SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogada
ALICIA LLOREDA RICAURTE

ASUNTO

Radicación	08 046 653
Trámite	011
Evento	378
Actuación	519
Oficio	
Folios	7

006731

Patente de Invención	✓			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	✓	Capitulo I	✓	Capítulo II	✓

No. Solicitud Internacional	PCT/GB2006/004205
Fecha de Presentación Internacional	13/Noviembre/2006

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:	Folios 18 a 26	08/Mayo/2008
Reivindicaciones:	Folios 43 a 45	08/Mayo/2008
Prioridad:	SE 0502515-0	16/Noviembre/2005

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.

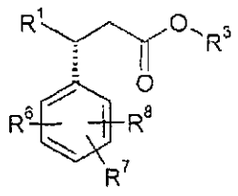
3. Objeto de la invención

Título de la solicitud: "Proceso para preparar derivados éster de beta-(fluorofenil)-propanoato".

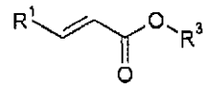
El problema planteado en esta solicitud consiste en la necesidad de tener un proceso de síntesis de derivados éster de β-(fluorofenil)-propanoato con velocidad de reacción aceptable y con menor consumo de especies de boro fluoradas.

Para resolver este problema técnico la solicitud en estudio proporciona un proceso para preparar un compuesto de fórmula (I) que comprende la reacción de un compuesto de fórmula (II) con 1 a 2 equivalentes molares de una especie de boro fluorada de fórmula (III) en presencia de 0,8 a 1,5 equivalentes molares de un

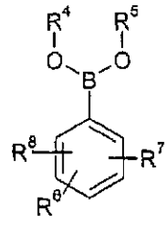
alcohol; una especie-precatalizadora de rodio (I); un ligando adecuado que se une a la especie pre-catalizadora de rodio (I) para formar un complejo catalizador; una base; y, un solvente adecuado; el proceso se realiza a una temperatura en el rango de 40 a 110°C



(I)



(II)



(III)

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07C 67/30, A61K 31/222

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es concisa porque las definiciones de R^1 y R^3 incluyen la expresiones "sustituido" y "opcionalmente sustituido" sin referenciar cuales son los posibles sustituyentes, R^4 y R^5 se unen para formar un anillo, sin definir el numero de átomos del anillo, si es saturado, insaturado, o si contiene o no otros heteroatomos etc, de forma general se definen componentes que participan en el proceso como "alcohol", "una base", "solvente adecuado", "especie pre-catalizadora de rodio" y "complejo catalizador", sin definir como tal los componentes, se sugiere restringir la solicitud a una razonable generalización de los procesos realizados o probados, es decir, que se encuentran debidamente soportados, se sugiere incluir los sustituyentes de las reivindicaciones 2, 3 y 4 en la reivindicación 1.

La expresión "solvente adecuado" en la reivindicación 1 es imprecisa y por lo tanto no permite distinguir la invención del estado de la técnica. Se sugiere reemplazarla por una razonable generalización de los solventes utilizados en el proceso, es decir, que se encuentran debidamente soportados.

La reivindicación 1 contiene la expresión "por ejemplo" precediendo una característica, la cual no es limitativa, porque hace opcional a la característica y no limita el alcance de la reivindicación. Se sugiere incluir las características opcionales o preferentes en una reivindicación dependiente.

La reivindicación 3 no es clara puesto que, se refiere a un compuesto de fórmula (I) en donde el piperidin-4-ilo N-sustituido es piperidin-4-ilo con alquiloC_{1-4}..., no es claro si la palabra "con" se refiere a los sustituyentes. Se solicita realizar las aclaraciones necesarias.

La reivindicación 7 no es concisa porque la definición de bases incluye términos generales como metal de álcali o metal alcalino térreo, que aunque conocidos en el campo técnico no permiten distinguir la invención del estado de la técnica. Se sugiere al solicitante restringir la solicitud a una razonable generalización de las bases que encuentran soporte descriptivo.

En la reivindicación 8 se utilizan abreviaturas como COD y Me en los nombres de la especie pre-catalizadora de rodio (I): $[Rh(COD)Cl]_2$ y $[Rh(COD)(MeCN)_2]BF_4$. Se

sugiere reemplazarlas por su correspondiente nombre o fórmula química según corresponda.

5. 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: 16/Noviembre/2005 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	WO 2005/007629	"Piperidine or 8-aza-bicyclo[3.2.1]oct-3-yl derivatives useful as modulators of chemokine receptor activity"	27/Enero/2005
D2	Miyaura, N. ET AL, Journal of Organic Chemistry, Vol. 65, Págs. 5951 - 5955	"Asymmetric conjugate 1,4-adition of arylboronic acids to α,β-unsaturated esters catalyzed by rhodium (I)/(S)-binap"	23/Agosto/2000
D3	Miyaura, N. ET AL, Organometallics, Vol. 16, N° 20. Págs. 4229 - 4231	"Rhodium-catalyzed conjugate addition of aryl- or 1-alkenylboronic acids to enones"	30/Septiembre/1997

D1 http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2005007629A1&KC=A1&FT=D&ND=3&date=20050127&DB=EPODOC&locale=en_EP divulga (pág. 43, renglón 17) el compuesto acido 3-(N-metanosulfonilpieridin-4il) propionico

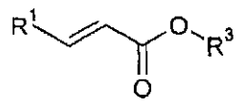
D2 divulga (pág. 5951, Fl. 64) un proceso de síntesis de β-aril esteres que comprende reacción de esteres α,β-insaturados con ácidos arilboronicos en la presencia de catalizador de rodio (I).

D3 divulga (pág. 4229, Fl. 69) un proceso de adición de ácidos aril o 1-alquenilboronicos a enonas, catalizado con rodio (I) y llevado a cabo en solvente acuoso.

6. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

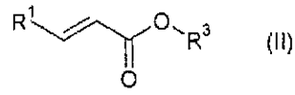
La reivindicación 9 consiste en un compuesto de fórmula (II)



(II)

En donde R^1 es N-(SO_2CH_3)piperidin-4ilo y R^3 es hidrogeno, etilo, iso-propilo o ter-butilo.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

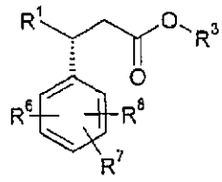
Características **esenciales**	**D1**
Compuesto  (II)	Ácido 3-(N-metanosulfonilpiperidina-4-il) propenoico
R^1: N-(SO_2CH_3)piperidin-4ilo	
R^3: hidrogeno, etilo, iso-propilo o ter-butilo	

Las características **esenciales** del compuesto de la reivindicación 9 habían sido divulgadas previamente en D1, el cual enseña, el compuesto ácido 3-(N-metanosulfonilpiperidina-4-il) propenoico (Pág. 43, renglón 17) que corresponde con a la fórmula II cuando R^1 es N-(SO_2CH_3)piperidin-4ilo y R^3 es hidrogeno.

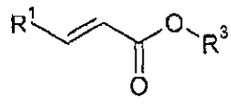
En consecuencia, la reivindicación 9 no es nueva, según lo divulgado en el documento D1.

Nivel Inventivo (Art18 D486)

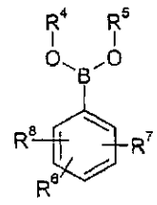
La reivindicación 1 consiste en un proceso para preparar un compuesto de fórmula (I):

 (I)

en donde R^1 es piperidin-4-ilo N-sustituido o fenilo opcionalmente sustituido; R^3 es alquiloC_{1-6}, fenilo opcionalmente sustituido o fenil(alquiloC_{1-4}) opcionalmente sustituido; R^6 es fluoro; y R^7 y R^8 son independientemente hidrógeno o fluoro; el proceso comprende la reacción de un compuesto de fórmula (II):

 (II)

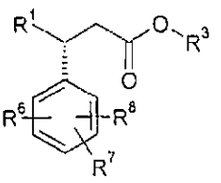
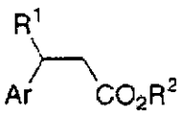
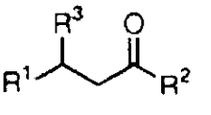
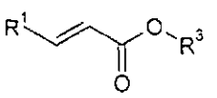
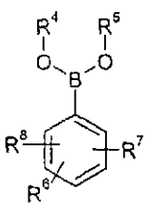
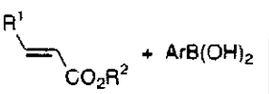
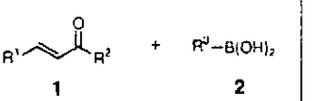
con 1 a 2 (por ejemplo 1 a 1,5) equivalentes molares de una especie de boro fluorada de fórmula (III):

 (III)

En donde R^4 y R^5 son, independientemente, hidrogeno, alquiloC_{1-6}, fenilo o

fenil(alquiloC_{1-4}); o R^4 y R^5 se unen para formar un anillo; en la presencia de: 0,8 a 1,5 equivalentes molares de un alcohol; una especie pre-catalizadora de rodio(I); un ligando adecuado que se une a la especie pre-catalizadora rodio (I) para formar un complejo catalizador; una base y, un solvente adecuado; el proceso se realiza a una temperatura en el rango de 40 a 110°C

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características **esenciales**	D2	D3
Proceso para preparar un compuesto de fórmula  (I) que comprende:	Proceso para preparar un compuesto de fórmula  **3** que comprende:	Proceso para preparar un compuesto de fórmula  **3** que comprende:
La reacción de un compuesto de fórmula  (II) con 1 a 2 equivalentes molares de una especie de boro fluorada de fórmula (III)  (III)	La reacción de un compuesto de fórmula 1 con un compuesto de fórmula 2  **1** **2**	La reacción de un compuesto de fórmula 1 con un compuesto de fórmula 2  **1** **2** R = aryl, 1-alkenyl
en la presencia de: 0,8 a 1,5 equivalentes molares de un alcohol; una especie pre-catalizadora de rodio(I); un ligando adecuado que se une a la especie pre-catalizadora rodio (I) para formar un complejo catalizador; una base y, un solvente adecuado;	En la presencia de un catalizador de rodio(I)-binap, etanol / metanol, solvente acuoso	En la presencia de un complejo catalizador de rodio (I) en metanol acuoso
el proceso se realiza a una temperatura en el rango de 40 a 110°C	Temperatura de 25 a 100°C	Temperatura de 50°C

Los documentos D2 y D3 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan procesos de síntesis en los que ácidos arilboronicos con esteres α,β-insaturados y ácidos aril o 1-alquenilboronicos con enonas en presencia de complejos catalizadores de rodio. El documento D2 divulga la reacción entre un α,β-insaturado de fórmula 1 y un acido arilboronico de fórmula 2 en la presencia de un catalizador rodio(I)-binap en solvente acuoso (Pág. 5951, Fl. 64), el solvente corresponde a metanol o etanol acuosos (Pág. 5952, Tabla 1, Fl. 65) y el proceso se realiza a temperaturas entre 25 a 100°C (Págs. 5951 y 5952, Fls. 64 y 65); en la fórmula 1 R^1 corresponde a $C(O)_2$alquilo, fenilo, alquilo-NO_2, H y alquilo y R^2 es alquilo (Pág. 5952, Tabla 1, Fl. 65; Pág. 5954, Tabla 4, Fl. 67), en la fórmula 2 Ar corresponde a fenilo (Pág. 5952, Pág. 5954, Tabla 4, Fl. 67). El documento D3 da a conocer un proceso de adición de ácidos aril o 1-alquenilboronicos a enonas, catalizado con rodio (I) (Pág. 4229, Fl. 69), como solvente se usa metanol acuoso (Pág. 4230, Fl. 70); R^3 es el acido fenilboronico que

puede estar sustituido con halógeno y R^1 es H, alquilo y fenilo (Pág. 4230, Tabla 2, Fl. 70).

El documento D2 también enseña que solventes acuosos en los que se combina agua con alcoholes presentaron buenos resultados (Pag. 5952, Fl. 65), así como especies precatalizadoras de rodio (I) como $[Rh(cod)(MeCN)_2]BF_4$ y $[Rh(cod)Cl]_2$ y $Rh(acac)(C_2H_4)_2$ (Pág. 5952, Fl. 65).

La diferencia entre la invención, definida en la reivindicación 1 y el procedimiento de D2 es que en el procedimiento de la solicitud se definen los equivalentes de la especie de boro fluorada de fórmula (III) y del alcohol, y en que se utiliza una base.

El efecto que logra el incluir los equivalentes de la especie de boro fluorada de fórmula (III) y del alcohol, y usar una base es permitir el uso de una cantidad más pequeña de especies de boro fluoradas.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede fórmular así: "cómo modificar el proceso conocido en D2 para sintetizar derivados de β-aril esteres para disminuir el uso de especies de boro fluoradas".

> Sin embargo, el documento D3 divulga la combinación de metanol y agua como un sistema altamente eficiente y ventajoso para un amplio rango de enonas y ácidos arilboronicos (Pág. 4230, Fl. 70), y enseña que para estas reacciones que se encuentran limitadas estéricamente por los ácidos arilboronicos, el uso de cantidades en exceso (2 equivalentes) de acido arilboronico fue ventajosa para alcanzar altos rendimientos, porque prolongar el tiempo de reacción no incrementa los rendimientos debido a la de-boronizacion de los acidos arilboronicos con agua (Págs. 4230 y 4231, Fls. 70 y 71).

En consecuencia, la persona del oficio normalmente versada en la materia, usaría cantidades de acidos arilboronicos y alcoholes en cantidades de equivalentes como las divulgadas en D3 en el procedimiento de D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones dependientes 2 – 8 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

Conclusión:
La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

7. Conclusión

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

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 2005/007629	9	Novedad
D2	Miyaura, N. ET AL, Journal of Organic Chemistry, Vol. 65, Págs. 5951 - 5955	1 – 8	Nivel Inventivo

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D3	Miyaura, N. ET AL. Organometallics, Vol. 16, N° 20. Págs. 4229 - 4231	1 – 8	Nivel Inventivo

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 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.

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 25 ABR. 2012

Elaborado por: Jeny Paola Villate Becerra P. Villate
Revisado por: Consuelo Leguizamón

J. Org. Chem. **2000**, *65*, 5951−5955

Asymmetric Conjugate 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Esters Catalyzed by Rhodium(I)/(*S*)-binap

Satoshi Sakuma, Masaaki Sakai, Ryoh Itooka, and Norio Miyaura*

Division of Molecular Chemistry, Faculty of Engineering, Hokkaido University, Sapporo 060-8628, Japan

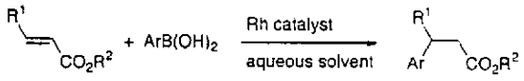
miyaura@org-rnc.eng.hokudai.ac.jp

Received February 15, 2000

Arylboronic acids underwent the conjugate 1,4-addition to α,β-unsaturated esters to give β-aryl esters in high yields in the presence of a rhodium(I) catalyst. The addition of arylboronic acids to isopropyl crotonate resulted in high yields and high enantioselectivity exceeding 90% ee in the presence of 3 mol % of $Rh(acac)(C_2H_4)_2$ and (*S*)-binap at 100 °C. The rhodium/(*S*)-binap complex provided (*R*)-3-phenylbutanoate in the addition of phenylboronic acid to benzyl crotonate. The effects on the enantioselectivity of chiral phosphine ligands, rhodium precursors, and substituents on α,β-unsaturated esters are discussed, as well as the mechanistic aspect of the catalytic cycle.

Conjugate 1,4-addition reactions by rhodium−,[1] nickel−,[2] ruthenium−,[3] or copper[4] complexes are of great value in asymmetric synthesis since various chiral auxiliaries are now available for the metal-catalyzed reactions.[5] We have recently reported the rhodium-catalyzed 1,4-conjugate addition reactions of aryl- and 1-alkenylboronic acids to enones in an aqueous solvent, which proceeds through a sequence of boron−rhodium transmetalation, yielding an organorhodium(I) species and its addition to enones.[6] Hayashi[7] and the joint research with them[8] demonstrated asymmetric variants by using a rhodium(I)−chiral phosphine complex. Among the chiral phosphines examined, the binap ligand[9] developed by Noyori for asymmetric hydrogenation of alkenes was found to be the best chiral auxiliary, achieving over 90% ee for cyclic and acyclic enones. The efficiency of transmetalation from boron to rhodium was also demonstrated in catalytic 1,2-additions of organoboronic acids to aldehydes[10] and *N*-sulfonyl imines.[11] The utility of potassium organotrifluoroborates (RBF_3K) as the nucleophile for both rhodium-catalyzed 1,4- and 1,2-additions was recently reported by Batey.[12]

Here, we report a conjugate 1,4-addition of arylboronic acids (**2**) to α,β-unsaturated esters (**1**) yielding optically active β-aryl esters (**3**) in the presence of a rhodium(I)−binap catalyst (eq 1).[13]



(1)

1 **2** **3**

Reaction Conditions

The 1,4-addition reactions of phenylboronic acid to the representative α,β-unsaturated esters in the presence of $[Rh(cod)(MeCN)_2]BF_4$ (3 mol %) are summarized in Table 1.

The reaction was highly dependent on the substituent (R^1 in **1**), which may affect the rate of insertion of **1** into a rhodium−carbon bond. Thus, the additions to both dimethyl fumarate and diethyl maleate smoothly proceeded at room temperature (entries 1 and 2), whereas the additions to cinnamate, acrylate, and crotonate were heated to 50, 80, and 100 °C to complete the reactions

(1) (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295−8296. (b) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439−4454.

(2) (a) Ikeda, S.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 1712−1713. (b) Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701−704. (c) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516−517. (d) Petrier, C.; Barbosa, J. C. S.; Dupuy, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 5761−5765. (e) Cacchi, S.; Palmieri, G. *J. Organomet. Chem.* **1985**, *282*, C3−6. (f) Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931−932. (g) Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. *Ibid.* **1980**, *102*, 3976−3978.

(3) (a) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436−12451. (b) Mitsudo, T.; Nakagawa, Y.; Watanabe, K.; Hori, Y.; Misawa, H.; Watanabe, H.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 565−571. (c) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

(4) (a) Alexakis, A. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, Chapter 3.10. (b) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; p 283.

(5) For reviews, see: (a) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, C1991; Vol. 4, Chapter 1.5. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771−806. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: NewYork, 1994; pp 207−212. (d) Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: NewYork, 1995. (e) Tomioka, K.; Nagaoka, Y.; Yamaguchi, M. In *Comprehensive Asymmetric Catalysis I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.

(6) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229−4231.

(7) (a) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591−11592. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; *Tetrahedron Lett.* **1998**, *39*, 8479−8482.

(8) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580.

(9) 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. See: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350.

(10) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3279−3280. Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450−4452.

(11) Ueda, M.; Miyaura, N. *J. Organomet. Chem.* **2000**, *595*, 31−35.

(12) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683−1686.

(13) Preliminary results were discussed in The Xth International Conference on Boron Chemistry; Durham, July 11−15, 1999 and Symposium on Organic and Inorganic Syntheses via Boranes in American Chemical Society 218th Meeting; New Orleans, Aug 22−25, 1999.

10.1021/jo0002184 CCC: $19.00
Published on Web 08/23/2000

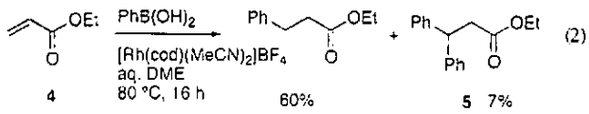
Table 1. Addition of Phenylboronic Acid to α,β-Unsaturated Esters with [Rh(cod)(MeCN)$_2$]BF$_4$[a]

entry	α,β-unsaturated ester	T/°C	yield[b]/%
1	(*E*)-MeO$_2$CCH=CHCO$_2$Me	25	84
2	(*Z*)-EtO$_2$CCH=CHCO$_2$Et	25	79
3	(*E*)-PhCH=CHCO$_2$Me	50	87
4	(*E*)-4-NO$_2$C$_6$H$_4$CH=CHCO$_2$Me	50	97
5	CH$_2$=CHCO$_2$Me	80	60[c,d]
6	(*E*)-MeCH=CHCO$_2$Me	100	82[d]
7	MeCH=C(CO$_2$Et)$_2$	100	9[d]
8	MeCH=C(CO$_2$Et)$_2$	70	76[e]
9	(*Z*)-EtO$_2$CCH=C(Me)CO$_2$Et	100	trace[d]

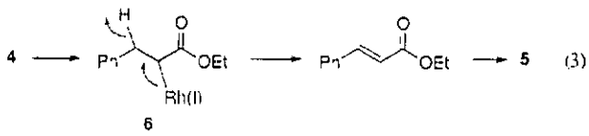
[a] A mixture of α,β-unsaturated ester (1 mmol) and phenylboronic acid (2 mmol) in aqueous MeOH (6/1) was stirred for 16 h in the presence of [Rh(cod)(MeCN)$_2$]BF$_4$ (3 mol %). [b] Isolated yields. The reaction was accompanied with methyl 3,3-diphenylpropionate (7%). [c] In aqueous dioxane (6/1). [d] The reaction was carried out in aqueous EtOH (5/2) at 70 °C for 24 in the presence of phenylboronic acid (4 mmol).

(entries 3−6). The relative reactivity is parallel to the order of rhodium/alkene complex stability or the insertion rate, which can be estimated by the LUMO energy level of alkenes.[14] However, the addition to trisubstituted alkenes was very slow, even at 100 °C, due to their large steric hindrance on the coordination to the rhodium metal center (entries 7 and 9). The prolongation of reaction time to 1 day improved the yield to 76% in the presence of 4 equiv of phenylboronic acid (entry 8). Similar to the results obtained in the addition to enones, aqueous solvents combining water and a weak donor solvent such as alcohols, dimethoxyethane (DME), or dioxane afforded good results. Judging from the recovery of the products, the saponification of the esters was very slow even at 100 °C.

The addition of phenylboronic acid to methyl acrylate (entry 5) was accompanied by 3,3-diphenylpropanoate (7%), which was derived from β-hydride elimination, giving ethyl cinnamate (eqs 2 and 3). A cinnamate intermediate was not detected in the reaction mixture since it is more reactive than the parent acrylate (entries 3 and 5).



4 (2)



(3)

The formation of a Heck-type product suggests the presence of a mechanism involving a rhodium species bound to the α-carbon (**6**). However, such byproducts were not observed, or were only observed in negligibly small amounts, in other substrates shown in entries 1−9.

Asymmetric Addition

The in situ preparation of a catalyst from rhodium complexes and (*S*)-binap was followed by the addition of phenylboronic acid to benzyl crotonate to reveal the effects of rhodium precursors on yields and enantioselectivities (Table 2).[15]

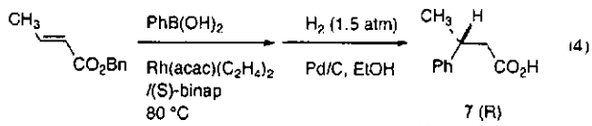
Table 2. Effect of Rhodium Precursor on the Asymmetric Addition of Phenylboronic Acid to Benzyl Crotonate[a]

entry	ligand	T/°C	time/h	yield[b]/%	% ee
1	[Rh(cod)(MeCN)$_2$]BF$_4$[c]	100	16	90	85
2	Rh(acac)(C$_2$H$_4$)$_2$	100	16	98	86
3	Rh(acac)(C$_2$H$_4$)$_2$	100	2	99	87
4	Rh(acac)(C$_2$H$_4$)$_2$	60	24	48	88
5	Rh(acac)(coe)$_2$[d]	100	16	98	86
6	Rh(acac)(CO)$_2$	100	16	98	86
7	[RhCl(cod)]$_2$	100	16	99	87
8	[RhCl(cod)]$_2$	60	24	64	33

[a] A mixture of benzyl crotonate (1 mmol) and phenylboronic acid (2 mmol) in aqueous dioxane was stirred in the presence of a rhodium complex (3 mol %) and (*S*)-binap (4.5 mol %). [b] Isolated yields. [c] cod = 1,5-cyclooctadiene. [d] coe = cyclooctene.

All of the cationic and neutral rhodium complexes examined, such as [Rh(cod)(CH$_3$CN)$_2$]BF$_4$, Rh(acac)(CH$_2$=CH$_2$)$_2$, Rh(acac)(coe)$_2$, Rh(acac)(CO)$_2$, and [Rh(cod)Cl]$_2$, were highly effective at 100 °C (entries 1−8). There were no large differences in yields or enantioselectivities (% ee) between cationic and neutral rhodium complexes, but neutral complexes were superior to cationic rhodiums because a combination of Rh(acac)(CH$_2$=CH$_2$)$_2$/(*S*)-binap revealed higher enantioselectivity (1−3% ee) than [Rh(cod)(CH$_3$CN)$_2$]BF$_4$/(*S*)-binap (entry 1). The reaction was completed within 2 h at 100 °C and overnight at 60 °C (entries 2 and 3). The enatioselectivity was not affected by the reaction temperatures or by the reaction times, although the RhCl complex resulted in significantly low enantioselectivity at 60 °C (entry 8). The isolated Rh(acac)[(*S*)-binap][15] showed essentially the same enatioselectivity as that of the in situ preparation.

The enatiomeric excess (% ee) was determined by HPLC analysis using a chiral stationary column (Dicel Chiralcel OD-H or OB-H). The addition of PhB(OH)$_2$ to benzyl crotonate with a cationic rhodium/(*S*)-binap catalyst (entry 1) provided benzyl 3-phenylbutanoate ([α]$_D$ −14.5 (*c* 1.02, CHCl$_3$), whose saponification with H$_2$ (1.5 atm, 10% Pd/C in EtOH at room temperature for 3 h) gave 3-phenylbutanoic acid ([α]$_D$ −42.6 (*c* 0.77, benzene) (eq 4). Thus, the absolute configuration of the ester (**7**) obtained from (*S*)-binap was established to be (*R*) by the specific rotation reported for (*R*)-3-phenylbutanoic acid ([α]$_D$ −45.8 (*c* 0.77, benzene).[16]



(4)

The effects of commercially available chiral ligands on the enantioselectivity in the addition of 3-methoxyphenylboronic acid to isopropyl crotonate are summarized in Table 3 and Figure 1.

(14) (a) Slexander, J. J. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Patai, S., Eds.; John Wiley & Sons: New York, 1985; Vol. 2, Chapter 5. (b) Yamamoto, A. *Organotransition Metal Chemistry-Fundemental Concepts and Applications*; Wiley: New York, 1986.

(15) The reaction of Rh(acac)(cod) with bisphosphine (P−P) yields a Rh(acac)(P−P) complex: Fennis, P. J.; Budzelaar, P. H. M.; Frijns, J. H. G.; Orpen, A. G. *J. Organomet. Chem.* **1990**, *393*, 287−298. For Rh(acac)[(*S*)-binap] complex, see ref 7.

(16) Suzuki, I.; Kin, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10139−10147.

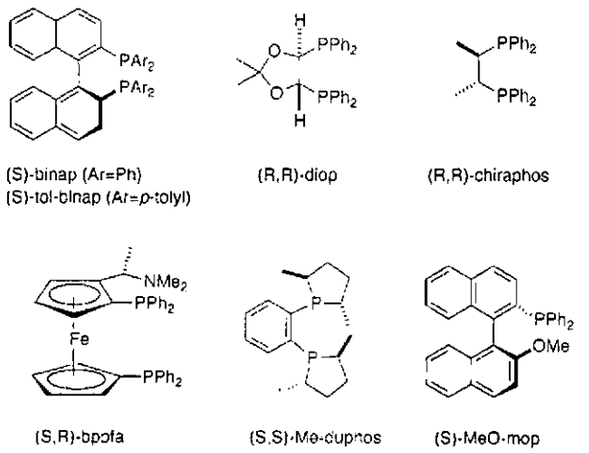


Figure 1. Chiral ligands.

Table 3. Effect of Ligand on the Asymmetric Addition of 3-Methoxyphenylboronic Acid to Isopropyl Crotonate[a]

entry	ligand	yield[b]/%	% ee
1	(*S*)-binap	91	91
2	(*S*)-tol-binap	43	91
3	(*R,R*)-diop	45	7
4	(*R,R*)-chiraphos	97	75
5	(*S,R*)-bppfa	9	0
6	(*S,S*)-Me-duphos	92	29
7	(*S*) MeO mop	trace	

[a] A mixture of isopropyl crotonate (1 mmol) and 3-methoxyphenylboronic acid (2 mmol) in aqueous dioxane was stirred for 16 h at 100 °C in the presence of $Rh(acac)(C_2H_4)_2$ (3 mol %) and ligand (4.5 mol %). [b] Isolated yields.

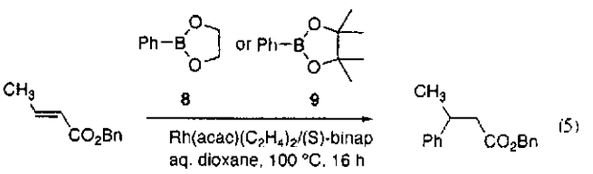
The complexes in situ obtained from binap, chiraphos, and Me-duphos afforded high yields of the addition product (entries 1, 4, and 6), but binap was again found to be the best ligand giving both high yields and high asymmetric induction, similar to those obtained by the 1,4-addition to enones (entry 1). Other bidentate ligands resulted in low yields or low enantioselectivities (entries 2, 3, and 5). The chiral monodentate ligand MeO-mop, reported in asymmetric hydrosilylation,[17] did not catalyze the reaction (entry 7).

The results of 1,4-addition of representative arylboronic acids to α,β-unsaturated esters in the presence of $Rh(acac)(C_2H_4)$/(S)-binap are summarized in Table 4.

3-Methoxyphenylboronic acid was added to a series of crotonates to reveal the effect of the ester group (R^2 in **1**) (entries 1−6). The bulkiness of the ester group improved the enantioselectivity in the order of ethyl ~ isobutyl ~ benzyl < isopropyl ~ cyclohexyl < *tert*-butyl, thus suggesting the superiority of secondary and tertiary alkyl esters, whereas the reaction was very slow for the *tert*-butyl ester (entry 6). Various arylboronic acids having ortho, meta, and para substituents smoothly underwent the addition to isopropyl crotonate with high enantioselectivity exceeding 90% ee (entries 4 and 7−12). There was no appreciable difference in yields or enantioselectivity between meta- and para-functionalized arylboronic acids (entries 4 and 7−9). However, ortho-substitution caused a significant increase in the enantioselectivity, though both reactions were very slow, even in the presence of a large excess of boronic acid (entries 10 and 11). The *o*-methoxy group in $Rh(2\text{-}MeOC_6H_4)(PMe_3)_3$ coordinates to the rhodium metal center,[18] but it is not obvious at present whether the significant effect of an *o*-methoxy group is derived not only from steric interaction but also from intramolecular chelation.

Together with the effect of the ester group (R^2), the β-substitution (R^1) significantly affected the yields and enantioselectivities. The enantioselectivity improved to 97% ee in the β-isopropyl derivative (entry 12), but the increase in steric interaction significantly reduced the chemical yield, which was not improved in the presence of a large excess of arylboronic acids or by prolongation of the reaction time. More flexible chiraphos was better ligand for improving the chemical yield, but the enantioselectivity was not sufficient for practical purposes (entry 13). Although bulky β-alkyl groups caused an increase in the enantioselectivity, all attempts at high-enantioselective addition to β-aryl derivatives such as cinnamate were unsuccessful (entries 14 and 15).

Under similar reaction conditions, arylboronic esters **8** and **9** also underwent the conjugate addition (eq 5).



8: 99%, 87%ee
9: 79%, 87%ee

The pinacol ester **9** resulted in a slightly lower yield, but the enantioselectivity thus obtained was the same as that of phenylboronic acid (entry 3). Various arylboronic pinacol esters are now accessible by the palladium-catalyzed cross-coupling reaction of bis(pinacolato)-diboron with aryl halides or triflates or by a similar coupling reaction of pinacolborane with aryl halides in the presence of triethylamine.[19] Thus, the stepwise bond-forming reactions catalyzed by palladium and rhodium may allow one-pot synthesis of β-aryl esters.

Mechanism

Although work on mechanistic details is still in progress, it is thought that the present transformation may have resulted from a catalytic cycle that involves the transmetalation of arylboronic acid to a rhodium(I) species **10** to give an arylrhodium(I) complex **11**, the coordination of an unsaturated ester to rhodium followed by insertion into the Rh−C bond to afford an equilibrium mixture of **12** and **13** and, finally, the hydrolysis of the rhodium enolate **13** with water to provide **14** and **10** (Figure 2).

The arylrhodium(I)/arylphosphine complexes are unstable, making isolation in pure form impossible, but they

(17) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887−9888.

(18) Jones, R. A.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1979**, 472−477.

(19) Th coupling between bis(pinacolato)diboron with aryl halides or triflates, see: (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450. The coupling of haloarenes with pinacolborane: (c) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1999**, *62*, 6458−6459. (d) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164−168.

Table 4. Asymmetric Addition of Arylboronic Acids to α,β-Unsaturated Esters[a]

entry	α,β-unsaturated ester	$ArB(OH)_2$	yield[b]/%	% ee	$[\alpha]^{20}_D$ (*c* in $CHCl_3$)
1	(*E*)-$CH_3CH{=}CHCO_2C_2H_5$	3-$MeOC_6H_4B(OH)_2$	81	87	−20.3 (1.01)
2	(*E*)-$CH_3CH{=}CHCO_2CH_2CH(CH_3)_2$	3-$MeOC_6H_4B(OH)_2$	98	88	−21.7 (1.01)
3	(*E*)-$CH_3CH{=}CHCO_2CH_2Ph$	3-$MeOC_6H_4B(OH)_2$	97	87	−12.3 (1.00)
4	(*E*)-$CH_3CH{=}CHCO_2i\text{-}C_3H_7$	3-$MeOC_6H_4B(OH)_2$	91	91	−21.2 (1.02)
5	(*E*)-$CH_3CH{=}CHCO_2cyclo\text{-}C_6H_{11}$	3-$MeOC_6H_4B(OH)_2$	97	91	−18.4 (1.01)
6	(*E*)-$CH_3CH{=}CHCO_2t\text{-}C_4H_9$	3-$MeOC_6H_4B(OH)_2$	54	92	−19.5 (1.01)
7	(*E*)-$CH_3CH{=}CHCO_2i\text{-}C_3H_7$	4-$MeC_6H_4B(OH)_2$	89	92	−23.5 (1.01)
8	(*E*)-$CH_3CH{=}CHCO_2i\text{-}C_3H_7$	4-$MeOC_6H_4B(OH)_2$	55	92	
9	(*E*)-$CH_3CH{=}CHCO_2i\text{-}C_3H_7$	4-$MeOC_6H_4B(OH)_2$	82[c]	92	−21.6 (0.99)
10	(*E*)-$CH_3CH{=}CHCO_2i\text{-}C_3H_7$	2-$MeC_6H_4B(OH)_2$	35[c]	94	−8.5 (1.00)
11	(*E*)-$CH_3CH{=}CHCO_2i\text{-}C_3H_7$	2-$MeOC_6H_4B(OH)_2$	43[c]	98	−2.0 (1.00)
12	(*E*)-$(CH_3)_2CHCH{=}CHCO_2i\text{-}C_3H_7$	3-$MeOC_6H_4B(OH)_2$	26	97	−17.5 (1.02)
13	(*E*)-$(CH_3)_2CHCH{=}CHCO_2i\text{-}C_3H_7$	3-$MeOC_6H_4B(OH)_2$	92[d]	77	
14	(*E*)-$PhCH{=}CHCO_2i\text{-}C_3H_7$	4-$MeC_6H_4B(OH)_2$	28	77	
15	(*E*)-$PhCH{=}CHCO_2i\text{-}C_3H_7$	4-$MeC_6H_4B(OH)_2$	37[c]	78	−2.9 (0.99)

[a] A mixture of α,β-unsaturated ester (1 mmol) and arylboronic acid (2 mmol) in aqueous dioxane was stirred for 16 h at 100 °C in the presence of $Rh(acac)(C_2H_4)_2$ (3 mol %) and (*S*)-binap (4.5 mol %). [b] Isolated yields by chromatography over silica gel. [c] Arylboronic acid (5 mmol) was used. [d] (*R,R*)-Chiraphos was used in place of (*S*)-binap.

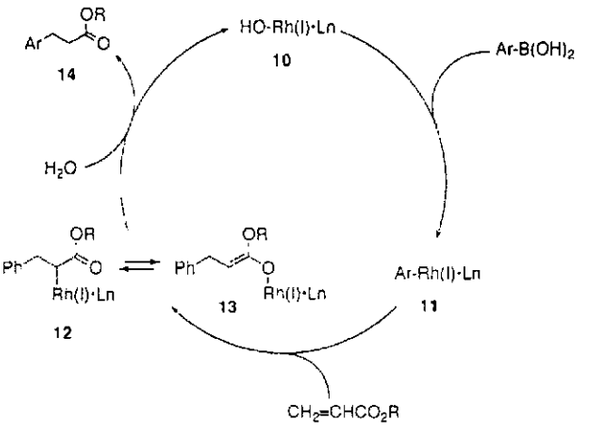
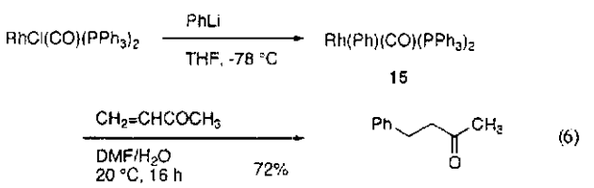


Figure 2. Proposed catalytic cycle.

are key intermediates for carrying out various coupling reactions with organic halides[20] and additions to alkenes and alkynes.[21] Preliminary results suggested a sequence of the formation of the ArRh(I) species and its addition to unsaturated esters because the Michael adduct was obtained when the in situ preparation of phenylrhodium(I) (**15**) from a Vaska complex was followed by the addition to methyl vinyl ketone (eq 6). The sequence involves insertion of the alkene double bond into the Rh−C bond and hydrolysis of the rhodium intermediate (**11** → **14**).



(6)

The synthesis of rhodium enolate and its applications to catalytic Aldol chemistry was extensively studied by Heathcock.[22] The η^1 oxygen-bound rhodium enolate complexes, synthesized from $RhCl(CO)(PMe_3)_2$ and potassium enolates or silyl enolates, exhibit a dynamic equilibrium between the O-bound and the C-bound forms, which are sufficiently nucleophilic to condense with carbonyl compounds. Thus, the hydrolysis of the rhodium enolate **13** with water lead to **14**, which avoids the β-hydride elimination from **12** giving the Heck-coupling product (eq 3) or Aldol-type condensation of **13**. Although there is no clear evidence that (hydroxo)rhodium(I)[24] exists as an active species for transmetalation (**10** → **11**), results of present study implied that there is a mechanism that involves transmetalation as a crucial step in the catalytic cycle. The high oxophilicity of the boron center and the basicity of transition metal hydroxides would induce transmetalation, which can be rationalized by the related catalyzed reactions by palladium and platinum complexes whereby organic groups on the boron atom readily transfer to $Pd(acac)_2$,[25] $[\eta^3\text{-}C_3H_5PdOAc]_2$,[26] $\eta^3\text{-}C_3H_5Pd(acac)$,[26] $RPd(OR)L_2$ (R = H, Me, Ac)[26,27,28] and $[Pt(OR)(S)\text{-}L_2]^+$ (R = H, Me)[29] under neutral conditions. The reaction of phenylboronic acid with benzyl crotonate with the Rh(acac)/(S)-binap complex (entry 2 in Table 2) was retarded completely by the addition of a 3 mol % of acid such as HBF_4, AcOH, or HCl, thus suggesting that neutralization of the (hydroxo)rhodium species inhibits transmetalation.

The stereochemical pathway in the insertion of the C−C double bond of **1** into the Rh−aryl bond can be explained by a mechanism similar to that of the 1,4-addition to enones.[6] The binap ligand was originally

(20) (a) Hegedus, L. S.; Kendall, P. M.; Lo, S. M.; Sheats, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 5448−5452. (b) Semmelhack, M. F.; Ryono, L. *Tetrahedron Lett.* **1973**, 2967−2970.

(21) Michman, M.; Balog, M. *J. Organomet. Chem.* **1971**, *31*, 395−402.

(22) The reaction of $(PPh_3)_3RhCl$ with PhMgBr or *trans*-$RhCl(CO)(PPh_3)_2$ with PhLi yields the phenylrhodium(I) complexes: Keim, W. *J. Organomet. Chem.* **1968**, *14*, 179−184. Hegedus, L. S.; Lo, S. M.; Bloss, D. E. *J. Am. Chem. Soc.* **1973**, *95*, 3040−3042.

(23) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938−949.

(24) (a) Brune, H.-A.; Unsin, J.; Hemmer, R.; Reichhardt, M. *J. Organomet. Chem.* **1989**, *369*, 335−342. (b) Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126. (c) Grushin, V. V.; Kuznetsov, V. F.; Bensimon, C.; Alper, H. *Organometallics* **1995**, *14*, 3927−3932.

(25) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083−1090.

(26) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972−980.

(27) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, *95*, 2457−2483. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; VCH: Weinheim, 1998; p 49.

(28) Miyaura, N. In *Advances in Metal−Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Stamford, 1998; Vol. 6, p 187.

(29) Siegmann, K.; Pregosin, P. S.; Venanzi, L. M. *Organometallics* **1989**, *8*, 2659−2664.

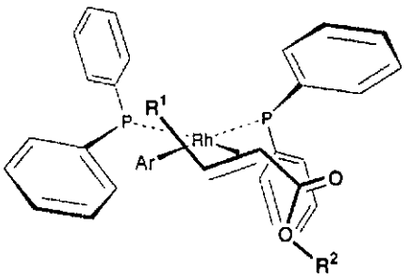
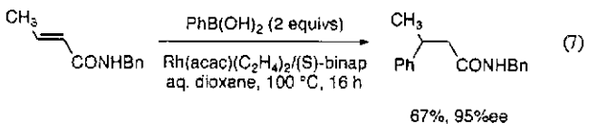


Figure 3. Transition state.

designed for asymmetric hydrogenation, but it also works well in the Heck reaction[30] and the conjugate addition because those reactions involve a similar molecular recognition mechanism. The configuration of a speculated intermediate of the rhodium−(*S*)-binap[30] and α,β-unsaturated ester coordinated is shown in Figure 3.

The coordination of **1** with its 2re face to a vacant orbital of the rhodium−(*S*)-binap complex provides (R)-**3** (Ar = Ph, R = Me, R′ = CH_2Ph) on the migratory insertion of the C−C double bond into the rhodium−carbon bond (eq 4). A comparison of a series of crotonic esters (entries 1−6 in Table 4) revealed the superiority of bulky R^2, which may interact with the upper phenyl group of the binap ligand at the coordination from its 2 si face.

In addition to our previous reports[6] on 1,4-additions of aryl- and 1-alkenylboronic acids to enones, the reaction with α,β-unsaturated esters was found to be efficiently catalyzed by a rhodium-binap catalyst. Because of the simple experimental procedure using a catalytic amount of a rhodium−binap complex, we anticipate the feasibility of conjugate additions to other Michael acceptors. Preliminary results for the addition of phenylboronic acid to *N*-benzyl crotonamide are shown in eq 7. Under reaction conditions similar to those used for the esters, various amides showed a higher enantioselectivity than that of the corresponding ester derivatives, the results of which will be reported elsewhere (eq 7).[13]



(7)

(30) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188−4196, and references therein.

Experimental Section

$Rh(acac)(CH_2{=}CH_2)_2$, $Rh(acac)(CO)_2$, and $[Rh(cod)Cl]_2$ are commercially available. $[Rh(cod)(CH_3CN)_2]BF_4$[31] and $Rh(acac)(coe)_2$[32] were synthesized by the reported procedures. HPLC analysis was directly performed with a chiral stationary phase column, Chiralcel OD-H and OB-H, purchased from Dicel Co., Ltd.

General Procedure. Rhodium complex (0.03 mmol), ligand (0.045 mmol), and arylboronic acid (2 or 5 mmol) were added to a flask containing a magnetic stirring bar, a septum inlet, and a reflux condenser. The flask was flashed with argon and charged with 1,4-dioxane (6 mL) and water (1 mL). After being stirred for 30 min, α,β-unsaturated ester (1.0 mmol) was added. The mixture was then stirred for 16 h at the temperature shown in Tables 1−4. The product was extracted with benzene, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel gave the desired product.

(*R*)-3-Phenylbutanoic Acid (Eq 4). $(acac)Rh(C_2H_4)_2$ (0.03 mmol), (*S*)-binap (0.045 mmol), and phenylboronic acid (2 mmol) were placed in a flask. The flask was flashed with argon and then charged with 1,4-dioxane (6 mL) and water (1 mL). After being stirred for 30 min, benzyl crotonate was added. The mixture was then stirred for 16 h at 100 °C. Chromatography over silica gel yielded benzyl 3-phenylbutanoate: yield 0.252 g (99%); 86% ee (HPLC, OD-H; hexane/2-propanol = 98:2).

To a glass pressure bottle containing a magnetic stirring bar and 10% Pd−C (10 mg) were added EtOH (3 mL) and benzyl 3-phenylbutanoate (1 mmol). The resulting mixture was stirred for 3 h at room temperature under 1.5 atmospheres of hydrogen. The catalyst was removed by filtration through Celite, and the acid was then extracted with 1 M NaOH (50 mL). The aqueous phase was treated with 1 M HCl (100 mL), and the product was then extracted with diethyl ether. Evaporation of solvent yielded 3-phenylbutanoic acid: yield 0.118 g (72%); $[\alpha]_D$ −42.6 (*c* 0.77, benzene).

Addition of Phenylrhodium(I) Complex to Methyl Vinyl Ketone (Eq 6). To a solution of Vaska complex $RhCl(CO)(PPh_3)_2$ (0.03 mmol) in THF (0.5 mL) was added phenyllithium (0.832 M in diethyl ether, 0.3 mmol) at −78 °C. After the mixture was stirred for 1.5 h at −78 °C, DMF (6 mL), H_2O (1 mL), and methyl vinyl ketone (1 mmol) were added. The resulting mixture was stirred overnight at room temperature. GC analysis revealed the formation of 4-phenyl-2-butanone in 72% yield based on the Vaska complex.

Supporting Information Available: Text describing experimental details and spectral and/or analytical data of the products. This material is available free of charge via Internet at http://pubs.acs.org.

JO0002184

(31) Green, M.; Kuc, T. A.; Taylor, S. H. *J. Chem. Soc. A* **1971**, 2334−2337.

(32) Bennett, M. A.; Mitchell, T. R. B. *J. Organomet. Chem.* **1985**, *295*, 223−231.

ORGANOMETALLICS

Volume 16, Number 20, September 30, 1997

Communications

Rhodium-Catalyzed Conjugate Addition of Aryl- or 1-Alkenylboronic Acids to Enones

Masaaki Sakai, Hiroyuki Hayashi, and Norio Miyaura*

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060, Japan

Received June 16, 1997[⊗]

Summary: The rhodium(I)-catalyzed conjugate addition of aryl- or 1-alkenylboronic acids to enones was carried out in high yields at 50 °C in an aqueous solvent. A combination of (acac)Rh(CO)$_2$ and dppb was recognized to be highly effective for the addition to acyclic and cyclic enones.

The conjugated addition of organometallic reagents to enones is a powerful tool for appending organic residues to cyclic and acyclic substrates. Although organocopper complexes have been widely used,[1] other related reactions induced by transition metals have provided additional applications and extensions of this protocol. Ni(acac)$_2$ or PdCl$_2$ catalyzes the conjugate addition of organozinc,[2] -zirconium,[3] -aluminum,[4] -mercury compounds[5] to enones. The addition of terminal alkynes to α,β-unsaturated ketones and esters with RhCl(PMe$_3$)$_3$[6a] or H$_2$Ru(PBu$_3$)$_4$[6b,c] and the Michael addition of activated nitriles or esters with ruthenium(II)[7a] or rhodium(I)[7b] complexes have been extensively studied. The corresponding reactions of organoboron compounds have not yet been well developed, but the addition of NaBPh$_4$ or arylboronic acids to enones with Pd(OAc)$_2$ in the presence of NaOAc or SbCl$_3$ was

Table 1. Addition of Phenylboronic Acid to MVK or 2-Octen-3-one[a]

			yield/%[b]	
entry	ligand (equivs)	solvent	MVK	2-octen-3-one
1	PBu$_3$ (3)	DMF/H$_2$O	93	
2	PPh$_3$ (3)	DMF/H$_2$O	83	0
3	AsPh$_3$	DMF/H$_2$O		0
4	TFP[c] (3)	DMF/H$_2$O	94	12
5	dppe[d] (1)	DMF/H$_2$O	70	0
6	dppp[e] (1)	DMF/H$_2$O	97	19
7	dppb[f] (1)	DMF/H$_2$O	99	28
8	dppb[f] (1)	DMF	91	
9	dppb[f] (1)	toluene/H$_2$O		34
10	dppb[f] (1)	cyclohexane/H$_2$O		61
11	dppb[f] (1)	MeOH/H$_2$O		96
12	dppb[f] (1)	MeOH		0

[a] All reactions were carried out at 50 °C for 16 h using PhB(OH)$_2$ (1.3 mmol), methyl vinyl ketone (MVK) or 2-octen-3-one (1.0 mmol), (acac)Rh(CO)$_2$ (0.03 mmol), and an additional ligand (0.03 or 0.09 mmol) in aqueous solvent (6/1, 7 mL). [b] GC yields based on the enones. [c] Trifurylphosphine. [d] 1,2-Bis(diphenylphosphino)-ethane. [e] 1,3-Bis(diphenylphosphino)propane. [f] 1,4-Bis(diphenylphosphino)butane.

[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1997.

(1) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; pp 283–382.

(2) Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931. Petrier, C.; Barbosa, J. C. S.; Dupuy, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 5761. Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516. Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701.

(3) (a) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045. (b) Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. *Ibid.* **1980**, *102*, 3976.

(4) Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297. Hansen, R. T.; Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2244.

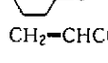
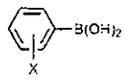
(5) Cacchi, S.; Palmieri, G. *J. Organomet. Chem.* **1985**, *282*, C3.

(6) (a) Nikishin, G. I.; Kovalev, I. P. *Tetrahedron Lett.* **1990**, *31*, 7063. (b) Mitsudo, T.; Nakagawa, Y.; Watanabe, K.; Hori, Y.; Misawa, H.; Watanabe, H.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 565. (c) Trost, B. M. *Angew. Chem.* **1995**, *107*, 285.

(7) (a) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuno, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (b) Sawamura, M.; Sudoh, M.; Ito, Y. *Ibid.* **1996**, *118*, 3309.

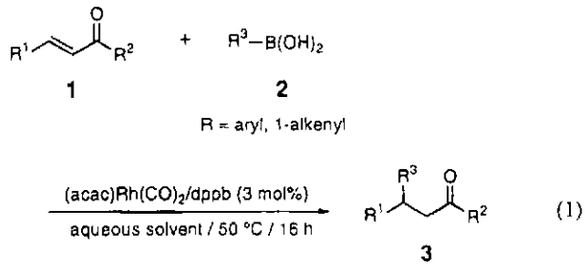
S0276-7333(97)00511-6 CCC: $14.00

Table 2. Rhodium-Catalyzed Conjugate Addition of Arylboronic Acids (Eq 1)[a]

entry	arylboronic acid	X	enone	yield/%[b] A[c]	B[d]	C[e]
1	$PhB(OH)_2$		CH_2=$CHCOCH_3$	82 (99)	(90)	(99)
2			CH_3CH=$CHCOC_4H_9$	28	60, 74[f]	96[f]
3			CH_3CH=$CHCOPh$		75[f]	
4			$PhCH$=$CHCOCH_3$		43[f]	99[f]
5			$PhCH$=$CHCOPh$		58[f]	86[f]
6				trace	52[f]	trace
7		4-Br	CH_2=$CHCOCH_3$	90		
8		4-CH_3O	CH_2=$CHCOCH_3$	84	82	86
9		2-CH_3O	CH_2=$CHCOCH_3$	68	81	84
10		4-CH_3CO	CH_2=$CHCOCH_3$	94		
11		2,4,6-$(CH_3)_3$	CH_2=$CHCOCH_3$	(44) (80)[f]		(9)[f]
12	$PhB(OH)_2$		CH_2=$CHCHO$	(56)	(43)	(59)

[a] The experimental procedure is given in the text.[11] [b] Isolated yields are based on the enones, and GC yields are given in parentheses. [c] DMF/H_2O (6/1). [d] Cyclohexane/H_2O (6/1). [e] MeOH/H_2O (6/1). [f] Two equivalents of $ArB(OH)_2$ was used.

recently reported by Uemura and co-workers.[8] The reaction was proposed to proceed through the oxidative addition of the C−B bond to the Pd(0) species; however, another probable process, the transmetalation to transition metals, may allow a similar catalytic transformation by the use of organoboronic acids. The efficiency of the transmetalation from boron to palladium was previously demonstrated in the cross-coupling reaction of organoboron compounds with organic electrophiles.[9] Now, we report the 1,4-addition reaction of organoboronic acids to enones catalyzed by a (acac)$Rh(CO)_2$/dppb complex (dppb 1,4-bis(diphenylphosphino)butane), which may involve the B−Rh transmetalation as the key step (eq 1).



(1)

A mixture of $Rh(acac)(CO)_2$ (3 mol %), a phosphine ligand, an enone (1 equiv), and phenylboronic acid (1.3 equiv) in aqueous solvent was stirred for 16 h at 50 °C (Table 1). Various phosphine ligands gave good results for methyl vinyl ketone (MVK), giving a quantitative yield of 4-phenyl-2-butanone as the sole product, but the reaction with less reactive 2-octen-4-one revealed the order of dppb > dppp > TFP > dppe, PPh_3, and $AsPh_3$ suggesting that the reaction is accelerated upon the increase of the P-Rh-P angles.[10] Other rhodium(I) complexes such as $[Rh(cod)_2]BF_4$/dppb (99%), $[Rh(CO)(PPh_3)_2]ClO_4$ (95%), (acac)Rh(cod)/dppb (99%), $RhCl(PPh_3)_3$ (16%), and $RhCl(CO)(PPh_3)_2$ (35%) were also effective for MVK. The solvent also affects the rate of addition. Aqueous DMF can be used for methyl vinyl ketone, but less polar solvents such as cyclohexane afforded a higher yield for 2-octen-4-one (entry 10). However, a combination of methanol and water was finally recognized to be a highly efficient system, having a wide generality for various enones (entry 11 and Table 2). Although the effect of added water has not yet been elucidated, the yields decreased in the absence of water (entries 8 and 12). The addition of a base, such as NaOH, NaOAc, and Et_3N, or the addition of $SbCl_3$ unexpectedly retarded the reaction, which is in sharp contrast to the palladium-catalyzed cross-coupling reaction[9] of organoboronic acids and the conjugate addition[8] with palladium(II) acetate.

The representative results obtained by the three procedures using $Rh(acac)(CO)_2$/dppb in aqueous solvents at 50 °C are compared in Table 2.[11] The addition to MVK worked well in aqueous DMF (procedure A), but aqueous MeOH (procedure C) was apparently advantageous for a wide range of enones and arylboronic acids (entries 2−12). Aqueous cyclohexane (procedure C) exceptionally gave the best result in the reaction with 2-cyclohexenone (entry 6). Various arylboronic acids having *ortho*- and *para*-substituents smoothly underwent the addition to methyl vinyl ketone (MVK) (entries 1 and 7−11). There is no appreciable difference in the yields between electron-withdrawing and -donating groups, but the *ortho*-substituents strongly retarded the addition (entries 9 and 11). For such reactions of sterically hindered arylboronic acids, the use of excess amounts (2 equiv) of arylboronic acids was advantageous to achieve high yields, because prolonging the reaction time did not improve the yields due to the competitive hydrolytic deboronation of arylboronic acids with water (entries 2 and 11). The reduction potential

(8) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 883.

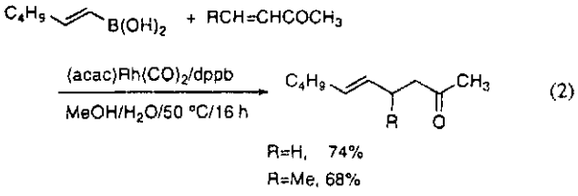
(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(10) The bond angle affects the rate of CO insertion into the C−Pd bond, see: Dekker, G. P. C.; Elsevier, C. J.; Vrieze, K. *Organometallics* **1992**, *11*, 1598.

(11) The following procedure for the synthesis of 2-phenyloctan-4-one is representative. Methanol (6 mL) was added to a flask charged with $Rh(acac)(CO)_2$ (0.03 mmol), dppb (0.03 mmol), and $PhB(OH)_2$ (2.0 mmol) and flushed with nitrogen. After being stirred for 15 min at room temperature, water (1 mL) and 2-octen-3-one (1 mmol) were added, and the resulting mixture was then stirred at 50 °C for 16 h. The product was extracted with benzene, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel with hexane/AcOEt (10/1) gave a colorless oil (96%): IR (neat) 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16−7.31 (m, 5H), 3.31 (ddq, 1H, J = 6.6, 6.8, and 7.8 Hz), 2.72 (dd, 1H, J = 6.6 and 16.1 Hz), 2.62 (dd, 1H, J = 7.8 and 16.1 Hz), 2.30 (8 lines, 2H, J = 7.3 Hz), 1.48 (tt, 2H, J = 7.3 and 7.3 Hz), 1.25 (d, 3H, J = 6.8 Hz), 1.23 (tq, 2H, J = 7.3 and 7.3 Hz), 0.86 (t, 3H, J = 7.3 Hz); MS *m/e* 105 (100), 119 (8), 129 (3), 147 (18), 162 (7), 189 (16), 204 (22, M^+). HRMS for $C_{14}H_{20}O$: 204.1507. Found: 204.1500.

of enones serves to estimate the addition rate of organocuprates[12] and perhaps the addition of other organometallics,[3b] but the reaction seemed to be more sensitive to the steric effect of the substituents than that of an electronic effect, presumably due to the steric hindrance at the steps of coordination and insertion to the enone (entries 1–5). The reaction under neutral conditions in the presence of water avoids the aldol condensation of substrates or products, thus allowing the conjugate addition to enals. The preliminary results for the addition of phenylboronic acid to acrolein gave a 59% yield of 3-phenylpropanal (entry 12).[13]

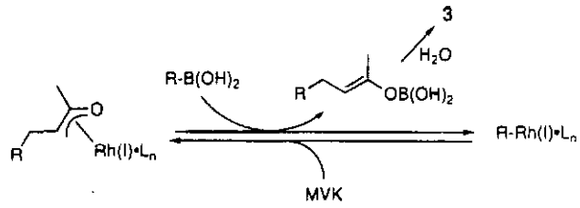
(*E*)-1-Hexenylboronic acids similarly participated in the rhodium-catalyzed conjugate addition to MVK giving (*E*)-5-decen-2-one in a 62% yield by procedure A, 74% yield by procedure B, and 74% yield by procedure C. The addition to 2-octen-4-one by procedure C resulted in a 68% yield, retaining its stereochemistry during the reaction (eq 2).



(2)

This research has been carried out based on the previous observations that the organic groups on the boron atom readily displace the RO–Pd(II)X bond (RO = acac, AcO, and MeO) under neutral conditions, whereas the halogen–metal complexes are quite inert to such transmetalation with organoboronic acids.[8] Work on the mechanistic details is in progress, but the present transformation may result from a catalytic cycle that involves the transmetalation between the rhodium(I) enolate[14] and arylboronic acid to give the arylrhodium(I) species[15] and the insertion of the enone into the Ar–Rh bond, as shown in Scheme 1.[16]

Scheme 1. Catalytic Cycle



The intermolecular transfer reactions of organoboron compounds such as the Grignard-type reaction are rare; however, several methods have been reported for the conjugate addition to enones.[17–19] The present rhodium-catalyzed reaction provides an additional method for the conjugate addition of aryl- and alkenylboronic acids to enones. Because of the simple experimental procedure under neutral conditions, the rhodium-catalyzed asymmetric addition will be the topic of further accounts from this laboratory.

OM9705113

(12) House, H. O.; Huber, L. E.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 8471.

(13) The addition to other α,β-unsaturated aldehydes, nitriles, or esters is in progress; however, these reactions are very slow under the above reaction conditions.

(14) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938.

(15) The reaction of $(PPh_3)_3RhCl$ with PhMgBr or *trans*-$RhCl(CO)(PPh_3)_2$ with PhLi gives the corresponding phenylrhodium(I) complexes, see: Keim, W. *J. Organomet. Chem.* **1968**, *14*, 179. Hegedus, L. D.; Lo, S. M.; Bloss, D. E. *J. Am. Chem. Soc.* **1973**, *95*, 3040. However, the isolation and characterization of arylrhodium species need to be investigated further.

(16) The hydrolysis of the rhodium(I) enolate with water to give a hydroxorhodium species and its transmetalation with arylboronic acid is another probable process to give a phenylrhodium(I) intermediate, see: Grushin, V. V.; Kuznetsov, V. F.; Bensimon, C.; Alper, H. *Organometallics* **1995**, *14*, 3927.

(17) Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H. C.; Rogic, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1967**, *89*, 5708.

(18) Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* **1992**, 695. Ishimura, S.; Hara, S.; Suzuki, A. *Synlett* **1996**, 993.

(19) Molander, G. A.; Shingaram, B.; Brown, H. C. *J. Org. Chem.* **1984**, *49*, 5024. Molander, G. A.; Brown, H. C. *Ibid.* **1977**, *42*, 3106.