)_n$	Me	1260	MeOH, 100 °C, 100 atm H_2	99 (*S*)	213a
$RuBr_2$[(*S*)-NAPhePHOS]	Me	100	MeOH, 50 °C, 50 atm H_2	97 (*S*)	56
Ru[(*R*)-BisbenzodioxanPhos]$Cl_2(DMF)_n$	Me	1000	MeOH, 80 °C, 3.3 atm H_2	98.1 (*R*)	53
$RuCl_2$[(*S*)-BIFAP]$(DMF)_n$	Me	1000	MeOH, 70 °C, 100 atm H_2	100 (*S*)	51
Ru[(+)-(TetraMe-BITIANP)]$Cl_2(DMF)_n$	Et	1000	MeOH, 70 °C, 100 atm H_2	99 (*R*)	57b
Ru[(+)-(TetraMe-BITIOP)]$Cl_2(DMF)_n$	Et	1000	EtOH, 70 °C, 100 atm H_2	98 (*S*)	58
Ru[(*S*)-P-Phos)]$Cl_2(DMF)_n$	Me	400	MeOH/CH_2Cl_2, 70 °C, 3.3 atm H_2	98.5	59
Ru[(*R*)-C_4-TunaPhos)]$Cl_2(DMF)_n$	Me	100	MeOH, 60 °C, 50 atm H_2	99.1 (*R*)	54
Ru[(*S*)-FUPMOP](p-cymene)I_2	Me	1000	MeOH/CH_2Cl_2, 30−40 °C, 30 atm H_2	100 (*S*)	38
Ru[(*R*)-BIMOP)](p-cymene)I_2	Me	1000	MeOH/CH_2Cl_2, 30−40 °C, 30 atm H_2	99 (*R*)	37
Ru[(*R*)-MeO-BIPHEP)]Br_2	Me	100	MeOH, 50 °C, 20 atm H_2	>99 (*R*)	201
Ru[(*S*)-BIPHEMP)]$RuBr_2$	Me	100	MeOH, 80 °C, 10 atm H_2	>99 (*S*)	201
Ru[(*S*)-[2,2]PHANEPHOS]$(CF_3COO)_2$	Me	250	MeOH/H_2O, TBAI, −5 °C, 3.3 atm H_2	96 (*R*)	122b
Ru(**29**)Br_2	Et	200	EtOH, 50 °C, 50 atm H_2	95.5 (*R*)	96a
Ru[(*R*,*R*)-^{i}Pr-BPE]Br_2	Me	500	MeOH/H_2O, 35 °C, 4 atm H_2	99.3 (*S*)	222
Ru[(*S*,*S*)-^{t}Bu-BisP*] Br_2	Me	200	MeOH/H_2O, 70 °C, 6 atm H_2	98	223
(*R*)-(*S*)-Josiphos-Rh	Et	100	MeOH, rt, 20 atm H_2	97 (*S*)	90

Table 13.



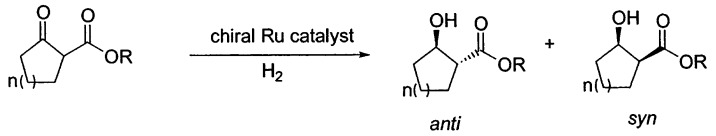
catalyst	R	S/C ratio	reaction conditions	% ee of product (confign)	ref
$RuBr_2$[(*R*)-BINAP]	Et	760	MeOH, 23−30 °C, 91 atm H_2	85 (*S*)	31a
$RuBr_2$[(*R*)-MeO-BIPHEP]	Et	50	EtOH, 50 °C, 1 atm H_2	96 (*S*)	221c
Ru[(−)-TetraMe-BITIOP]Cl_2	Et	257	MeOH/H_2O, 45 °C, 100 atm H_2	93 (*S*)	58
$[NH_2Me_2][\{RuCl[(R)\text{-SEGPHOS}]\}_2(\mu\text{-}Cl)_3]$	Me	10000	MeOH, 80 °C, 30 atm H_2	97.6 (*S*)	52b
Ru(**32**)Br_2	Et	200	MeOH, 50 °C, 50 atm H_2	96 (*S*)	96a
Ru(**33**)Br_2	Et	200	MeOH, 50 °C, 50 atm H_2	98 (*R*)	97
Ru[(*R*)-Xyl-P-Phos)] $Cl(C_6H_6)Cl$	Et	800	EtOH/CH_2Cl_2, 90 °C, 20 atm H_2	96.2 (*S*)	59a
Ru[(*S*)-Xylyl-*o*-BINAPO)]$Cl_2(DMF)_n$	Et	100	EtOH/CH_2Cl_2, 50 °C, 5.3 atm H_2	99 (*R*)	130

complex is found to be effective for hydrogenation of ethyl 3-oxobutanoate.[90] Some efficient examples of hydrogenation of 3-oxobutanoic acid esters with different chiral phosphorus ligand systems are listed in Table 12.

Although the BINAP-Ru (II) system has been recognized as an efficient and general catalyst for the hydrogenation of β-alkyl β-keto esters, the enantioselectivity obtained in hydrogenation of 3-oxo-3-phenylpropionic ester is low, providing the corresponding chiral 3-hydroxyl-3-phenylpropionic ester in 85% ee.[31a] Many other atropisomeric ligands have provided better enantioselectivity for this substrate, as shown in Table 13. One bisphosphinite ligand *o*-Xylyl-BINAPO has provided up to 99% ee in Ru-catalyzed hydrogenation of a series of β-aryl β-keto esters.[130] The BINAP-Ru system is also efficient for hydrogenation of β-keto amide and β-keto thioesters.[31b,224]

When a coordinative functional group such as a chloride or methoxy group exists in the proximity of

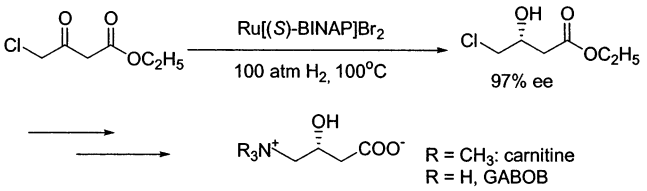
Table 14.



catalyst	*n*	R	S/C ratio	reaction conditions	anti:syn	% ee of the anti product (confign)	ref
Ru[(*R*)-BINAP]Cl(C_6H_6)Cl	1	Me	1170	CH_2Cl_2, 50 °C, 100 atm H_2	99:1	93 (*R*,*R*)	31d
Ru[(+)-(TetraMe-BITIANP)]Cl_2(DMF)$_n$	1	Me	1000	MeOH, 70 °C, 100 atm H_2	93:7	99 (*R*,*R*)	57b
[Ru(+)-(TetraMe-BITIOP)(cymene)I]I	1	Me	1000	MeOH, CF_3COOH, 80 °C, 100 atm H_2	94:6	99 (*S*,*S*)	58
Ru[(*R*)-C4-TunaPhos)]Cl_2(DMF)$_n$	1	Me	200	MeOH, 60 °C, 50 atm H_2	N/A	96.8 (*R*,*R*)	54
Ru[(*R*)-MeO-BIPHEP)]Cl_2(DMF)$_n$	1	Me	200	MeOH, 60 °C, 50 atm H_2	N/A	97.5 (*R*,*R*)	54
Ru(**29**)Br_2	1	Et	200	CH_2Cl_2/EtOH, 50 °C, 50 atm H_2	99:1	90.9 (*R*,*R*)	96a
Ru [(*R*,*R*)-^{i}Pr-BPE]Br_2	1	Me	500	MeOH/H_2O (9:1), 35 °C, 4 atm H_2	24:1	98.3 (*S*,*S*)	222
Ru [(*R*,*R*)-^{t}Bu-BisP*]Br_2	1	Me	200	MeOH/H_2O (10:1), 70 °C, 6 atm H_2	70:13	96	223
Ru[(*R*)-BINAP]Cl(C_6H_6)Cl	2	Et	500	CH_2Cl_2, 50 °C, 100 atm H_2	95:5	90 (*R*,*R*)	227
Ru[(*R*)-BINAP]Cl(C_6H_6)Cl	3	Et	500	CH_2Cl_2, 50 °C, 100 atm H_2	93:7	93 (*R*, *R*)	227

the carbonyl group of a β-keto ester, lower enantioselectivity might be observed due to the competition of two different coordination patterns. 4-Benzyloxy- and 4-chloro-3-oxobutanoate are hydrogenated at room temperature with a BINAP-Ru catalyst to give alcohols in 78% and 56% ee, respectively.[225] However, the enantioselectivity can be dramatically improved under higher reaction temperatures. 97% ee is observed when the hydrogenation of 4-chloro-3-oxobutanoate is carried out at 100 °C (Scheme 23). The

Scheme 23



chiral product has allowed the efficient synthesis of GABOB and (*R*)-carnitine, a carrier of long-chain fatty acids through the mitochondrial membrane.

When a racemic α-mono substituted β-keto ester is subjected to asymmetric hydrogenation, efficient dynamic resolution can be realized if the racemization of the substrate is fast and the chiral recognition of hydrogenation catalyst is good.[31d,226] In fact, excellent dynamic kinetic resolution has been discovered in hydrogenation of several α-mono substituted β-keto esters with a few Ru catalysts under appropriate conditions. Hydrogenation of 2-alkoxycarbonylcycloalkanones has been a standard reaction to test the efficiency of different Ru catalysts (Table 14). The anti hydrogenation product is preferentially formed. 99% ee has been obtained for the anti product when a TetraMe-BITIANP-Ru[57b] or TetraMe-BITIOP-Ru[58] complex is used as the catalyst. Different reaction solvent and catalyst precursor dramatically affect both diastereoselectivity and enantioselectivity of the reaction.

Hydrogenation of a racemic 3-acetyltetrahydrofuran-2-one is successfully catalyzed by the BINAP-Ru system to give the cis hydrogenation product in 97% ee with 99:1 diastereoselectivity (Scheme 24).[217] A TetraMe-BITIANP-Ru complex is also effective for this transformation.[57b] The BINAP-Ru system also provides efficient dynamic kinetic resolution on hydrogenation of α-acylamino and α-amidomethyl β-keto esters.[31d,217,228] High enantio- and diastereoselectivities are obtained for the cis hydrogenation product. Excellent enantio- and diastereoselectivities are also obtained in hydrogenation of 2-benzamidomethyl-3-oxobutanoate with a (−)-DTBM-SEGPHOS-Ru catalyst.[52b] The *cis*-(2*S*, 3*R*)-methyl 2-benzamidomethyl-3-hydroxybutanoate is obtained in 99.4% ee and in 98.6% de. The product can be transformed into a key intermediate of carbapenem antibiotics. 99% ee and 94% de are obtained when a (−)-TetraMe-BITIOP-Ru complex is used as the catalyst.[58] When a BIPHEP-Ru complex is applied as a catalyst in hydrogenation of racemic methyl-2-acetamido-3-keto-6-phthalimidohexanoate for the synthesis of (2*S*,3*R*)-3-hydroxylysine, again excellent enantio- and diastereoselectivities are obtained.[229] Efficient dynamic kinetic resolution is also observed in hydrogenation of α-chloro-β-keto esters with *anti*-chlorohydrin as the major product.[230] With (COD)Ru(methallyl)$_2$-(*S*)-BINAP as the catalytic system and CH_2Cl_2 as the solvent, hydrogenation of racemic ethyl 2-chloro-3-phenyl-3-oxopropionate provides the *anti*-chlorohydrin product in 99% ee with 98% de, this product can be directly converted into chiral (2*S*,3*R*)-methylglycidate.

3.2.1.3. γ-Keto Esters. γ-Keto esters can also be efficiently hydrogenated by chiral Ru catalysts associated with atropisomeric ligands using prolonged reaction times.[231] For example, with an in situ formed Ru-BINAP catalyst from Ru(BINAP)(OAc)$_2$ and HCl, a series of chiral lactones can be efficiently synthesized through asymmetric hydrogenation of 4-oxo carboxylates (Scheme 25). Hydrogenation of ethyl levulinate is performed with a (*R*)-SEGPHOS-Ru catalyst to give (*R*)-ethyl 4-hydroxypentanoate in up to 99% ee.[52b]

3.2.1.4. Amino Ketones. Amino ketones or their hydrochloride salts can be effectively hydrogenated with chiral Rh or Ru catalysts (Table 15). The Rh catalysts combined with chiral phosphorus ligands, such as BPPFOH,[24b] MCCPM,[41f−k] Cy,Cy-oxoProNOP,[135c,e] Cp,Cp-oxoProNOP,[135c,e] and IndoNOP,[135g] have provided excellent enantioselectivities and reactivities in hydrogenation of some α, β, or γ-alkyl

Scheme 24

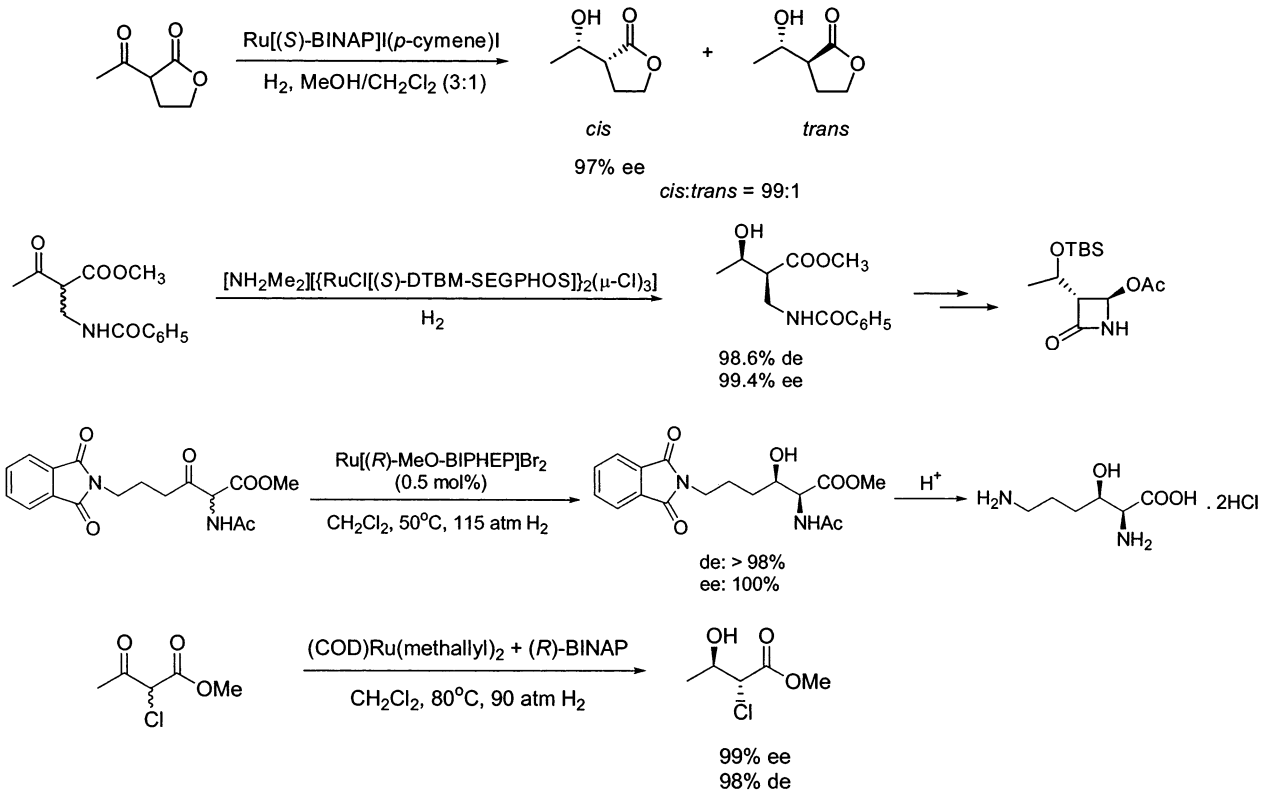
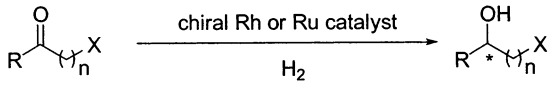
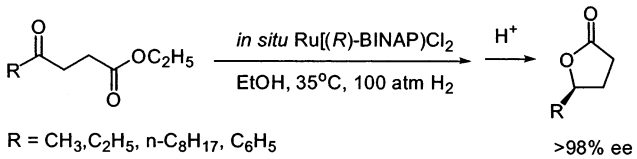


Table 15.



catalyst	R	*n*	X	S/C ratio	reaction conditions	% ee of product (confign)	ref
(*R*)-(*S*)-BPPFOH-Rh	(3,4)-$(OH)_2$Ph	1	NHMe.HCl	100	NEt_3, MeOH, rt, 50 atm H_2	95 (*R*)	24b
(2*S*,4*S*)-MCCPM-Rh	Ph	1	NEt_2·HCl	100000	NEt_3, MeOH, 50 °C, 20 atm H_2	96 (*S*)	232
(*S*)-Cp,Cp-oxoProNOP-Rh	Ph	1	NMe_2·HCl	200	MeOH, 20 °C, 50 atm H_2	96 (*S*)	135e
(*S*)-Cp,Cp-oxoProNOP-Rh	Me	1	NMe_2·HCl	200	MeOH, 20 °C, 50 atm H_2	97 (*S*)	135e
(*S*)-Cp,Cp-IndoNOP-Rh	Ph	1	NMe_2·HCl	200	toluene, 20 °C, 50 atm H_2	99 (*S*)	135g
(*S*)-Cy,Cy-oxoProNOP-Rh	Ph	2	NMe_2·HCl	200	toluene, 20 °C, 20 atm H_2	93 (*R*)	135g
(2*S*,4*S*)-MCCPM-Rh	Ph	2	N(Me)Bn·HCl	1000	MeOH, 50 °C, 30 atm H_2	91 (*R*)	41g
(*S*)-Cy,Cy-oxoProNOP-Rh	Ph	3	NMe_2·HCl	200	toluene, 80 °C, 50 atm H_2	92 (*R*)	135g
[Ru-(*S*)-BINAP]Br_2	Ph	1	NMe_2	490	MeOH, 20−32 °C, 100 atm H_2	95 (*S*)	31b
RuI[(*S*)-BINAP)] (p-cymene)I	Me	1	NMe_2	1100	CH_2Cl_2/MeOH, 30 °C, 105 atm H_2	99.4 (*S*)	217
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*)-daipen]	Me	1	NMe_2	2000	^{t}BuOK, ^{i}PrOH, 25°C, 8 atm H_2	92 (*S*)	233
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*)-daipen]	Ph	1	NMe_2	2000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	93 (*R*)	233
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*)-daipen]	Ph	1	N(Ac)Me	2000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	99 (*R*)	233
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*)-daipen]	Ph	1	N(Boc)Me	2000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	99 (*R*)	233
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*)-daipen]	Ph	2	NMe_2	10000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	97.5 (*R*)	233

Scheme 25



amino ketone hydrochloride salts. For example, hydrogenation of 2-diethylaminoacetophenone catalyzed by a MCCPM-Rh complex at 50 °C under 20 atm hydrogen pressure afforded the chiral amino alcohol product in 96% ee with a S/C ratio of 100 000.[232] A BINAP-Ru catalyst has also shown excellent enantioselectivity in hydrogenation of α-dimethylamino ketones under high hydrogen pressure.[31b,217] The *trans*-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen] complex has been proven to be very efficient for hydrogenation of a wide range of α, β, or γ-amino ketones,[233] with

Scheme 26

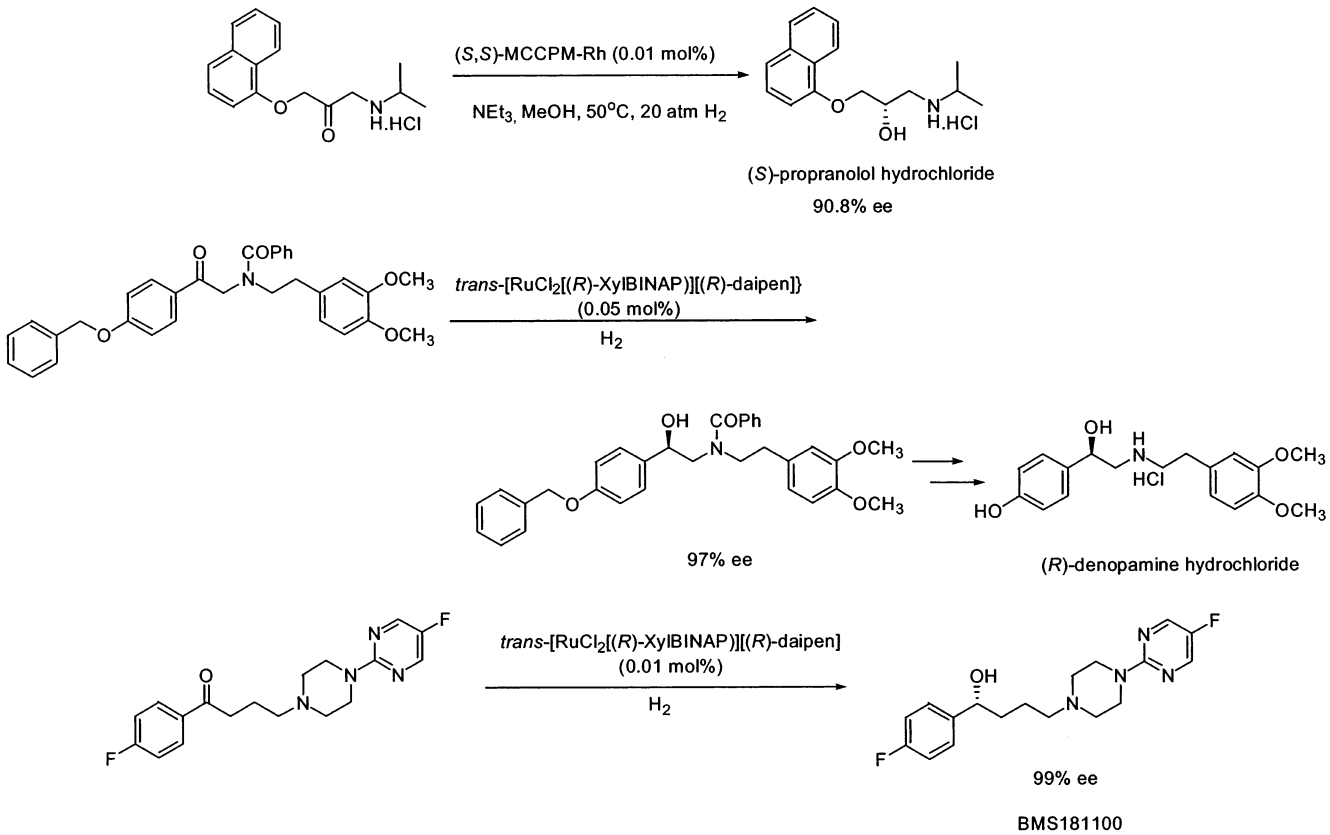
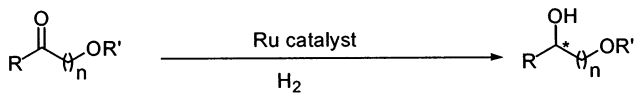


Table 16.



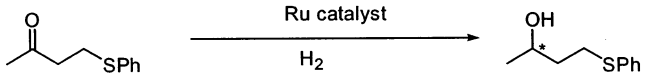
catalyst	R	*n*	R′	S/C ratio	reaction condition	% ee of product (confign)	ref
$RuCl_2$[(*R*)-BINAP]	Me	1	H	230	MeOH, 20−32 °C, 93 atm H_2	92 (*R*)	31b
$[NH_2Me_2][\{RuCl[(R)\text{-SEGPHOS}]\}_2(\mu\text{-}Cl)_3]$	Me	1	H	10000	MeOH, 65 °C, 30 atm H_2	98.5 (*R*)	52b
$RuCl_2$[(*R*)-BINAP]	Me	2	H	900	EtOH, 20−32 °C, 70 atm H_2	98 (*R*)	31b
trans-Ru[(*R*)-XylBINAP][(*R*)-daipen]	Me	1	Ph	2000	^{t}BuOK, ^{i}PrOH, 25−28 °C, 8 atm H_2	80 (*S*)	3j
trans-Ru[(*R*)-XylBINAP][(*R*)-daipen]	Ph	1	Me	2000	^{t}BuOK, ^{i}PrOH, 25−28 °C, 8 atm H_2	95 (*R*)	3j

which high enantioselectivities and turnover numbers are achieved under mild conditions.

Many excellent examples of hydrogenation of amino ketones have been applied in the synthesis of chiral drugs (Scheme 26). For example, enantioselective hydrogenation of 3-aryloxy-2-oxo-1-propylamine derivatives can directly lead to 1-amino-3-aryloxy-2-propanol derivatives as chiral β-adrenergic blocking agents. This has been successfully accomplished with a neutral MCCPM-Rh complex as the catalyst. With 0.01 mol % of a (*S*,*S*)-MCCPM-Rh complex, (*S*)-propranolol is obtained in 90.8% ee from the corresponding α-amino ketone substrate.[41f] The *trans*-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen] complex has been applied as a catalyst in enantioselective synthesis of (*R*)-denopamine, a β_1-receptor agonist used for treatment of congestive heart failure.[233] A γ-functionalized amino ketone is also hydrogenated efficiently in 99% ee to provide BMS181100, a potent antipsychotic agent.[233]

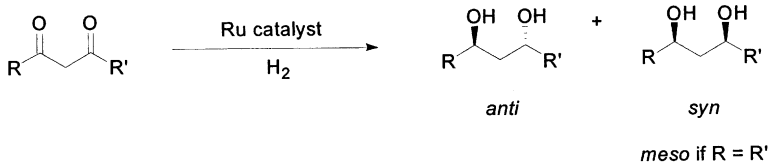
3.2.1.5. Hydroxyl Ketones, Alkoxy Ketones, Phenylthio Ketones, and *ortho*-Haloaryl Ketones. Enantioselective hydrogenation of α- or β-hydroxyl ketones (Table 16) has been realized by a BINAP-Ru catalyst.[31b] A SEGPHOS-Ru complex has also been demonstrated as a superior catalyst for asymmetric hydrogenation of α-hydroxyl ketones.[52b] The chiral diol can be obtained in 98% ee with a substrate-to-catalyst ratio of 10 000. α-Alkoxy ketones can also be reduced in high enantioselectivity with a Ru-XylBINAP/daipen complex as the catalyst.[3j] Although the alkoxy group of the substrates do not participate in coordination with the Ru catalyst, they possess a significant stereo-directing ability in achieving high enantioselectivity. For example, the methoxy acetophenone is hydrogenated with a Ru-(*R*)-XylBINAP/(*R*)-daipen complex to provide the corresponding (*R*)-diol in 95% ee. Hydrogenation of an α,α′-dialkoxy ketones is catalyzed by the Ru-BINAP system to give chiral 1-*o*-octadecyl-3-*o*-trityl glycerol in over 96%

Table 17.



catalyst	S/C ratio	reaction conditions	% ee of product (confign)	ref
Ru[(*S*)-MeO-BIPHEP]Br_2	50	MeOH, rt, 30 atm H_2	98 (*S*)	237
Ru[(*S*)- BINAP]Br_2	50	MeOH, rt, 30 atm H_2	96 (*S*)	237
Ru[(*S*,*S*)-BDPP]Br_2	100	MeOH, rt, 30 atm H_2	94 (*S*)	238
Ru[(*S*,*S*)-^{i}Pr-CnrPhos]Br_2	100	MeOH, 80 °C, 80 atm H_2	97 (*S*)	76d

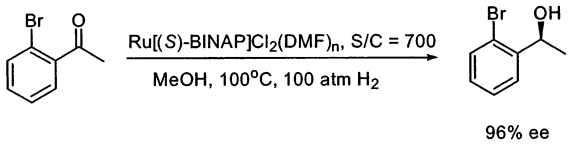
Table 18.



ligand	R	R′	S/C ratio	reaction conditions	% de (anti vs syn)	% ee of the anti product (confign)	ref
(*R*)-BINAP	Me	Me	2000	MeOH, rt, 72 atm H_2	98	100 (*R*,*R*)	31b
(*R*)-BIPHEMP	Me	Me	2000	EtOH, 50 °C, 100 atm H_2	98	>99.9 (*R*,*R*)	241
(*S*,*S*)-BDPP	Me	Me	1700	MeOH, 80 °C, 80 atm H_2	50	97 (*S*,*S*)	239
(*S*,*S*)-^{i}Pr-CnrPhos	Me	Me	50	MeOH, 80 °C, 70 atm H_2	>95	98 (*R*,*R*)	76d
(*S*,*S*)-Cy-BPE-4	Me	Me	100	MeOH, 80 °C, 80 atm H_2	95	98 (*R*,*R*)	76f
34	Me	Me	1000	MeOH, 80 °C, 100 atm H_2	>98	97 (*R*,*R*)	98
(*S*,*S*)-^{i}Pr-CnrPhos	^{i}Pr	^{i}Pr	50	MeOH, 80 °C, 70 atm H_2	>95	98 (*S*,*S*)	76d
29	Ph	Ph	200	EtOH, 50 °C, 50 atm H_2	98	98.2 (*S*,*S*)	96a
33	Ph	Ph	200	EtOH, 50 °C, 50 atm H_2	>99	>99 (*R*,*R*)	97
(*R*)-BINAP	$ClCH_2$	$ClCH_2$	314	MeOH, 102 °C, 85 atm H_2	–	92–94 (*R*,*R*)	240b
(*S*)-BINAP	Ph	Me	–	MeOH, rt, 72 atm H_2	88	94 (*R*,*R*)	31b
29	Ph	Me	200	EtOH, 50 °C, 50 atm H_2	97.2	98.2 (*S*,*S*)	96a

ee.[234] A halogen atom at an appropriate position in the substrate can also exert great directing influence through interaction with Ru.[31b,221a] Hydrogenation of *ortho*-halo aryl ketones can be catalyzed by the Ru-BINAP system with excellent ee's. For example, *ortho*-bromo acetophenone can be converted into the corresponding chiral alcohol in 96% ee (Scheme 27).

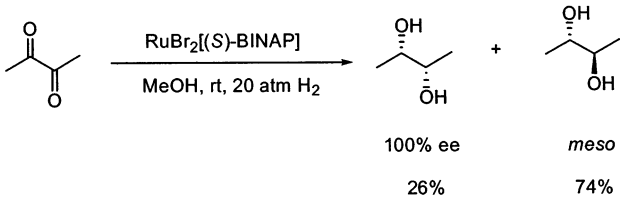
Scheme 27



However, this type of substrates can be hydrogenated more effectively with the Ru/chiral phosphine/diamine system.[236] Asymmetric hydrogenation of phenylthioketones has been realized with several Ru catalysts. BINAP,[31b] MeO-BIPHEP,[237] BDPP,[238] and Me-CnrPHOS[76d] are efficient ligands for this transformation (Table 17).

3.2.1.6. Diketones. Several chiral Ru complexes have been applied successfully for asymmetric hydrogenation of α, *β*, and *γ*-diketones. Hydrogenation of an α-diketone, 2, 3-butandione, catalyzed by a (*R*)-BINAP-Ru complex affords the optically pure (*R*,*R*)-2,3-butanediol and the meso diol in a ratio of 26:74 (Scheme 28).[31b]

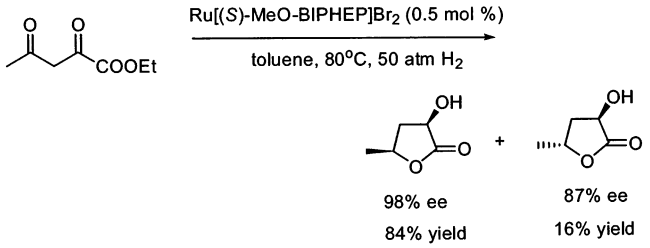
Scheme 28



Asymmetric hydrogenation of *β*-diketones prefers to provide anti 1,3-diols (Table 18). When symmetric *β*-diketones are subjected for hydrogenation, the chiral 1,3-diols will be formed dominantly over the meso diols. Hydrogenation of 2,4-pentadione catalyzed by an (*R*)-BINAP-Ru catalyst gives enantiomerically pure (*R*,*R*)-2,4-pentadiol in 99% yield along with 1% of meso compound.[31b] BIPHEMP,[241] BDPP,[239] ^{i}Pr-CnrPhos,[76d] Cy-BPE-4,[76f] and WalPhos **34**[98] are also very effective ligands for this transformation. Various symmetric or asymmetric *β*-diketones have been hydrogenated with chiral Ru complexes associated with BINAP,[31b,240] MeO-BIPHEP,[242] TaniaPhos **29**[96a] and **33**,[97] and ^{i}Pr-CnrPhos[76d] to give chiral anti diol products in excellent enantioselectivities and diastereoselectivities. The methodology has been used for synthesis of important chiral intermediates and natural products. For example, ethyl 2,4-dioxovalerate is hydrogenated with an (*S*)-MeO-BIPHEP-Ru catalyst to give the syn product (2*R*,4*S*)-α-hydroxyl-*γ*-butyrolactone in 98% ee and in 84% yield, along

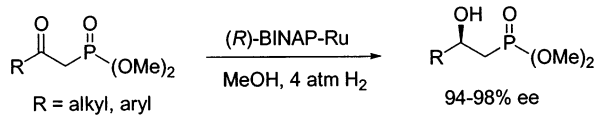
with the anti (2*R*,4*R*)-isomer in 87% ee and in 16% yield (Scheme 29).[242]

Scheme 29



3.2.1.7. Keto Phosphonates. A series of β-keto phosphonates have been hydrogenated with the Ru-BINAP system to give various chiral β-hydroxyl phosphonates (Scheme 30).[243] A Ru-MeO-BIPHEP

Scheme 30



catalyst is also effective for this transformation.[244] β-Keto thiophosphonates can also be smoothly transformed into β-hydroxyl thiophosphonates in high ee's.[244]

An efficient dynamic kinetic resolution is observed when an α-Br or α-acetylamino β-keto phosphate is subjected for hydrogenation with a Ru-BINAP catalyst under suitable conditions. With $RuCl_2$[(*S*)-BINAP](DMF)$_n$ (0.18 mM) as the catalyst, a racemic α-bromo-β-keto phosphonate is hydrogenated at 25 °C under 4 atm H_2 pressure to give the syn product (1*R*,2*S*)-α-Br-β-hydroxy phosphonate in 98% ee (Scheme 31). The syn product after acid-catalyzed hydrolysis followed by base treatment provides fosfomycin, an antibiotic reagent.[243] Hydrogenation of an α-acetylamino-β-keto phosphonate under similar conditions provides a syn (1*R*,2*R*) product in 98% ee and an anti (1*S*,2*R*) product in >90% ee with a ratio of 97:3.[245]

3.2.2. Hydrogenation of Unfunctionalized Ketones

Asymmetric hydrogenation of unfunctionalized ketones is a more challenging task than hydrogenation of functionalized ketones.[246,3j] Due to lack of secondary coordination to the metal, most chiral Rh or Ru catalysts which are quite effective for functionalized ketones usually cannot provide high enantioselectivity and reactivity for hydrogenation of unfunctionalized ketones. Nevertheless, asymmetric hydrogenation of unfunctionalized ketones has developed rapidly in the past few years due to the discovery of several efficient catalytic systems. Two notable catalytic systems are the *trans*-[$RuCl_2$(diphosphane)(1,2-diamine)] catalyst developed by Noyori[32] and the Rh-PennPhos system reported by Zhang.[79] PennPhos is an electron-donating diphosphane with a bulky, rigid, and well-defined chiral backbone. Its Rh complex (combined with additives: 2,6-lutidine and KBr) has allowed efficient hydrogenation of simple aromatic and aliphatic ketones. The *trans*-[$RuCl_2$(bisphosphine)-(1,2-diamine)] catalyst is an efficient catalyst for hydrogenation of a variety of simple aryl ketones. With this catalyst, heteroaryl ketones can also be hydrogenated efficiently with high substrate-to-catalyst ratio. The high specificity of the catalyst for hydrogenation of ketones has allowed unsaturated ketones to be reduced into chiral alcohols, leaving olefin functionalities intact. Functionalized olefins such as alkoxy and amino ketones can also be hydrogenated in great enantioselectivity, which has been discussed before.[233,3j]

3.2.2.1 Aromatic Ketones. Enantioselective hydrogenation of simple aromatic ketones has been studied with some chiral Rh, Ir, and Ru catalysts (Table 19). The DIOP-Rh[247] and the DBPP-Rh[248] complexes with a tertiary amine have been used in catalyzing hydrogenation of acetophenone. and moderate ee's (80% and 87% respectively) have been achieved. A Me-PennPhos-Rh complex has been applied for hydrogenation of a set of aromatic ketones, and enantioselctivities as high as 96% have been achieved.[79] The additives 2,6-lutidine and KBr are very important for achieving the high selectivity although the mechanism has not been fully understood. A BINAP-Ir(I)-aminophosphine system has been found to be effective for hydrogenation of some cyclic aromatic ketones.[249] A series of substituted 1-tetralones, 1-indanones, or heteroatom contained cyclic ketones have been reduced and up to 96% ee has been achieved. The *trans*-[$RuCl_2$(bisphosphine)-(1,2-diamine)] catalyst, combined with ^{t}BuOK as the base and 2-propanol as the solvent, is a very effective catalytic system for hydrogenation of a diverse range of simple aromatic ketones.[250,251] Chiral BINAP, TolBINAP, or XylBINAP with a chiral diamine such as dpen or daipen is a good combination for the system. With *trans*-[$RuCl_2$(*S*)-Xyl-BINAP][(*S*)-daipen] as the metal complex, ^{t}BuOK as the base, and ^{i}PrOH as the solvent, various substituted acetophenones and acetylnaphthalenes are reduced quantitatively with high enantioselectivity and turnover numbers. Chiral BICP,[83f] Xylyl-PHANEPHOS,[122c] and Xyl-P-Phos[252] combined with chiral diamine ligands are also effective for this system. A variety of ortho-substituted benzophenone derivatives can also be hydrogenated in excellent enantioselectivity by using the *trans*-[$RuCl_2$(*S*)-Xyl-BINAP][(*S*)-daipen] complex as the catalyst.[236] Noyori has also reported the synthesis of *trans*-RuH(η^1-BH_4)(BINAP)(1,2-diamine) by reducing *trans*-[$RuCl_2$(*R*)-TolBINAP][(*R*,*R*)-dpen] with $NaBH_4$.[253] This complex can directly catalyze the

Scheme 31

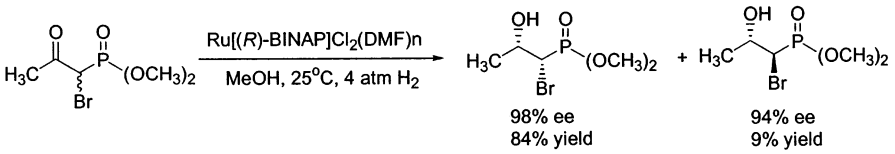
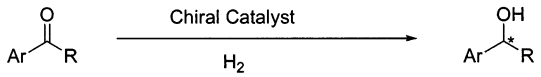


Table 19.



catalyst	Ar	R	S/C ratio	reaction conditions	% yield	% ee of product (confign)	ref
$[RhCl(nbd)]_2$-(*S*,*S*)-DIOP+NEt_3	Ph	Me	200	MeOH, 50°C, 69 atm H_2, 6 h	64	80	247
$[RhCl(nbd)]_2$-(*S*,*S*)-BDPP+NEt_3	Ph	Me	100	MeOH, 50°C, 69 atm H_2, 24 h	72	82 (*S*)	248
$[RhCl(cod)]_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos+2,6-lutidine	Ph	Me	100	MeOH, rt, 30 atm H_2, 24 h	97	95 (*S*)	79
[Ir{(*S*)-BINAP}(cod)]BF_4+ PPh(2-NMe_2Ph)	Ph	Me	100	Dioxane-MeOH (5:1), 54−61 atm H_2, 60 °C, 126 h	63	54 (*S*)	255
trans-$RuCl_2$[(*S*)-XylBINAP] [(*S*)-daipen] + ^{t}BuOK	Ph	Me	10000	^{i}PrOH, 28−30 °C, 8 atm H_2, 60 h	97	99 (*R*)	251
trans-RuH(η^1-BH_4)[(*S*)-XylBINAP] [(*S*,*S*)-dpen]	Ph	Me	10000	^{i}PrOH, 45 °C, 8 atm H_2, 7 h	100	99 (*R*)	253
trans-$RuCl_2$[(*R*)-XylylPHANEPHOS] [(*S*,*S*)-dpen]+ ^{t}BuOK	Ph	Me	20,000	^{i}PrOH, 18−20 °C, 8 atm H_2, 1.5 h	100	99 (*R*)	122c
trans-$RuCl_2$[(*R*)-Xyl-P-Phos] [(*R*,*R*)-dpen] + ^{t}BuOK	Ph	Me	100,000	^{i}PrOH, 25−28 °C, 33 atm H_2, 36 h	99.7	99.1 (*S*)	252
$[RhCl(cod)]_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos+2,6-lutidine+KBr	Ph	Et	100	MeOH, rt, 30 atm H_2, 88 h	95	93 (*S*)	79
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*,*R*)-dpen] + ^{t}BuOK	Ph	Et	2000	^{i}PrOH, 26−30 °C, 4 atm H_2, 15 h	100	99 (*S*)	3i
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*,*R*) -dpen] + ^{t}BuOK	Ph	*cyclo*-C_3H_5	2000	^{i}PrOH, 28−30 °C, 8 atm H_2, 14 h	99.7	96 (*R*)	3i
trans-$RuCl_2$[(*S*)-TolBINAP] [(*S*,*S*)-dpen] + ^{t}BuOK	1-Np	Me	100,000	^{i}PrOH, 24−30 °C, 10 atm H_2, 40 h	99.5	98 (*R*)	250
trans-$RuCl_2$[(*S*)-XylBINAP] [(*S*) -daipen] + ^{t}BuOK	Ph	CF_3	11,000	^{i}PrOH, 26−30 °C, 10 atm H_2, 16 h	100	96 (*S*)	251
$RuCl_2$[(*R*,*R*)-BICP](tmeda) + (*R*,*R*)-dpen + KOH	2-thienyl	Me	500	^{i}PrOH, rt, 4 atm H_2, 24 h	100	93 (*S*)	83f
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*) -daipen] + ^{t}BuOK	2-thienyl	Me	5000	^{i}PrOH, 25 °C, 8 atm H_2, 12 h	100	99 (*S*)	254
trans-$RuCl_2$[(*R*)-XylBINAP] [(*R*)-daipen] + ^{t}BuOK + B(O^iPr)$_3$	2-Py	Me	2000	^{i}PrOH, 25 °C, 8 atm H_2, 12 h	100	96 (*S*)	254
trans-$RuCl_2$[(*S*)-XylBINAP] [(*S*) -daipen] + ^{t}BuOK	*o*-Me-Ph	Ph	2000	^{i}PrOH, 28 °C, 8 atm H_2, 14 h	99	93 (*S*)	236
trans-$RuCl_2$[(*S*)-XylBINAP] [(*S*) -daipen] + ^{t}BuOK	*o*-F-Ph	Ph	20,000	^{i}PrOH, 28 °C, 8 atm H_2, 14 h	99	97 (*S*)	236
trans-$RuCl_2$[(*S*)-XylBINAP] [(*S*) -daipen] + ^{t}BuOK	ferrocenyl	Ph	2000	^{i}PrOH, 28 °C, 8 atm H_2, 14 h	100	95 (*S*)	236

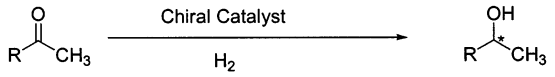
hydrogenation of ketones under base-free conditions. Hydrogenation of a series of heteroaromatic ketones catalyzed by *trans*-[$RuCl_2$(*R*)-Xyl-BINAP][(*R*)-daipen] provides excellent yields and enantioselectivities.[254] A ternary system consisting of $RuCl_2$[(*R*,*R*)-BICP]-(tmeda), (*R*,*R*)-dpen, and KOH hydrogenated an array of 2-acetylthiophene derivatives in up to 93% ee's.[81f]

3.2.2.2. Aliphatic Ketones. Asymmetric hydrogenation of simple aliphatic ketones remains a difficult area since it requires a chiral catalyst to effectively differentiate between two alkyl groups or between methyl and other alkyl groups. The PennPhos-Rh system, combined with 2,6-lutidine and KBr, has given some promising results in asymmetric hydrogenation of aliphatic ketones (Table 20).[79] With this catalytic system, hydrogenation of *tert*-butyl methyl ketone provides the chiral alcohol in 94% ee. Isopropyl methyl ketone and *n*-butyl methyl ketone are also reduced into chiral alcohols in 85% ee and 75% ee, respectively. The cyclohexyl methyl ketone is hydrogenated by the PennPhos-Rh system with a 92% ee. A cyclopropyl methyl ketone can be effectively hydrogenated by the *trans*-$RuCl_2$[(*S*)-Xyl-BINAP][(*S*)-daipen] complex with ^{t}BuOK as the base to give the *R* alcohol in 95% ee.[251] The Ru catalyst also provides a good ee (85%) for hydrogenation of cyclohexyl methyl ketone.

A racemic 2-isopropylcyclohexanone has been hydrogenated with a ternary chiral Ru catalyst consisting of $RuCl_2$[(*S*)-BINAP](DMF)$_n$, (*R*,*R*)-dpen, and KOH. An efficient dynamic kinetic resolution is observed with excellent enantioselectivity and cis-trans ratio (Scheme 32).[256] The cis (1*R*, 2*R*) alcohol is obtained in 93% ee. With the same catalytic system, another good dynamic kinetic resolution is observed in hydrogenation of (−)-menthone.[256] When a base-free catalyst, *trans*-RuH(η^1-BH_4) [(*S*)-XylBINAP][(*R*,*R*)-dpen], is used for hydrogenation of racemic 1-isopropylcyclohexanone, a good kinetic resolution is observed.[253] After 53% conversion, the unreacted (*S*)-ketone is recovered in 91% ee along with the (1*R*,2*R*) alcohol product in 85% ee.

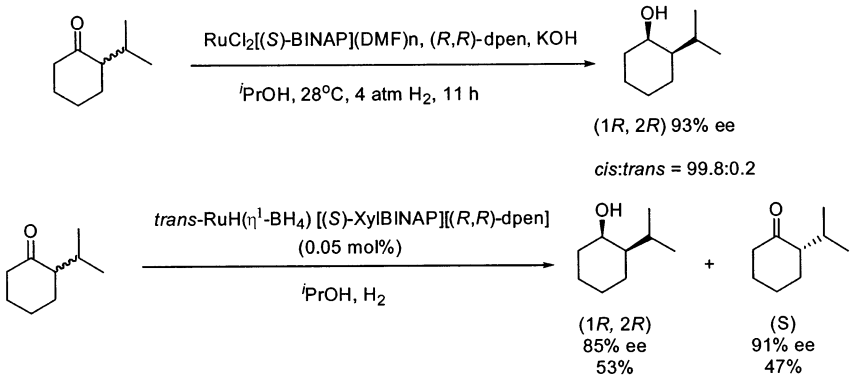
5.2.2.3. Unsaturated Ketones. For a long time, hydrogenation of unsaturated ketones has been considered as a difficult area since most present hydrogenation catalysts prefer to hydrogenate the C=C double bond rather than the C=O bond. The Ir-DIOP[257] and [Ir(BINAP)(COD)]BF_4-aminophosphine systems[258] have shown excellent chemoselectivity for hydrogenation of C=O bonds over C=C bonds, but only moderate ee's have been obtained in

Table 20.

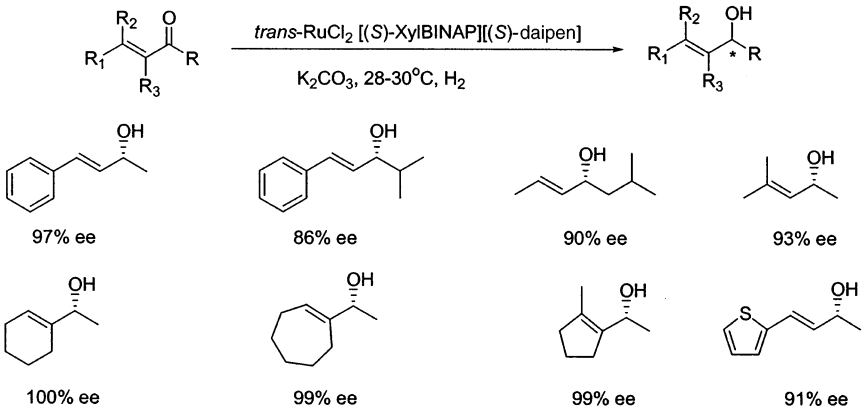


catalyst	R	S/C ratio	reaction conditions	% yield	% ee of product (confign)	ref
[RhCl(cod)]$_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos+ 2,6-lutidine + KBr	^{n}Bu	100	MeOH, rt, 30 atm H_2, 48 h	96	75 (*S*)	79
[RhCl(cod)]$_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos+ 2,6-lutidine + KBr	^{i}Bu	100	MeOH, rt, 30 atm H_2, 75 h	66	85 (*S*)	79
[RhCl(cod)]$_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos+ 2,6-lutidine + KBr	^{i}Pr	100	MeOH, rt, 30 atm H_2, 94 h	99	84 (*S*)	79
[RhCl(cod)]$_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos+ 2,6-lutidine + KBr	*cyclo*-hexyl	100	MeOH, rt, 30 atm H_2, 106 h	90	92 (*S*)	79
[RhCl(cod)]$_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos+ 2,6-lutidine + KBr	^{t}Bu	100	MeOH, rt, 30 atm H_2, 96 h	51	94 (*S*)	79
trans-RuCl$_2$[(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	*cyclo*-hexyl	11000	^{i}PrOH, 28 °C, 8 atm H_2, 20 h	99	85 (*R*)	251
trans-RuCl$_2$[(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	*cyclo*-C_3H_5	11000	^{i}PrOH, 28 °C, 8 atm H_2, 12 h	96	95 (*R*)	251

Scheme 32

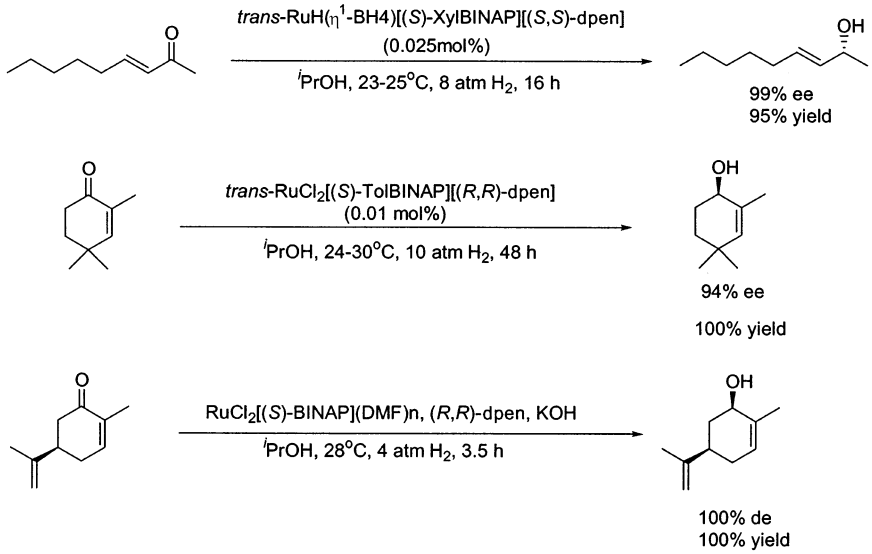


Scheme 33



hydrogenation of 4-phenyl-3-buten-2-one or cyclic enones. The situation has changed dramatically after Noyori developed the *trans*-RuCl$_2$(BINAP)(1,2-diamine) catalyst for hydrogenation of ketones. The *trans*-RuCl$_2$[(*S*)-XylBINAP][(*S*)-daipen] complex with K_2CO_3 as a base can efficiently hydrogenate a diverse array of α,*β*-unsaturated ketones with excellent chemoselectivity and enantioselectivity (Scheme 33).[251] The highly base-sensitive substrate 3-nonen-2-one can also be hydrogenated to give the (*R*)-allylic alcohol product in 99% ee and in 95% yield by using a base-free catalyst *trans*-RuH(η^1-BH$_4$)[(*S*)-XylBINAP][(*S*,*S*)-dpen] (Scheme 34).[253] *Trans*-RuCl$_2$ [(*S*)-XylylPHANEPHOS][(*R*,*R*)-dpen] with ^{t}BuOK is also effective for the transformation.[122c] Certain cyclic enones can also be hydrogenated with high enantioselectivity.[259] For example, hydrogenation of 2,4,4-trimethyl-2-cyclohexenone using *trans*-RuCl$_2$[(*S*)-TolBINAP][(*R*,*R*)-dpen] and ^{t}BuOK as the catalytic system gives (*R*)-2,4,4-trimethyl-2-cyclohexenol in 94% ee and 100% yield. Interestingly, unlike the case of hydrogenation of aryl ketones and acyclic α,*β*-unsaturated ketones where Ru-(*R*)-BINAP-(*R*)-diamine or Ru-(*S*)-BINAP-(*S*)-diamine provides best enantioselectivity, hydrogenation of this cyclic hexenone requires ligand combination of (*R*)-BINAP-(*S*)-

Scheme 34



diamine or (*S*)-BINAP-(*R*)-diamine. The presence of the methyl group at the C-2 position is crucial for achieving high enantioselectivity since only moderate ee's are obtained for hydrogenation of 2-cyclohexen-1-one and 4,4-dimethyl-2-cyclohexen-1-one. By using the combination of $RuCl_2$[(*S*)-BINAP](DMF)$_n$, (*R*,*R*)-DPEN, and KOH as the catalytic system, (*R*)-carvone is hydrogenated into a cis product, (*R*,*R*)-carveol, in 100% yield with perfect diastereoselectivity, while the two C=C double bonds in the structure are intact. Under the same reaction conditions, the racemic carvone is also resolved kinetically with a K_R/K_S ratio of 33:1. Asymmetric hydrogenation of α, β-acetylenic ketones to chiral propargylic alcohols is still unavailable.

3.3. Asymmetric Hydrogenation of Imines

Although excellent results have been achieved in the enantioselective hydrogenation of prochiral alkenes and ketones, relatively limited progress has been made in the asymmetric hydrogenation of prochiral imines.[260] A number of efficient asymmetric catalysts for reduction of alkenes and ketones are unfortunately ineffective for the hydrogenation of related imine compounds. Currently, only a few efficient chiral catalytic systems are available for hydrogenation of imines. The recent development of chiral Ir complexes with chiral phosphanes,[3m] *trans*-[$RuCl_2$(bisphosphine)(1,2-diamine)] complexes,[261,262] chiral titanocene,[18] and zirconocene catalysts[263] provides great promise in this area. Some success has also been achieved in asymmetric hydrogenation of functionalized C=N double bonds, such as *N*-acyl hydrozones, sulfonimides, and *N*-diphenylphosphinyl ketimines.

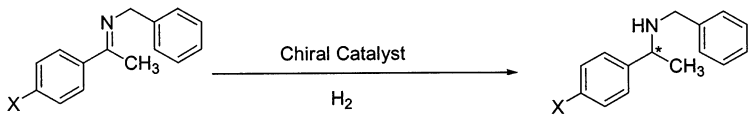
3.3.1. Acyclic N-Alkylimines

Although several chiral Rh, Ir, Ti, and Zr catalysts have been applied for asymmetric hydrogenation of acyclic *N*-alkylimines, only limited success has been achieved for this transformation. Except a chiral titanocene catalyst which has shown moderate to good enantioselectivities for a variety of acyclic *N*-alkylimines,[18] most chiral Rh and Ir catalysts provide limited substrate scope such as acetophenone *N*-benzylimine and its derivatives; the employed substrates are generally mixtures of *E* and *Z* isomers. Some successful examples have been listed in Table 21. With a halide additive KI, a neutral CycPhos-Rh complex has shown moderate to good enantioselectivities (up to 91% ee) in hydrogenation of acetophenone *N*-benzylimine and its derivatives.[264] BDPP is also an effective ligand for this transformation: up to 83% ee is observed when acetophenone *N*-benzylimine is reduced by a neutral (*S*,*S*)-BDDP-Rh complex at 0°C, although a low conversion is observed.[248b] A catalytic system consisting of a cationic (*S*,*S*)-BDPP complex, reversed micelles aggregated of sodium bis(2-ethylhexyl)sulfosuccinate (AOT), and 15-crown-5 provides a better ee (89% ee).[265] The best enantioselectivity (94% ee) for hydrogenation of acetophenone *N*-benzylimine is obtained with a neutral mono-sulfonated (*S*,*S*)-BDPP-Rh complex in a mixed solvent (EtOAc/H_2O).[266] The *para*-chloro and *para*-methoxy substituted derivatives also provide over 90% ee's. Interestingly, di-, tri-, and tetra-sulfonated (*S*,*S*)-BDPP ligands are much less enantioselective for this transformation.[267] Some chiral Ir systems such as [Ir(COD)Cl]/(*S*)-TolBINAP/$BnNH_2$[268] and Ir-PhOx[269] complexes also provide moderate ee's for the asymmetric hydrogenation of acetophenone *N*-benzylimine.

3.3.2. Acyclic Aromatic Imines

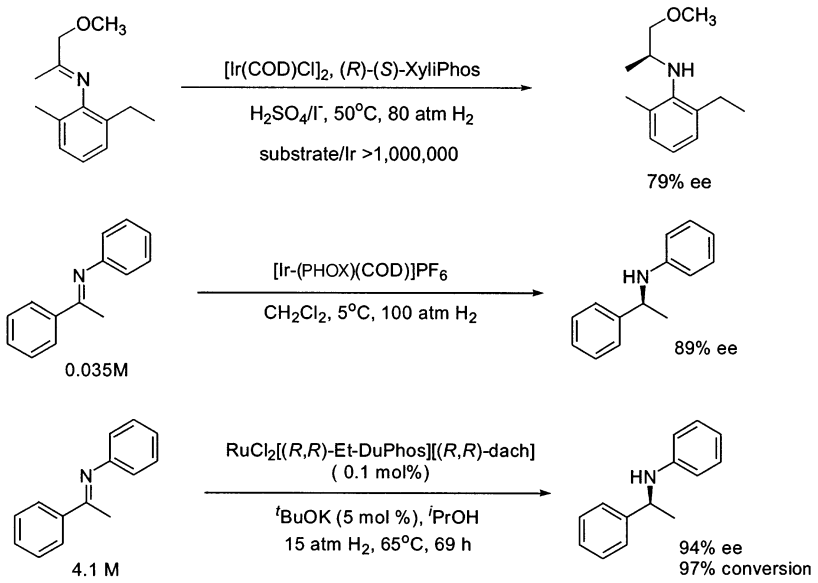
Much advance has been achieved in hydrogenation of acyclic aromatic imines. A notable example is the successful manufacture of (*S*)-metolachlor via asymmetric hydrogenation of an *N*-aryl ketimine (Scheme 35).[92] The hydrogenation is efficiently conducted with [Ir(COD)Cl]$_2$ and (*R*)-(*S*)-Xyliphos as the catalytic system in the presence of some acid and iodide. Under a hydrogen pressure of 80 atm at 50 °C with a substrate-to-catalyst ratio of >1 million, the hydrogenation is complete within 4 h with 79% ee

Table 21.



catalyst	X	S/C ratio	additive	reaction conditions	yield	% ee of product (confign)	ref
$[Rh(NBD)Cl]_2$+ (*R*)-CycPhos	H	100	KI	benzene/MeOH (1:1), 20 °C, 67 atm H_2, 90 h	>99	79 (*S*)	264
$[Rh(NBD)Cl]_2$+ (*R*)-Cycphos	OMe	100	KI	benzene/MeOH (1:1), −25 °C, 67 atm H_2, 144 h	>99	91 (*S*)	264
$[Rh(COD)Cl]_2$+ (*S*,*S*)-BDPP	H	100	$N(Et)_3$	MeOH, 0 °C, 70 atm H_2, 6 h	55	83 (*R*)	248b
$[Rh(COD)Cl]_2$+ (*S*,*S*)-BDPP	H	100		MeOH, 20 °C, 70 atm H_2, 6 h	96	84 (*R*)	266
$[Rh(COD)Cl]_2$+ monosulfonated (*S*,*S*)-BDPP	H	100		EtOAc/H_2O, 20 °C, 70 atm H_2	>98	94 (*R*)	266
$[Rh(COD)Cl]_2$+ monosulfonated (*S*,*S*)-BDPP	OMe	100		EtOAc/H_2O, 20°C, 70 atm H_2	>98	92 (*R*)	266
$[Rh(COD)Cl]_2$+ monosulfonated (*S*,*S*)-BDPP	Cl	100		EtOAc/H_2O, 20°C, 70 atm H_2	>98	92 (*R*)	266
[Rh(*S*,*S*)-BDPP(NBD)]ClO_4	H	100	15-crown-5	AOT/benzene, 8 °C, 70 atm H_2, 73 h	98	89 (*R*)	265
[Rh(*S*,*S*)-BDPP(NBD)]ClO_4	OMe	100		AOT/benzene, 4 °C, 70 atm H_2, 21 h	96	92 (*R*)	265
$[Ir(COD)Cl]_2$+ (*S*)-TolBINAP	H	100	$BnNH_2$	MeOH, 20 °C, 60 atm H_2, 18 h	100	70 (*R*)	268
[Ir(*S*)-PHOX(NBD)]PF_6	H	100		CH_2Cl_2, 23 °C, 100 atm H_2	100	76 (*R*)	269

Scheme 35



and an initial tof of 1.8 million h^{-1}. The enantiomeric purity of amine product, although only moderate, is enough for application as an herbicide. Some other chiral Ir complexes combined with (*S*,*S*)-BDPP or (*S*,*S*)-DIOP have shown up to 90% ee on hydrogenation of 1-methoxypropanone-(2,6-dimethyl)-anilineimine.[270,272b]

High enantioselectivities have been recently obtained in hydrogenation of acetophenone *N*-aryl imine derivatives. Up to 89% ee was achieved in hydrogenation of acetophenone aniline imine with a cationic PHOX-Ir complex as the catalyst.[269a] The low concentrations of substrate and catalyst are important for achieving the high enantioselectivity; a substrate-to-catalyst ratio as high as 1000 can be employed. Supercritical carbon dioxide can also be used as the solvent instead of CH_2Cl_2, although a slightly lower selectivity is observed.[269b] A *trans*-[$RuCl_2$(bisphosphine)(1,2-diamine)] complex with Et-DuPhos and dach as the ligand combination is also very effective.[261] Up to 94% ee has been obtained in hydrogenation of acetophenone aniline imine under basic conditions.[261a] A neutral Ir-f-binaphane complex[105] provided excellent enantioselectivity in hydrogenation of a series of acetophenone N-aryl imine derivatives at −5 °C under 1000 psi H_2 pressure with I_2 as the additive (Table 22). The acetophenone aniline imine is hydrogenated to the corresponding amine in 95% ee; over 99% ee is achieved on hydrogenation of acetonephenone 2,6-dimethyl aniline imine, although a lower conversion is observed. When acetophenone (2′-Me-6′-MeO-)aniline imine is subject to hydrogenation, the corresponding chiral amine product after treatment with cerium ammonium nitrate provides chiral phenyl ethylamine in 98% ee (Scheme 36). The additive I_2 is beneficial to the enantioselectivity for hydrogenation of *N*-phenyl or *N*-4′-methoxy phenyl imines but detrimental for

Scheme 36

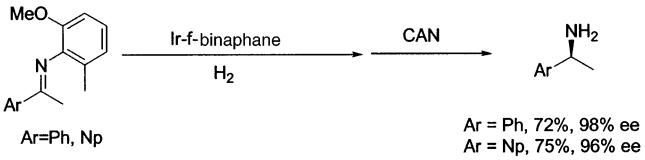
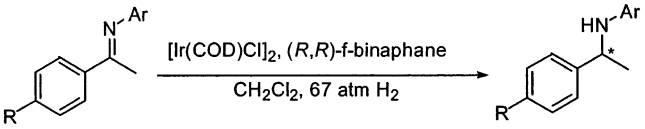


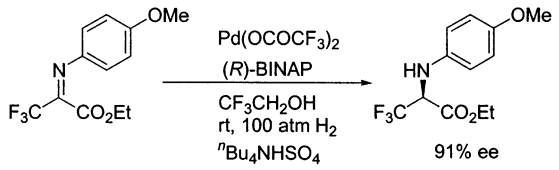
Table 22.



R	Ar	S/C ratio	reaction conditions	conv. (%)	ee %
H	Ph	100	I_2, −5 °C, 40 h	100	94
MeO	Ph	100	I_2, −5 °C, 24 h	100	95
H	2,6-Me_2Ph	100	rt, 44 h	77	>99
MeO	2,6-Me_2Ph	100	rt, 44 h	77	98
CF_3	2,6-Me_2Ph	100	rt, 44 h	88	99

N-2′,6′-dimethylphenyl imines. A BINAP-Pd complex has been successfully applied in hydrogenation of a series of fluorinated α-iminoesters and enantioselectivities up to 91% ee have been obtained.[271] The hydrogenation solvent 2,2,2-trifluoroethanol is important for achieving high reactivities and enantioselectivities (Scheme 37).

Scheme 37



3.3.3. Cyclic Imines

The most efficient catalytic system to date for hydrogenation of cyclic imines is a chiral titanocene catalyst developed by Buchwald.[18] This non-phosphorus-containing catalyst has shown excellent enantioselectivity for a diverse array of cyclic imines, albeit with relatively high catalyst loading. Several Ir complexes associated with chiral phosphorus ligands such as DIOP, MOD-DIOP, BCPM, BINAP, BICP, and BDPP have shown good to excellent ee's for hydrogenation of several cyclic imines, but they generally have very limited substrate scope. In many cases, the presence of some additives plays an important role in achieving high enantioselectivity.

Hydrogenation of 2,3,3-trimethylindolenine has been studied as a typical reaction (Table 23). An (*S*,*S*)-BDPP Ir(III) hydride complex showed high reactivity for this reaction and the amine product was obtained in 80% ee.[272] In the presence of an additive BiI_3, a neutral (2*S*,4*S*)-BCPM-Ir complex provided the hydrogenation product in 91% ee at −30 °C;[274] without the additive, a much lower ee was obtained. At 0 °C, a neutral BICP-Ir complex with phthalimide as the additive provided 95% ee for this reaction.[273] A *trans*-[$RuCl_2$((*S*)-MeO-BIPHEP)((*S*,*S*)-ANDEN)] complex is also effective. Up to 88% ee has been obtained albeit with a low conversion.[261]

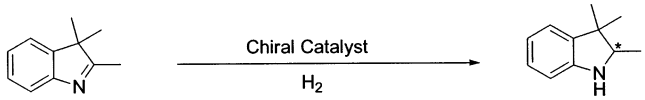
Asymmetric hydrogenation of 3,4-hydroisoquinolines with Ir-chiral phosphorus ligand complexes has also been studied. Although the highest enantioselectivity to date was obtained with a chiral titanocene catalyst,[18] chiral BCPM-Ir or BINAP-Ir complexes with additive phthalimide or F_4-phthalimide have shown some good selectivities. Some examples are listed in Table 24.

A (*S*)-TolBINAP-Ir complex with a protic amine such as benzylamine as the additive has been applied for hydrogenation of 2-phenyl-3,4,5,6-tetrahydropyridine and up to 90% ee is obtained.[268] An orthometalated Ir dihydride complex has been used in hydrogenation of 2-methylquinoxaline, and up to 90% ee has been obtained for the 2-methyl-1,2,3,4-tetrahydroquinoxaline product (Scheme 38).[279]

3.3.4. C=N—X Substrates

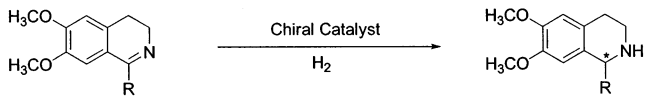
When a heteroatom is directly connected with the nitrogen atom of a C=N double bond, the C=N double bond is generally activated and the hydrogenation may occur at mild conditions. Additionally, the functionality on the heteroatom may create a second coordination with the catalyst. Indeed, some successful results have been achieved on hydrogenation of *N*-acylhydrazone, sulfonimide, and *N*-diphenylphosphinylketimines. An Et-DuPhos-Rh complex is efficient for hydrogenation of a variety of *N*-acylhydrazone compounds.[280] As shown in Table 25, a series of *N*-aroylhydrazones are hydrogenated to form chiral *N*-benzoylhydrazine products in up to 97% ee; the hydrogen pressure as low as 4 atm can be applied. The *N*-benzoylhydrazines derived from α-keto esters are also hydrogenated with excellent enantioselectivity. The α-hydrazino acid products can be easily

Table 23.



catalyst	S/C ratio	reaction conditions	% ee of product (sign)	ref
[Ir((*S*,*S*)-BDPP)HI_2]$_2$	1000	THF/CH_2Cl_2(3:1), 30 °C, 39 atm H_2, 43 h	80 (+)	272
[Ir(COD)Cl]$_2$+(4*R*,5*R*)-MOD-DIOP+Bu_4NI	100	benzene/MeOH(1:1), 20 °C, 100 atm H_2, 48 h	81.4 (+)	275
[Ir(COD)Cl]$_2$+(2*S*,4*S*)-BCPM+BiI_3	100	benzene/MeOH(1:1), −30 °C, 100 atm H_2, 90 h	91 (+)	264
[Ir(COD)Cl]$_2$+(*R*,*R*)-BICP+phthalimide	100	toluene, 0 °C, 67 atm H_2, 100 h	95.1 (+)	273
[$RuCl_2$((*S*)-MeO-BIPHEP)((*S*,*S*)-anden)]	100	^{t}BuOK (1 eq.), ^{i}PrOH, 50 °C, 15 atm H_2, 18 h	88	261a

Table 24.



catalyst	R	S/C ratio	reaction conditions	% ee of product (config)	ref
$[Ir(COD)Cl]_2$+(*S*,*S*)-BCPM+ phthalimide	Me	100	toluene, 2−5 °C, 100 atm H_2, 24 h	85−93 (*S*)	276
$[Ir(COD)Cl]_2$+(*S*)-BINAP+ F_4-phthalimide	CH_2OBn	200	toluene/MeOH, 2−5 °C, 100 atm H_2, 72 h	86 (*S*)	277
$[Ir(COD)Cl]_2$+(*S*)-BINAP+ F_4-phthalimide	$(CH_2)_3OBn$	200	toluene/MeOH, 2−5 °C, 100 atm H_2, 72 h	89 (*S*)	277
$[Ir(COD)Cl]_2$+(*S*,*S*)-BCPM+ F_4-phthalimide	3,4-$(MeO)_2$-$PhCH_2$	100	toluene, 5 °C, 100 atm H_2, 20 h	88 (*S*)	278
$[Ir(COD)Cl]_2$+(*S*,*S*)-BCPM+ phthalimide	3,4-$(MeO)_2$-$PhCH_2CH_2$	100	toluene, 2 °C, 100 atm H_2, 22 h	87 (*S*)	278
$[Ir(COD)Cl]_2$+(*S*)-BINAP+ F_4-phthalimide	3,4-$(MeO)_2$-$PhCH_2CH_2$	100	toluene/MeOH, 2 °C, 100 atm H_2, 40 h	86 (*S*)	278
$[Ir(COD)Cl]_2$+(*S*,*S*)-BCPM+ phthalimide	(*E*)-(3,4)-$(MeO)_2$-PhCH=CH	100	toluene, 2 °C, 100 atm H_2, 24 h	86 (*S*)	278

Scheme 38

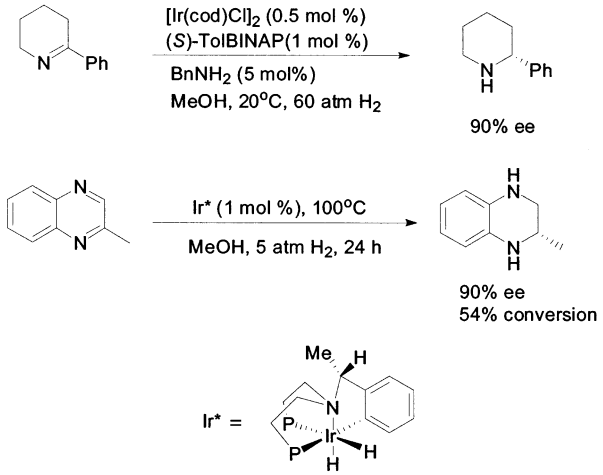
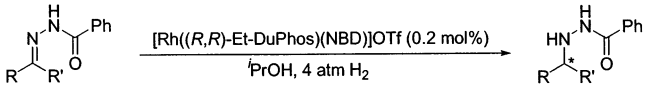


Table 25.

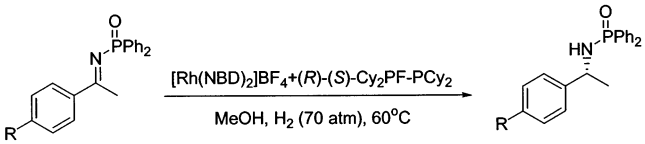


R	R′	temp (°C)	time (h)	% ee of product (config)
Ph	Me	−10	24	95 (*S*)
4-MeOPh	Me	0	24	88 (*S*)
4-EtO_2CPh	Me	0	12	96 (*S*)
4-NO_2Ph	Me	0	12	97 (*S*)
Ph	Et	−10	24	85 (*S*)
2-NP	Me	0	12	95 (*S*)
COOEt	Et	0	24	91 (*S*)
$PO(OEt)_2$	Ph	−10		90

converted into chiral α-amino acids. Other *N*-benzoylhydrazine products can be converted into chiral amines by treatment with samarium diiodide.

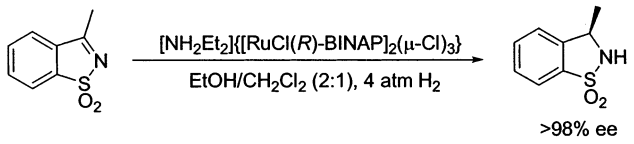
Some success has been achieved in asymmetric hydrogenation of *N*-tosylimines with a Ru-BINAP complex as the catalyst. Moderate to good enantioselectivities have been obtained for several *N*-tosylimines derived from aryl ketones, albeit with low conversions.[281] A BINAP-Ru dimer $[NH_2Et_2]\{[RuCl(R)\text{-BINAP}]_2(\mu\text{-}Cl)_3\}$ is very efficient for hydrogenation of a cyclic sulfonamide (Scheme 39).[282] Under 4 atm of hydrogen pressure, the hydrogenation proceeds completely to give the chiral sultam product in over 98% ee.

Table 26.



R	S/C ratio	time (h)	% ee of product (config)
H	500	1	99 (*R*)
OMe	100	19	62 (*R*)
Me	100	21	97 (*R*)
CF_3	100	18	93 (*R*)
Cl	100	53	30 (*R*)

Scheme 39



Asymmetric hydrogenation of *N*-diphenylphosphinylketimines has been achieved with an (*R*)-(*S*)-Cy_2-PF-PCy_2-Rh complex as the catalyst (Table 26).[283] *N*-Diphenylphosphinyl acetophenone imine is hydrogenated at 60 °C under 70 atm of H_2, yielding chiral product in 99% ee. The reaction temperature is crucial for achieving the high enantioselectivity. The high basicity of the ligand is also responsible for both the reactivity and the enantioselectivity of the transformation. While *para*-Me- and *para*-CF_3-substituted acetophenone derivatives provide 97% ee and 93% ee respectively, the enantioselectivities for *para*-MeO- and *para*-Cl-substituted derivatives are much lower. This dramatic difference has not been explained. The hydrogenation products can be readily transformed into chiral amines via acidic hydrolysis.

4. Concluding Remarks

It is undoubted that the development of chiral phosphorus ligands has made significant impact in asymmetric hydrogenation. Transition metal catalysts with efficient chiral phosphorus ligands have enabled the synthesis of a variety of chiral products from prochiral olefins, ketones, and imines very efficiently, and many practical hydrogenation processes have been exploited in industry for the synthesis of chiral drugs and fine chemicals.

However, many challenges remain in the field of asymmetric hydrogenation. The current hydrogenation methods still cannot reduce numerous prochiral olefins, ketones, and imines in high ee's and with high turnover numbers. To expand the substrate scope of asymmetric hydrogenation as well as enhance the efficiency of known hydrogenation processes remains an urgent and important objective. More effort in searching for new, efficient chiral phosphorus ligands as well as new applications in asymmetric hydrogenation is necessary and the advance in the field should be of great significance in catalytic asymmetric synthesis.

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CRITERIOS PARA LA BÙSQUEDA (anexar pantallazo o reporte en PDF, junto con los boleanos utilizados)	
Palabras clave utilizadas	5-[2-[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]acetyl]-8-hydroxy-1H-quinolin-2-one; 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one; (R)-tol-BINAP RuCl2 DAIPEN; Abediterol; “adrenergic agonist” and ruthenium; ALMIRALL
CLASIFICACIONES INTERNACIONALES UTILIZADAS PARA LA BÚSQUEDA	A61K31/4738, C07D491/22

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EUROPEA	08-04-2014	WO2010102831	1-22	Nivel Inventivo	x	
		WO2008093188	1-22	Nivel inventivo	x	
USPTO	02-02-2015	US8524908	-	-		x

DOCUMENTOS ADICIONALES ENCONTRADOS POR EL EXAMINADOR DE ACUERDO A LOS CRITERIOS DE BÙSQUEDA.

Rev. 2003, 103, 3029−3069. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation.

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1	EP	1957644	**ENZYMATIC ENCODING METHODS FOR EFFICIENT SYNTHESIS OF LARGE LIBRARIES** ...aminoketon.....adrenergi.....agonis.....reductio.....aminoketon...	2006-12-01	nuevolution as	husemoen birgitte nystrup
2	AU	2004200545	**Metering and packaging of controlled release medication** ...aminoketon.....reductio.....adrenergi.....agonis.....reductio...	2004-02-12	microdose technologies inc	gumaste anand v
3	AU	2004305563	**Combination of a sedative and a neurotransmitter modulator, and methods for improving sleep quality and treating depression** ...aminoketon.....adrenergi.....reductio.....agonis.....reductio...	2004-12-08	sepracor inc	thomas wessel
4	EP	1401433	**Azole acid derivatives, alone or in combination, for treating diabetes and dyslipidemias; and for treating malignant diseases** ...aminoketon.....adrenergi.....reductio.....agonis.....aminoketon...	2002-05-23	squibb bristol myers co	wang wei
5	EP	1593667	**AMINE DERIVATIVE** ...aminoketon.....reductio.....adrenergi.....agonis.....reductio...	2004-02-12	takeda pharmaceutical	takekawa shiro
6	WO	2005035526	**BICYCLIC COMPOUNDS AND THEIR THERAPEUTIC USE** ...aminoketon.....adrenergi.....reductio.....agonis.....reductio...	2004-10-11	dyke hazel joan	dyke hazel joan
7	WO	2003055474	**TREATMENT OF FAECAL INCONTINENCE AND OTHER CONDITIONS WITH 1R, 2S-METHOXAMINE** ...aminoketon.....Adrenergi.....Reductio.....agonis.....aminoketon...	2002-12-20	thompson jeffrey martin	thompson jeffrey martin
8	GB	1158775	**Basically Substituted Ethers of Diphenyl and processes for their manufacture** ...adrenergi.....aminoketon.....reductio.....agonis.....aminoketon...	1966-07-12	hoechst ag	
9	GB	2135883	**Anti-inflammatory B2 agonists** ...aminoketon.....reductio.....adrenergi.....agonis.....aminoketon...	1984-03-02	bristol myers co	temple davis l
10	WO	2004052864	**PYRAZOLE AND IMIDAZOLE COMPOUNDS AND USES THEREOF** ...aminoketon.....adrenergi.....reductio.....agonis.....aminoketon...	2003-12-03	dow robert lee	hammond marlys
11	WO	2004072018	**AMINE DERIVATIVE** ...aminoketon.....reductio.....adrenergi.....agonis.....reductio...	2004-02-12	takekawa shiro	takekawa shiro
12	US	7105556	**Conformationally constrained analogs useful as antidiabetic and antiobesity agents and method**	2002-05-22	squibb bristol myers co	wang wei

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5	FT=((((((((((difluoro near phenylethoxy) near hexyl)) near amino)) near hydroxyethyl)) near hydroxyquinolin)) near one))) and PD=19800101:20111007	0	
4	FT=(BINAP and RuCl2 and DAIPEN) and PD=19800101:20111007	44	View | Browse | Hits | Optimise | more...
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Rank	CC	DocNo	Title	Filed	Applicant	Inventor
1	EP	1885684	DERIVATIVES OF 4-(2-AMINO-1-HYDROXYETHYL)PHENOL AS AGONISTS OF THE BETA-2 ADRENERGIC RECEPTOR ...acety.....quinoli.....difluor.....phenylethox.....hexy...	2006-05-17	almirall sa	puig duran carlos
2	EP	2228368	Process for manufacturing 5-(2-{[6-(2,2-difluoro-2-phenylethoxy) hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one	2009-03-12	almirall sa	marchueta hereu iolanda
3	WO	2010102831	PROCESS FOR MANUFACTURING 5-(2-{[6-(2,2-DIFLUORO-2-PHENYIETHOXY) HEXYL]AMINO}-L-HYDROXYETHYL)-8-HYDROXYQUINOLIN-2(1H)-ONE.	2010-03-12	almirall sa	marchueta hereu lolanda
4	EP	2263998	Derivatives of 4-(2-amino-1-hydroxyethyl) phenol as agonists of the beta2 adrenergic receptor	2006-05-17	almirall sa	gual roig silva
5	WO	2006122788	DERIVATIVES OF 4-(2-AMINO-1-HYDROXYETHYL)PHENOL AS AGONISTS OF THE ß2 ADRENERGIC RECEPTOR	2006-05-17	gual roig silvia	castro palomino laria julio ce

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Rank	CC	DocNo	Title	Filed	Applicant	Inventor
1	EP	2228368	Process for manufacturing 5-(2-{[6-(2,2-difluoro-2-phenylethoxy) hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one	2009-03-12	almirall sa	marchueta hereu iolanda
2	WO	2010102831	PROCESS FOR MANUFACTURING 5-(2-{[6-(2,2-DIFLUORO-2-PHENYIETHOXY) HEXYL]AMINO}-L-HYDROXYETHYL)-8-HYDROXYQUINOLIN-2(1H)-ONE.	2010-03-12	almirall sa	marchueta hereu lolanda
3	US	7964615	Derivatives of 4-(2-amino -1-hydroxyethyl)phenol as agonists of the Beta2 adrenergic receptor	2006-05-17	almirall sa	puig duran carlos

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Inventor:	Applicant:	CPC:	IPC:	Publication info:	Priority date:
GEMMA AMAT MESTRES [ES] ELVIRA BALAGUER ARDANUY [ES] (+3)	ALMIRALL SA [ES]	A61K31/4704 A61K45/06 C07B2200/13 (+2)		PH12014502097 (A1) 2014-11-24	2012-03-20

2. Substituted benzamides with activity towards EP4 receptors

Inventor:	Applicant:	CPC:	IPC:	Publication info:	Priority date:
VIRGILI BERNADO MARINA	ALMIRALL SA [ES]	C07C2101/04	A61K31/196	TW201443003 (A)	2013-02-07

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2		AU2012320612A1	[EN] Process for preparing 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexl]amino}-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one via a novel intermediate			Search
3		AU2010214854A1	[EN] 5- (2-{ [6- (2, 2-difluoro-2-phenylethoxy) hexyl] amino} -1-hydroxyethyl) -8-hydroxyquinolin-2 (1H)-one for the treatment of lung function			Search
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5		AU2008213109B2	[EN] Napadisylate salt of 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one as agonist of the beta 2 adrenergic receptor			Search
6		AU2008213109A1	[EN] Napadisylate salt of 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one as agonist of the beta 2 adrenergic receptor			Search
7		CA000002862934A1	[EN] NOVEL POLYMORPHIC CRYSTAL FORMS OF 5-(2-{[6-(2,2-DIFLUORO-2-PHENYLETHOXY)HEXYL]AMINO}-1-(R)-HYDROXYETHYL)-8-HYDROXYQUINOLIN-2(1H)-ONE, HEMINAPADISYLATE AS AGONIST OF THE S2 ADRENERGIC RECEPTOR [FR] ...			Search
8		CA000002846444A1	[EN] PROCESS FOR PREPARING 5-(2-{[6-(2,2-DIFLUORO-2-PHENYLETHOXY)HEXYL]AMINO}-1(R)-HYDROXYETHYL)-8-HYDROXYQUINOLIN-2(1H)-ONE VIA A NOVEL INTERMEDIATE [FR] PROCEDE DE PREPARATION DE 5-(2-{[6-(2,2-DIFLUORO-2-PHENYLETHOXY)HEXYL]AMINO}-1(R)-HYDROXYETHYL)-8-HYDROXYQUINOLINE-2(1H)-ONE ...			Search

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