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Señor
SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL
DIVISION DE NUEVAS CREACIONES
E. S. D.

Ref: **P1.-ELI LILLY AND COMPANY.-Expediente No. 02-103.452.-**

1. Me refiero al asunto de la referencia.

2. Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **ELI LILLY AND COMPANY.**

3. En consecuencia, atentamente solicito a ese Despacho reconocerme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.

4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.

5. Solicito a ese Despacho proceder de conformidad.

Atentamente,

ALICIA LLOREDA RICAURTE
T.P. 53.215
Código 231

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

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Ref: P1.-ELI LILLY AND COMPANY.-Expediente No. 02-103.452.-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e inscrito, identificado como aparece al pie de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad industrial de **ELI LILLY AND COMPANY**, sociedad organizada y existente de conformidad con las leyes del Estado de Indiana, Estados Unidos de América, domiciliada en Indianapolis, Estado de Indiana, Estados Unidos de América, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e inscrita, identificada con la cédula de ciudadanía No. 39.690.713 de Usaquén y Tarjeta Profesional No. 53.215, para que continúe representando a la mencionada sociedad en el expediente de la referencia.

De conformidad con el artículo 66 del C.P.C., manifiesto bajo la gravedad de juramento que los demás apoderados citados en el documento otorgado a mi favor no desean ejercer el poder a ellos conferido.

El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, desistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los intereses de la sociedad en cuyo nombre hablo.

Atentamente,

NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. 25 AGO. 2004
Ante mi PABLO MENDEZ BARAJAS
NOTARIO SEXTO(E) DEL CIRCULO DE BOGOTA
Comparecieron: José Antonio Lloreda
quien (es) exhibió(eron) la(s) C.C.
y declaró(aron) que la(s) firma(s) en el presente documento es(son) la(s) suya (s) y que el contenido del mismo es cierto.
En constancia se firma esta diligencia y se imprime

JOSE ANTONIO LLOREDA
T.P. 10784
Código 231

JOSE ANTONIO LLOREDA
C.C. No. 17.159.681 de Bogotá

NOTARIA SEXTA
PABLO MENDEZ BARAJAS
NOTARIO SEXTO BOGOTA

Industria y Comercio
SUPERINTENDENCIA

83 80

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **02-103452**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION - PCT** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **532**, DE FECHA **30** DE **SEPTIEMBRE** DE **2003**, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **30** DE **DICIEMBRE** DE **2003**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____ _____ NO ____ X ____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCI
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, DC, 09 de enero de 2007

Apoderado: Alicia Lloreda Ricaurte Oficio:

ASUNTO Radicación: 02-103452 ... 609
Trámite 002
Evento 001
Actuación 430
Folios

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 le comunica:

Documentos estudiados:

- Capitulo descriptivo, folios 23 a 59;
- Capitulo reivindicatorio, folios 60 a 56;
- Solicitud PCT /01/11745 en fase nacional;
- Solicitud del examen de patentabilidad, folios 77 a 80;

Objeto de la invención:

El título de la invención "PROCESO PARA LA PREPARACIÓN DE COMPUESTOS BIFENILO"

Tienen como objeto un proceso para la obtención de un compuesto bifenilo del estado de la técnica.

El campo de la invención, según la Clasificación Internacional de Patentes:, C07C15/24, A61K 31/145

-Evaluación de la Unidad de Invención:

Esta solicitud de patente comprende más de una invención o un grupo de invenciones no relacionadas entre sí, de manera que se integra un único concepto inventivo conforme al artículo 25 de la Decisión 486 de la Comisión de la C munidad Andina.

Para el presente caso se conforman múltiples invenciones, de acuerdo a los procesos independientes, ya que los derivados bifenilo no son nuevos:

i-proceso para la preparación de compuestos bifenilo.

ii-Un proceso para reducir el dimero quiral a partir de los compuestos de formula I.

y se conforma la unidad inventiva con la o las características técnicas especiales, o sea, las características nuevas e inventivas que se aportan al estado de la técnica y que además se deben conservar en todas las reivindicaciones esas mismas características especiales.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: "*El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizo la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la solicitud PCT. Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

No.	Documento No.	Título	Fecha de Publicación
D1	WO0006537	N-substituted sulfonamide derivatives	10-feb-2000
D2	WO9733846	Process for preparing nitrobipheylene	18-sep-1997
D3	J.Org.Chem	Higly efficient and eccererated Suzuki Aryl couplings mediated by phosphine-free palladium sources	1994
D4	Chemicals note	The Suzuki reaction in biaryl ynthesis	1999

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

La solicitud en estudio reclama, "un proceso para la preparación de un compuesto bifenilo que comprende la combinación de un derivado del ácido fenilbórico con un derivado apropiado del benceno en presencia de un aditivo apropiado en un solvente orgánico apropiado con un catalizador apropiado y una base apropiada."

-La anterioridad D1 enseña procesos para la obtención de bifenilos, donde la reacción se lleva acabo usando como material de partida ácido 2-

fluorobencenboronico que reacciona con un derivado de bencénico, catalizado por un catalizador apropiado de paladio y una base por ejemplo como carbonato de potasio en un solvente como dioxano-agua, tal como se puede ver en la preparación 39 y en los ejemplos 45, 47, 51, 65, 73, 77, 86B, 94A, 123B, 132 a 142. Con lo que se demuestra claramente que la solicitud en estudio no tiene novedad.

-D2 describe un proceso para la obtención de compuestos bifenilos, donde la reacción se lleva a cabo entre un derivado de ácido fenilboronico de formula (IIIa) con un derivado halo-bencénico en presencia de un catalizador de paladio y una base apropiada y un solvente conveniente, tal como se describe y se reivindica en esta anterioridad, por lo tanto el proceso reclamado como nuevo en la presente solicitud ya era conocido en el estado de la técnica.

-D3 enseña un proceso versátil eficiente y acelerado para la síntesis de compuestos derivados biaril me diante el acople de Suzuki. Reaccionan aril haluros y arylsulfonatos derivados ácidos fenilboronicos, como se muestra en el esquema I, con catalizadores de paladio libres de fosfina, con una base como carbonato de potasio en un solvente como THF ó acetona o tolueno. Tal como se puede ver esta anterioridad se anticipa a describir lo que se reclama como nuevo en la presente solicitud.

-D4 enseña que para obtener compuestos biaril derivados, se puede hacer mediante la reacción descrita por Suzuki y Miyaura en 1981, que consiste en hacer reaccionar un derivado de ácido definil boronico con un arilbromuro en presencia de un catalizador de paladio en una base para obtener el correpondiente biaril, por lo tanto el proceso de síntesis reclamado en la solicitud en estudio no es nuevo, era conocido en el estado de la técnica.

Cuando una solicitud esta afectada su novedad, obviamente no posee nivel inventivo.

En conclusión los requisitos de Patentabilidad de la presente solicitud están afectadas así:

No.	Documento	Reivindicaiones	Requisito que afecta
D1	WO0006537	1 a 23	Novedad
D2	WO9733846	1 a 23	Novedad
D3	J.ORG.CHEM	1 a 23	Novedad
D4	Chemical Note	1 a 23	Novedad

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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 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.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 19 ENE. 2007

CONCEPTO TÉCNICO No. 46	EXAMINADOR TÉCNICOCódigo No.202012

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

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(74) Agents: LENTZ, Nelsen, L. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

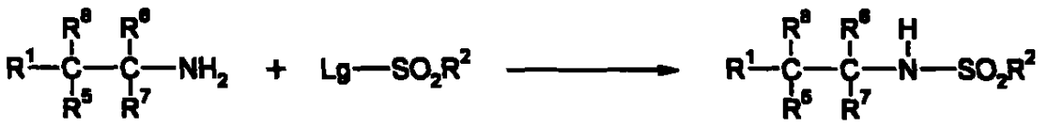
(54) Title: N-SUBSTITUTED SULFONAMIDE DERIVATIVES

(57) Abstract

The present invention provides certain N-substituted sulfonamide derivatives useful for potentiating glutamate receptor function in a mammal and therefore, useful for treating a wide variety of conditions, such as psychiatric and neurological disorders.

The compounds of formula I can be prepared from compounds of formula II.. Compounds of formula II can be prepared, for example, as described in Scheme I below. The reagents and starting materials are readily available to one of ordinary skill in the art. All the substituents, unless otherwise specified are previously defined.

Scheme I



formula III formula IV formula II

In Scheme I, the compound of formula III is reacted with the compound of formula IV under standard conditions well known in the art to provide the compound of formula II. The leaving atom or group represented by Lg may be, for example, a halogen atom such as a chlorine or bromine atom. The reaction is conveniently performed in the presence of a base, for example an alkali metal hydroxide, such as sodium hydroxide, an alkali metal carbonate such as potassium carbonate, or a tertiary amine such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene. Suitable solvents include halogenated hydrocarbons such as dichloromethane. The reaction is conveniently performed at a temperature in the range of from -20 to 100°C, preferably from -5 to 50°C.

In addition, the compounds of formula II in which R^1 represents a 4-bromophenyl group may conveniently be converted into other compounds of formula II in which R represents another 4-substituted phenyl group by reaction with an appropriate boronic acid derivative, for example, a benzeneboronic acid derivative. The reaction is conveniently performed in the presence of a tetrakis (triarylphosphine)palladium(0) catalyst, such as tetrakis (triphenylphosphine)palladium(0) and a base such as potassium carbonate. Convenient solvents for the reaction include aromatic hydrocarbons, such as toluene. The temperature at which the reaction is conducted is conveniently in the range of from 0 to 150°C, preferably 75 to 120°C. Bis aromatic intermediates useful in the preparation of compounds of formula II may be prepared by reacting

a bromoaromatic or bromoheteroaromatic compound with an aromatic or heteroaromatic boronic acid in an analogous manner.

The boronic acid derivative used as a starting material may be prepared by reacting a trialkyl borate, such as triisopropyl borate with an appropriate organolithium compound at reduced temperature. For example, 2-fluoro-benzeneboronic acid may be prepared by reacting 2-fluorobromobenzene with butyllithium in tetrahydrofuran at about -78°C to afford 2-fluorophenyl lithium, and then reacting this organolithium compound with triisopropyl borate..

Alternatively, the compounds of formula II in which R^1 represents a 4-bromophenyl group may be converted to a 4-(trimethylstannyl)phenyl or 4-(tri-*n*-butylstannyl)phenyl group by treatment of the corresponding bromide with a palladium(0) catalyst, such as tetrakis(triphenylphosphine)-palladium(0) and hexaalkyldistannane, where the alkyl group is methyl or *n*-butyl, in an aprotic solvent such as toluene in the presence of a tertiary amine base such as triethyl-amine, at temperatures ranging from 80 to 140°C, preferably from 90 to 110°C.

The compounds of formula II in which R^1 represents a 4-(tri-*n*-butylstannyl)phenyl group may then be reacted with an aryl- or heteroarylbromide, such as 2-bromothiophene-5-carboxaldehyde, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0), or a palladium(II) catalyst, such as bis(triphenylphosphine)-palladium(II) dichloride, in an aprotic solvent, such as dioxane, at temperatures ranging from 80 to 140°C, preferably from 90 to 110°C, to afford the corresponding 4-(aryl)phenyl or 4-(heteroaryl)phenyl substituted compound.

The compounds of formula II in which R^1 represents a 4-bromophenyl group may be converted into other compounds of formula II in which R^1 represents a 4-substituted alkyl- or cycloalkylphenyl group, such as 4-cyclopentylphenyl by treatment of the corresponding bromide with an appropriate alkyl- or cycloalkyl Grignard reagent, such as cyclopentyl-magnesium bromide, in the presence of a palladium(II) catalyst, such as [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)($PdCl_2$(dppf)), in an

dichloromethane. The organics were concentrated in vacuo to afford 3.0 g of the title compound (83%).

Preparation 39

N-2-(4-bromophenyl)propyl 2-propanesulfonamide

A solution of 15.0 g (59.9 mmol) of the material from Preparation 31 and 18.4 mL (131.8 mmol) of triethylamine in 150 mL of dichloromethane was stirred 20 min at room temperature, then cooled to 0°C and treated dropwise over 5 min with 8.1 mL (71.9 mmol) of 2-propylsulfonyl chloride in 10 mL of dichloromethane. After stirring overnight at room temperature, the reaction was washed once with 200 mL of 10% aqueous sodium bisulfate, the layers separated and the aqueous layer extracted twice with 100 mL each of dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (500 g of silica gel, 30% ethyl acetate/ hexane) of the residue afforded 11.0 g (57%) of the title compound.

Preparation 40

N-2-(4-tri-n-butylstannylphenyl)propyl 2-propanesulfonamide

To a degassed solution of 4.8 g (15.1 mmol) of material from Preparation 39, 2.1 mL (15.1 mmol) of triethylamine and 8.0 mL (15.9 mmol) of hexabutylditin in 35 mL of toluene add 0.9 g (0.8 mmol) of tetrakis (triphenylphosphine) palladium (0). The mixture was heated to 100° C for 16 hours, cooled to room temperature and diluted with 35 mL of ethyl acetate. The mixture was washed with 50 mL of 10% aqueous sodium bisulfate, the organic layer was separated and the aqueous layer was extracted two times with 50 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (350 g of silica gel, 20 % ethyl acetate/hexane) of the residue afforded 3.5 g (44%) of the title compound as a clear, colorless oil.

Analysis calculated for $C_{24}H_{45}NO_2SSn$: %C, 54.35; %H, 8.55; %N, 2.64. Found: %C, 54.41; %H, 8.16; %N, 2.74.

Mass Spectrum: M = 530.

gel, 35% ethyl acetate/hexane) of the residue afforded 1.5 g (37%) of the title compound.

EXAMPLE 44

N-1-methyl-2-(4-(2-fluorophenyl)phenyl)ethyl 2-methanesulfonamide

To a degassed solution of 1.5 g (5.1 mmol) of the product of Example 43, 1.1 g (7.7 mmol) of the product of Preparation 3 and 1.1 g (7.7 mmol) of potassium carbonate in 20 mL of toluene was added 0.3 g (0.2 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90°C for 18 hours. It was then cooled to ambient temperature and 20 mL of water were added. The organic layer was separated and the aqueous layer was extracted three times with 10 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was suspended in diethyl ether and filtered to afford 0.673 g (43%) of the title compound.

Field Desorption Mass Spectrum: M = 307

Analysis for $C_{16}H_{18}FNO_2S$:

Theory:	C, 62.52; H, 5.90; N, 4.56.
Found:	C, 62.26; H, 5.92; N, 4.49.

EXAMPLE 45

N-2-(4-(4-formylphenyl)phenyl)propyl 2-propanesulfonamide

A degassed solution of 2.4 g (7.5 mmol) of the material from Preparation 39, 1.7 g (11.2 mmol) of 4-formylphenylboronic acid, 1.6 g (11.2 mmol) of potassium carbonate and 0.4 g (0.4 mmol) of tetrakis(triphenyl-phosphine)palladium(0) in 33 mL of dioxane and 11 mL of water was heated to 100°C overnight. The mixture was cooled to room temperature, diluted with 20 mL of water, and extracted three times with 50 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (175 g of silica gel, 35% ethyl acetate/hexane) of the residue afforded 1.8 g (71%) of the title compound.

between 10 mL of dichloromethane and 5 mL of 5 N aqueous sodium hydroxide. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting solid was suspended in hexane, filtered, rinsed once with hexane and dried *in vacuo* at ambient temperature to afford 0.4 g (88%) of the title compound.

Analysis calculated for $C_{20}H_{28}N_2O_2S$: %C, 66.63; %H, 7.83; %N, 7.77. Found: %C, 66.93; %H, 7.79; %N, 7.94.

Mass Spectrum: M = 360.

EXAMPLE 51

N-2-(4-(4-(2-methanesulfonamido ethyl)phenyl)phenyl)propyl 2-propanesulfonamide

To a room temperature solution of 0.1 g (0.3 mmol) of material from Example 50 and 0.06 mL (0.4 mmol) of triethylamine in 2 mL of dichloromethane was added 0.03 mL (0.4 mmol) of methanesulfonyl chloride. The mixture was stirred at ambient temperature for 16 hours. Chromatography (10 g silica gel, 50% ethyl acetate/hexane) of the reaction mixture afforded 0.1 g (94%) of the title compound.

Analysis calculated for $C_{21}H_{30}N_2O_4S_2$: %C, 57.51; %H, 6.89; %N, 6.39. Found: %C, 57.90; %H, 6.72; %N, 6.33.

Mass Spectrum: M = 438.

EXAMPLE 52

N-2-(4-(4-hydroxymethyl)phenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.5 mmol) of material from Example 45 in 5 mL ethanol was added 0.06 g (1.5 mmol) of sodium borohydride. The mixture was stirred at ambient temperature for 16 hours, concentrated *in vacuo* and partitioned between 10 mL of ethyl acetate and 5 mL of water. The organic layer was separated and the aqueous portion was extracted three times with 5 mL each of ethyl acetate. The combined organics were dried (MgSO4), filtered and

Analysis calculated for $C_{14}H_{21}N_5O_2S$: %C, 51.99; %H, 6.54; %N, 21.65. Found: %C, 52.28; %H, 6.54; %N, 21.83.
Mass Spectrum: M = 323.

EXAMPLE 65

N-2-(4-(2-thiazolyl)phenyl)propyl 2-propanesulfonamide

A solution of 0.7 g (2.1 mmol) of material from Preparation 39, 0.5 g (2.2 mmol) of material from Preparation 46 and 0.1 g (0.1 mmol) of tetrakis-(triphenylphosphine)palladium(0) in 6 mL of dioxane was heated to 100°C for 16 hours. The mixture was cooled to ambient temperature, diluted with 10 mL of ethyl ether and washed once with 10 mL of saturated aqueous potassium fluoride. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of ethyl ether. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (30 g of silica gel, 45% ethyl acetate/hexane) of the residue afforded an oil which was crystallized from ethyl ether, filtered and dried *in vacuo* at 60°C to afford 0.3 g (41%) of the title compound.
Analysis calculated for $C_{15}H_{20}N_2O_2S_2$: %C, 55.53; %H, 6.21; %N, 8.63. Found: %C, 55.75; %H, 6.29; %N, 8.63.
Mass Spectrum: M = 324.

EXAMPLE 66

N-2-(4-(2-(4S-methoxycarbonyl-4,5-dihydro)thiazolyl)phenyl)propyl 2-propanesulfonamide

A solution of 0.3 g (0.9 mmol) of material from Example 53, 0.3 g (1.9 mmol) of L-cysteine methyl ester hydrochloride and 0.3 mL (1.9 mmol) of triethylamine in 5 mL of ethanol was heated to reflux for 16 hours. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was dissolved in 5 mL of ethyl acetate and washed once with 5 mL of water. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of ethyl acetate. The combined organic were dried ($MgSO_4$),

EXAMPLE 73

N-2-(4-4-carboxyphenyl)phenyl)propyl 2-propanesulfonamide

To a degassed solution of 1.0 g (3.1 mmol) of material from Preparation 39, 0.8 g (4.7 mmol) of 4-carboxyphenylboronic acid and 0.7 g (4.7 mmol) of potassium carbonate in 20 mL of 75% dioxane/water was added 0.2 g (0.2 mmol) of tetrakis(triphenylphosphine)-palladium(0). The mixture was heated to 100°C for 16 hours, cooled to ambient temperature and diluted with 15 mL of 10% aqueous sodium bisulfate. The mixture was extracted three times with 20 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallization of the residue from chlorobutane afforded 0.4 g (37%) of the title compound. A 0.1 g sample was recrystallized to afford 0.07 g of pure title compound.

Analysis calculated for $C_{19}H_{23}NO_4S$: %C, 63.14; %H, 6.41; %N, 3.88. Found: %C, 63.25; %H, 6.42; %N, 3.79.

Mass Spectrum: M = 361.

EXAMPLE 74

N-2-(4-(4-carbamoylphenyl)phenyl)propyl 2-propanesulfonamide

To a 0°C solution of 0.3 g (0.9 mmol) of material from Example 73 and 0.1 mL (0.9 mmol) of 4-methyl-morpholine in 5 mL of dichloromethane was added 0.1 mL (0.9 mmol) of isobutylchloroformate and the mixture was stirred at 0°C for 30 minutes. One third of the mixture was added to 2 mL of 2.0 M ammonia in methanol at 0°C and the cooling bath was removed. After 20 minutes, the resulting solid was filtered and dried *in vacuo* at 60°C to afford 0.034 g (33%) of the title compound.

Analysis calculated for $C_{19}H_{24}N_2O_3$: %C, 63.31; %H, 6.71; %N,7.77. Found: %C, 63.68; %H, 6.85; %N, 7.61.

Mass Spectrum: M = 360.

EXAMPLE 77

N-2-(4-(4-acetylphenyl)phenyl)propyl 2-propanesulfonamide

To a degassed solution of 1.0 g (3.1 mmol) of material from Preparation 39, 0.8 g (4.7 mmol) of 4-acetylphenylboronic acid and 0.7 g (4.7 mmol) of potassium carbonate in 20 mL of 75% dioxane/water was added 0.2 g (0.2 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was heated to 100°C for 4.5 hours, cooled to ambient temperature and diluted with 15 mL of water. The resulting solid was filtered, dried and recrystallized from chlorobutane to afford 0.7 g (65%) of the title compound.

Analysis calculated for $C_{20}H_{25}NO_3S$: %C, 66.82; %H, 7.01; %N, 3.90. Found: %C, 66.95; %H, 7.16; %N, 3.63.

Mass Spectrum: M = 359.

EXAMPLE 78

N-2-(4-(2-(5-formyl)thienyl)phenyl)propyl 2-propanesulfonamide

To a degassed solution of 0.4 g (0.8 mmol) of material from Preparation 40 and 0.09 mL (0.8 mmol) of 5-bromo-2-thiophenecarboxaldehyde in 3 mL of dioxane was added 0.05 g (0.04 mmol) of tetrakis(triphenylphosphine)-palladium(0). The mixture was heated to 100°C for 16 hours, 0.04 mL (0.4 mmol) of 5-bromo-2-thiophene-carboxaldehyde was added and heating was continued for 6 hours. The mixture was cooled to ambient temperature and concentrated *in vacuo*. Chromatography (25 g silica gel, 35% ethyl acetate/hexane) of the residue afforded a solid which was suspended in ethyl ether, filtered and dried *in vacuo* to afford 0.06 g (24%) of the title compound.

Analysis calculated for $C_{17}H_{21}NO_3S_2$: %C, 58.09; %H, 6.02; %N, 3.99. Found: %C, 58.22; %H, 6.07; %N, 3.69.

Mass Spectrum: M = 351.

EXAMPLE 79

N-2-(4-(2-(5-hydroxymethyl)thienyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.03 g (0.08 mmol) of material from Example 78 in 1 mL ethanol was added 0.003 g (0.08 mmol) of sodium borohydride. The mixture was

for 16 hours. The mixture was cooled to ambient temperature and chromatographed (25 g silica gel, 35% ethyl acetate/-hexane) to afford an oil which was crystallized from chlorobutane/hexane to afford 0.06 g (20%) of the title compound.

Analysis calculated for $C_{18}H_{24}N_2O_2S$: %C, 65.03; %H, 7.28; %N, 8.43. Found: %C, 65.17; %H, 7.40; %N, 8.29.

Mass Spectrum: M = 332.

EXAMPLE 82

N-2-(4-(4-phenyl)phenyl)propyl 2-propanesulfonamide

To a degassed solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.3 g (2.3 mmol) of phenylboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 9 mL of 7: dioxane/water was added 0.09 g (0.08 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was heated to 100°C for 16 hours, cooled to ambient temperature and diluted with 5 mL of water. The mixture was extracted three times with 5 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (25 g of silica gel, 25% ethyl acetate/hexane) of the residue afforded 0.4 g (71%) of the title compound.

Analysis calculated for $C_{18}H_{23}NO_2S$: %C, 68.14; %H, 7.30; %N, 4.41. Found: %C, 67.81; %H, 7.23; %N, 4.61.

Mass Spectrum: M = 317.

EXAMPLE 83

N-2-(4-(2-(5-carboxy)thiazolyl)phenyl)propyl 2-propanesulfonamide

To a solution of 1.4 g (3.7 mmol) of material from Example 80, in 25 mL of 4:1 methanol/tetrahydrofuran was added 4.1 mL (4.1 mmol) of 1 N aqueous sodium hydroxide. After 5 hours was added 1.0 mL (1.0 mmol) of 1 N aqueous sodium hydroxide. The mixture stirred for 16 hours and was concentrated *in vacuo*. The residue was dissolved in 25 mL of water and extracted once with ethyl ether. The organic layer was discarded and the aqueous layer was acidified to pH 2 with 10% aqueous sodium bisulfate. The aqueous layer was

organic layer was separated, washed once with 1 N aqueous sodium hydroxide, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in 1 mL of dichloromethane, filtered through a plug of silica gel eluting with 35% ethyl acetate/hexane and concentrated *in vacuo* to afford 0.1 g (72%) of the title compound.

Analysis calculated for $C_{18}H_{20}NO_2S_2$ Br: %C, 47.76; %H, 5.01; %N, 3.48. Found: %C, 48.02; %H, 5.22; %N, 3.48.

Mass Spectrum: M +2 = 404.

EXAMPLE 86

N-2-(4-(4-(2-(N-(t-butoxycarbonyl)methylsulfonamido)ethanoyl)-phenyl)phenyl)propyl 2-propanesulfonamide

A. N-(4-tri-n-butylstannylphenyl)carbonylmethyl-N-t-butoxycarbonyl-methanesulfonamide. To a degassed solution of 5.0 g (12.7 mmol) of material from Preparation 44 (Step B), 7.1 mL (14.0 mmol) of bis(tributyltin) and 2.0 mL (14.0 mmol) of triethylamine in 35 mL of toluene was added 0.7 g (0.6 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was heated to reflux for 16 hours, cooled to ambient temperature and diluted with 35 mL of ethyl acetate. The mixture was washed once with 30 mL of 10% aqueous sodium bisulfate, the organic layer was separated and the aqueous layer was extracted three times with 15 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (200 g of silica gel, 5% ethyl acetate/hexane) of the residue afforded 2.2 g (28%) of the title compound.

Analysis calculated for $C_{28}H_{49}NO_5S$ Sn: %C, 51.84; %H, 7.53; %N, 2.33. Found: %C, 52.12; %H, 7.56; %N, 2.57.

Mass Spectrum: M+2 = 604.

B. To a degassed solution of 1.1 g (3.5 mmol) of material from Preparation 39, 2.1 g (3.5 mmol) of material from Step A in 10 mL of toluene was added 0.2g (0.2 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was heated to 92°C for 16 hours, 0.2g (0.2 mmol) of tetrakis(triphenylphosphine)palladium(0) was added and heating continued for four hours. The mixture was cooled to ambient temperature and diluted with 5 mL of ethyl acetate. 5 mL of saturated

aqueous potassium fluoride was added and the mixture stirred for one hour. The mixture was filtered through diatomaceous earth, the organic layer was separated and the aqueous layer was extracted three times with 5 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (50 g of silica gel, 40% ethyl acetate/hexane) of the residue afforded a tan solid which was suspended in ethyl ether, filtered and dried *in vacuo* to afford 0.2 g (10%) of the title compound.
Analysis calculated for $C_{28}H_{36}N_2O_7S_2$: %C, 56.50; %H, 6.57; %N, 5.07. Found: %C, 56.56; %H, 6.73; %N, 5.18.
Mass Spectrum: M = 552.

EXAMPLE 87

N-2-(4-(4-(2-methanesulfonamido)-ethanoyl)phenyl)phenyl)propyl 2-propanesulfonamide

A solution of 0.2 g (0.3 mmol) of material from Example 86 in 2.5 mL of 20% trifluoroacetic acid/-dichloromethane was stirred at ambient temperature for 1.5 hours. The mixture was concentrated *in vacuo*, dissolved in 5 mL of dichloromethane and washed with 5 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography (10 g of silica gel, 60% ethyl acetate/hexane) of the residue afforded 0.1 g (60%) of the title compound.
Analysis calculated for $C_{21}H_{28}N_2O_5S_2$: %C, 55.73; %H, 6.24; %N, 6.19. Found: %C, 55.44; %H, 6.17; %N, 6.15.
Mass Spectrum: M = 452.

EXAMPLE 88

N-2-(4-(4-(4-(1,1-dioxotetrahydro-1,2-thiazinyl)phenyl)phenyl)propyl 2-propanesulfonamide

A solution of 0.1 g (0.4 mmol) of material from Preparation 49 and 0.2 g (0.4 mmol) of material from Preparation 40 in 2 mL of 20% dioxane/toluene was

Analysis calculated for $C_{16}H_{25}N_5O_2S$: %C, 54.68; %H, 7.17; %N, 19.93. Found: %C, 54.78; %H, 6.93; %N, 19.76.
Mass Spectrum: M + 1 = 352.

Example 93

N-2-(4-(5-(2-prop-3-enyl)tetrazolyl)phenyl)propyl 2-propanesulfonamide

The title compound was prepared from the product of Example 63 as described in Example 64 with the exception that allyl bromide was used instead of iodomethane.

Analysis calculated for $C_{16}H_{23}N_5O_2S$: %C, 54.99; %H, 6.63; %N, 20.04. Found: %C, 54.99; %H, 6.40; %N, 19.77.
Mass Spectrum: M + 1 = 350.

Example 94

N-2-(4-(4-aminophenyl)phenyl)propyl 2-propanesulfonamide

A. N-2-(4-(4-t-butoxycarbonylaminophenyl)phenyl)propyl 2-propanesulfonamide: A degassed solution of 0.9 g (2.9 mmol) of material from Example 39, 1.4 g (2.8 mmol) of material from Preparation 51 and 0.2 g (0.1 mmol) of tetrakis(triphenylphosphine)palladium(0) in 10 mL of toluene was heated to reflux for 5 hours. The mixture was cooled to ambient temperature and concentrated *in vacuo*. Chromatography (100 g of silica gel, 30% ethyl acetate/hexane) of the residue afforded 0.15 g (12%) of the title compound.
Mass Spectrum: M = 432.

B. A solution of 0.2 g (0.5 mmol) of material from Step A in 2.5 mL of 20% trifluoroacetic acid/-dichloromethane was stirred at ambient temperature for two hours. The mixture was concentrated *in vacuo*, dissolved in 2 mL of dichloromethane and washed once with 1 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted three times with 1 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was crystallized from chlorobutane/hexane to afford 0.03 g (20%) of the title compound.

EXAMPLE 122

N-2-(4-(4-cyanophenyl)phenyl)ethyl 2-propanesulfonamide

To a solution of 1.7 g (3.4 mmol) of material from Preparation 48 and 0.6 g (3.4 mmol)of 4-bromobenzonitrile in 10 mL of toluene was added 0.2 g (0.17 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 100 °C for 18 h. The mixture was cooled and the solid was filtered and rinsed with 10 mL hexane to afforded 0.4 g (36%) of the title compound.
Analysis calculated for $C_{18}H_{20}N_2O_2S$: %C, 65.83; %H, 6.14; %N, 8.53.
Found: %C, 65.61; %H, 5.87; %N, 8.44.
Field Desorption Mass Spectrum: M = 328.

EXAMPLE 123

N-2-(4-(4-N',N'-diethylaminophenyl)phenyl)propyl 2-propanesulfonamide

A. 4-N,N-diethylaminobenzeneboronic acid: A solution of 10 g (43.8 mmol) of 4-bromo-N,N-diethylaniline in 150 mL of tetrahydrofuran was cooled to -78 °C and 30 mL (48.2 mmol) of 1.6M n-butyllithium was added dropwise. The mixture was stirred at -78 °C for 60 min then 15.2 mL (65.7 mmol) of triisopropyl borate was added dropwise and stirring was continued for 60 min. The cooling bath was removed and then 75 mL of water and 5N hydrochloric acid was added until pH=6 and stirring was continued for 18 h. The aqueous layer was separated and the organic layer was extracted two times with 25 mL each of 1N sodium hydroxide. The combined aqueous extracts were acidified with conc. hydrochloric acid to pH=7. The resulting solid was filtered and washed with 20 mL methyl alcohol to 2.8 g (33%) of the title compound.

B. To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.36 g (1.9 mmol) of material from Example 123A and 0.33 g (2.4 mmol) of potassium carbonate in 4 mL of dioxane and 1 mL of water was added 0.09 g (0.07 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 10 mL of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer

was extracted three times with 5 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (25 g of silica gel, 25% ethyl acetate/hexane) of the residue afforded 0.38 g (61%) of the title compound.

Analysis calculated for $C_{22}H_{32}N_2O_2S$: %C, 68.00; %H, 8.30; %N, 7.21.
Found: %C, 67.70; %H, 8.52; %N, 6.98.
Field Desorption Mass Spectrum: M = 388.

EXAMPLE 124

N-2-(4-(2-fluorophenyl)phenyl)propyl 1-chloromethanesulfonamide

A solution of 0.4 g (1.7 mmol) of material from Preparation 6 and 0.27 mL (1.9 mmol) of triethylamine in 10 mL of dichloromethane was cooled to 0 °C. A solution of 0.15 mL (1.7 mmol) of methanesulfonyl chloride in 1 mL of dichloromethane was added. The ice-bath was removed and the mixture was stirred at room temperature for 3 h. The mixture was washed with 10 mL of 10% aqueous sodium bisulfate, the organic layer was separated and the aqueous layer extracted three times with 5 mL of 1:1 dichloromethane/ether. The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo to afford 0.60 g (100%) of the title compound.

Analysis calculated for $C_{16}H_{17}ClFNO_2S$: %C, 56.22; %H, 5.01; %N, 4.10.
Found: %C, 56.55; %H, 5.27; %N, 4.10.
Field Desorption Mass Spectrum: M = 341.

EXAMPLE 125

N-2-(4-(4-(1-(2-(2-propane)sulfonylamino)propyl)phenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 1.3 g (2.5 mmol) of material from Preparation 40 and 0.65 g (5.0 mmol)of 3-chloro-6-methyl pyridazine in 10 mL of toluene was added 0.14 g (0.12 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled and filtered through diatomaceous earth and rinsed with 10 mL ethyl acetate. The filtrate was

EXAMPLE 132

N-2-(4-(3-acetylphenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 3.2 g (10.2 mmol) of material from Preparation 39, 2.0 g (12.2 mmol) of 3-acetylbenzeneboronic acid and 2.1 g (15.2 mmol) of potassium carbonate in 28 mL of dioxane and 7 mL of water was added 0.59 g (0.51 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 30 mL of water and 30 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 10 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (150 g of silica gel, 35% ethyl acetate/hexane) of the residue afforded 2.4 g (66%) of the title compound.

Analysis calculated for $C_{20}H_{25}NO_3S$: %C, 66.82; %H, 7.01; %N, 3.89. Found: %C, 66.38; %H, 6.96; %N, 3.73.

Field Desorption Mass Spectrum: M = 359.

EXAMPLE 133

N-2-(4-(3-(1-hydroxyethyl)phenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.4 mmol) of material from Example 132 in 5 mL of ethyl alcohol was added 0.05 g (1.4 mmol) of sodium borohydride. The mixture was stirred at ambient temperature for 2 hr, concentrated in vacuo and then 10 mL of ethyl acetate and 10 mL of water was added. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (40 g of silica gel, 50% ethyl acetate/hexane) of the residue afforded 0.3 g (65%) of the title compound.

Analysis calculated for $C_{20}H_{27}NO_3S$: %C, 66.40; %H, 7.53; %N, 3.87. Found: %C, 66.56; %H, 7.65; %N, 3.92.

Field Desorption Mass Spectrum: M = 361.

EXAMPLE 134

N-2-(4-(2-benzothienyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.5 mmol) of material from Preparation 39, 0.3 g (1.9mmol) of benzo[b]thiophene-2-boronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 4 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL of water and 5 mL of ether and 10 mL ethyl acetate was added. The mixture was concentrated in vacuo and the residue was dissolved in 10 mL of ethyl acetate and washed with 10 mL of brine. The organic layer was separated and dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (50 g of silica gel, 35% ethyl acetate/hexane) of the residue afforded 0.08 g (14%) of the title compound.

Analysis calculated for $C_{20}H_{23}NO_2S_2$*0.1 $CHCl_3$: %C, 62.40; %H, 6.07; %N, 3.63. Found: %C, 62.63; %H, 6.04; %N, 3.63.

Field Desorption Mass Spectrum: M = 373.

EXAMPLE 135

N-2-(4-(3,4-dichlorophenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.4 g (1.9 mmol) of 3,4-dichlorobenzeneboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (75 g of silica gel, 35% ethyl acetate/hexane) of the residue afforded 0.52 g (86%) of the title compound. A second chromatography (40 g of silica gel, 35% ethyl acetate/hexane) of the title compound afforded 0.25 g (41%) of the title compound.

Analysis calculated for $C_{18}H_{21}Cl_2NO_2S$: %C, 55.95; %H, 5.48; %N, 3.62.
Found: %C, 56.22; %H, 5.28; %N, 3.56.
Field Desorption Mass Spectrum: M-1 = 385.

EXAMPLE 136

N-2-(4-(4-methylphenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.25 g (1.9 mmol) of 4-methylbenzeneboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (30 g of silica gel, 35% ethyl acetate/hexane) of the residue afforded 0.42 g (82%) of the title compound. A second chromatography (25 g of silica gel, 35% ethyl acetate/hexane) of the title compound afforded 0.24 g (46%) of the title compound.
Analysis calculated for $C_{19}H_{25}NO_2S$: %C, 68.80; %H, 7.60; %N, 4.20. Found: %C, 69.11; %H, 7.70; %N, 4.10.
Field Desorption Mass Spectrum: M = 331.

EXAMPLE 137

N-2-(4-(4-chlorophenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.29 g (1.9 mmol) of 4-chlorobenzeneboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 3 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo.

Chromatography (35 g of silica gel, 35% ethyl acetate/hexane) of the residue afforded 0.36 g of the title compound. The compound was recrystallized to purity with ether to afford 0.36 g (65%) of the title compound.

Analysis calculated for $C_{18}H_{22}ClNO_2S$: %C, 61.40; %H, 6.30; %N, 3.98.

Found: %C, 61.48; %H, 6.11; %N, 3.62.

Field Desorption Mass Spectrum: M = 351.

EXAMPLE 138

N-2-(4-(2-methylphenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.25 g (1.9 mmol) of 2-methylbenzeneboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 4 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo.

Chromatography (30 g of silica gel, 30% ethyl acetate/hexane) of the residue afforded 0.35 g (68%) of the title compound.

Analysis calculated for $C_{19}H_{25}NO_2S$: %C, 68.8; %H, 7.60; %N, 4.20. Found: %C, 68.82; %H, 7.75; %N, 4.23.

Field Desorption Mass Spectrum: M = 331.

EXAMPLE 139

N-2-(4-(3,5-dichlorophenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.36 g (1.9 mmol) of 3,5-dichlorobenzeneboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 hr and then 0.36 g (1.9 mmol) of 3,5-dichlorobenzeneboronic acid was added. The mixture was heated at 90 °C for another 18 h. The mixture was cooled to room temperature and 10 mL of water

and 10 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (35 g of silica gel, 10% ethyl acetate/toluene) of the residue afforded 0.36 g (60%) of the title compound.

Analysis calculated for $C_{18}H_{21}NCl_2O_2S$: %C, 55.90; %H, 5.50; %N, 3.60.

Found: %C, 56.22; %H, 5.50; %N, 3.39.

Field Desorption Mass Spectrum: M-1 = 385.

EXAMPLE 140

N-2-(4-(4-trifluoromethylphenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.35 g (1.9 mmol) of 4-trifluoromethylbenzeneboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 4 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (50 g of silica gel, 20% ethyl acetate/hexane) of the residue afforded 0.40 g (67%) of the title compound.

Analysis calculated for $C_{19}H_{22}F_3NO_2S$: %C, 59.20; %H, 5.75; %N, 3.60.

Found: %C, 59.14; %H, 5.67; %N, 3.34.

Field Desorption Mass Spectrum: M = 385.

EXAMPLE 141

N-2-(4-(3-trifluoromethylphenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.35 g (1.9 mmol) of 3-trifluoromethylbenzeneboronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL

of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 4 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (50 g of silica gel, 20% ethyl acetate/hexane) of the residue afforded 0.44 g (73%) of the title compound.

Analysis calculated for $C_{19}H_{22}F_3NO_2S$: %C, 59.20; %H, 5.75; %N, 3.60.

Found: %C, 59.20; %H, 5.72; %N, 3.62.

Field Desorption Mass Spectrum: M = 385.

EXAMPLE 142

N-2-(4-(3-nitrophenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.6 mmol) of material from Preparation 39, 0.31 g (1.9 mmol) of 3-nitrobenzene-boronic acid and 0.3 g (2.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.09 g (0.08 mmol) of tetrakis (triphenylphosphine) palladium(0). The mixture was heated at 90 °C for 18 h. The mixture was cooled to room temperature and 5 mL of water and 5 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 4 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (50 g of silica gel, 35% ethyl acetate/hexane) of the residue afforded 0.40 g (71%) of the title compound.

Analysis calculated for $C_{18}H_{22}N_2O_4S$: %C, 59.60; %H, 6.12; %N, 7.73.

Found: %C, 59.59; %H, 6.07; %N, 7.74.

Field Desorption Mass Spectrum: M = 362.

EXAMPLE 143

N-2-(4-(3-thienyl)phenyl)propyl 1-(2-methyl)-propanesulfonamide

A. Isobutylsulfonyl chloride: A solution of diisobutyldisulfide 13 g (73 mmol) in 100 mL of water is cooled to 0 °C. Chlorine gas was bubbled through the aqueous solution until a yellow solution persists and then nitrogen gas was bubbled through for 15 min. The reaction mixture was diluted with 100 mL of

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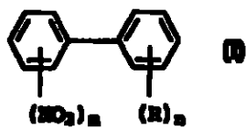
Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: PROCESS FOR PREPARING NITROBIPHENYLENE

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON NITROBIPHENYLEN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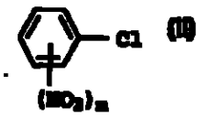
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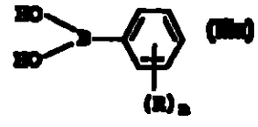

(IIIa)

(57) Abstract

The invention concerns a process for preparing nitrobiphenylene of formula (I) wherein n stands for 1 or 2, R means halogen, R' or OR', R' being a C-organic group which can carry groups which are inert in the reaction conditions, n stands for 0, 1, 2 or 3 and, if n is 2 or 3, the R groups can also be different. According to the invention, a chloronitrobenzene of formula (II) is reacted in the presence of a palladium catalyst and a base in a solvent with a phenyl boric acid (IIIa), one of its alkyl esters of formula (IIIb), R^1 meaning C_1-C_6 alkyl, or one of its anhydrides. The compounds (I) are suitable as initial products for biphenylenines which are in turn intermediate products for fungicidal plant-growth substances.

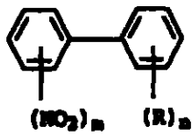
(57) Zusammenfassung

Verfahren zur Herstellung von Nitrobiphenylen der Formel (I), in der n für 1 oder 2 steht, R Halogen, R' oder OR' bedeutet, wobei R' ein C-organischer Rest ist, welcher unter den Reaktionsbedingungen inerte Gruppen tragen kann, wobei n für 0, 1, 2 oder 3 steht, und im Falle, daß n 2 oder 3 ist, die Reste R auch verschieden sein können, indem man ein Chlornitrobenzol der Formel (II) in Gegenwart eines Palladium-Katalysators und einer Base in einem Lösungsmittel mit einer Phenylborsäure (IIIa) einem ihrer Alkylester der Formel (IIIb), wobei R^1 die Bedeutung C_1-C_6-Alkyl hat, oder einem ihrer Anhydride umsetzt. Die Verbindungen (I) eignen sich als Vorprodukte für Biphenylenine, welche ihrerseits Zwischenprodukte sind für fungizide Pflanzenschutz-Wirkstoffe.

Verfahren zur Herstellung von Nitrobiphenylen

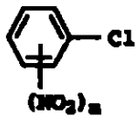
Beschreibung

Die vorliegende Erfindung betrifft ein Verfahren zur Herstellung von Nitrobiphenylen der Formel I



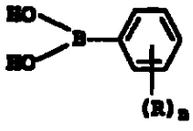
(I)

in der n für 1 oder 2 steht, R Halogen, R' oder OR' bedeutet, wobei R' ein C-organischer Rest ist, welcher unter den Reaktionsbedingungen inerte Gruppen tragen kann, wobei n für 0, 1, 2 oder 3 steht und im Falle, daß n 2 oder 3 ist, die Reste R auch verschieden sein können, welches dadurch gekennzeichnet ist, daß man ein Chlornitrobenzol der Formel II

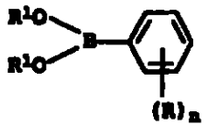


(II)

in Gegenwart eines Palladium-Katalysators und einer Base in einem Lösungsmittel mit einer Phenylboronsäure (IIIa)



(IIIa)



(IIIb)

einem ihrer Alkylester der Formel IIIb, wobei R^1 die Bedeutung C_1-C_6-Alkyl hat, oder einem ihrer Anhydride umsetzt.

Aus Synth. Commun. 11, Seite 513 (1981) ist bekannt, daß Phenylboronsäure mit Chlorbenzol in Gegenwart von Tetrakis(triphenylphosphan)palladium und Natriumethanolat nicht zu Biphenyl gekuppelt werden kann.

Tetrahedron Lett. 32, Seite 2277 (1991) ist zu entnehmen, daß die Kupplungsreaktion zwischen Phenylboronsäure und Chlorbenzol bei Verwendung des Katalysators [1,4-bis-(Diphenylphosphan)butan]pal-

ladium(II)dichlorid mit einer Ausbeute von lediglich 28 % verläuft.

Der vorliegenden Erfindung lag daher die Aufgabe zugrunde, ein wirtschaftliches Verfahren zur Herstellung von Nitrobiphenylen bereitzustellen, welches mit gut zugänglichen Palladium-Katalysatoren arbeitet.

Demgemäß wurde das eingangs definierte Verfahren gefunden.

Die Phenylboronsäuren IIIa, deren Ester IIIb und Anhydride wie IIIc, welche im folgenden zusammenfassend als "Borverbindungen III" bezeichnet werden, sind allgemein bekannt oder in an sich bekannter Weise erhältlich (vgl. z.B. Org. Synth. Coll. Vol. IV, Seite 68).

Bevorzugte C-organische Reste R' sind:

- Alkyl- und Alkenylgruppen, insbesondere mit 1 bis 12 Kohlenstoffatomen wie Methyl, Ethyl, Propyl, Butyl und Allyl,

- Alkylcarbonyl- und Alkoxycarbonylgruppen, insbesondere mit 1 bis 6 Kohlenstoffatomen wie Acetyl, Methoxycarbonyl und Ethoxycarbonyl,

- Cycloalkylgruppen, insbesondere mit 3 bis 10 Kohlenstoffatomen wie Cyclopentyl, Cyclohexyl und 1-Methylcyclohexyl sowie

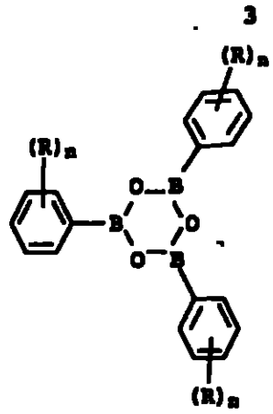
- Phenyl- und Phenoxygruppen.

Unter den Reaktionsbedingungen inerte Substituenten des C-organischen Restes R' sind vorzugsweise Halogen und daneben Alkyl- und Alkoxygruppen.

Weitere C-organische Reste R' sind:

- Cyano- und die Formylgruppen (-CHO)

In den Anhydriden sind normalerweise Produkte der Zusammenlagerung von zwei oder mehreren Äquivalenten Phenylboronsäure IIIa unter Wasseraustritt, welche intermolekulare B-O-B-Brücken enthalten. Bevorzugt sind cyclische Anhydride der Formel IIIc.



(IIIc)

Bei den Stoffmengenangaben, welche sich auf die Borverbindungen III beziehen, ist das im folgenden zu berücksichtigen. Diese Mengenangaben beziehen sich stets auf Phenylborsäure-Äquivalente.

Im allgemeinen können Alkylester der Formel IIIb, in der R^1 die Bedeutung C_1-C_8-Alkyl hat, eingesetzt werden. Bevorzugte Alkylester IIIb sind die Dimethylester und die Diethylester.

Vorzugsweise geht man bei dem erfindungsgemäßen Verfahren von den Phenylboronsäuren IIIa aus.

Weiterhin geht man bevorzugt von Borverbindungen der Formel III aus, in denen R für eine C_1-C_4-Alkylgruppe oder Halogen und insbesondere für Methyl, Fluor oder Chlor steht.

Darüberhinaus sind Borverbindungen III als Ausgangsmaterial bevorzugt, in denen n für 1 und insbesondere für 0 steht.

Ganz besonders bevorzugt sind 4-Methylphenylboronsäure, 4-Fluorphenylboronsäure und vor allem 4-Chlorphenylboronsäure als Ausgangsverbindung IIIa.

Vorzugsweise geht man von Nitrochlorbenzolen II aus, welche eine einzige Nitrogruppe tragen (m = 1), insbesondere 4-Nitrochlorbenzol und vor allem 2-Nitrochlorbenzol.

Die Borverbindungen III (Phenylboronsäure-Äquivalente) werden, bezogen auf die Verbindungen II, normalerweise mit bis zu 50-prozentigem, vorzugsweise mit bis zu 20-prozentigem Überschuß und besonders bevorzugt äquimolar eingesetzt.

Als Base können organische Basen wie z.B. tertiäre Amine eingesetzt werden. Bevorzugt verwendet man z.B. Triethylamin oder Dimethylcyclohexylamin.

Als Base verwendet man vorzugsweise Alkalimetallhydroxide, Erdalkalimetallhydroxide, Alkalimetallcarbonate, Erdalkalimetallcarbonate, Alkalimetallhydrogencarbonate, Alkalimetallacetate, Erdalkalimetallacetate, Alkalimetallalkoholate und Erdalkalimetallalkoholate, im Gemisch und insbesondere einzeln.

Als Base besonders bevorzugt sind Alkalimetallhydroxide, Erdalkalimetallhydroxide, Alkalimetallcarbonate, Erdalkalimetallcarbonate und Alkalimetallhydrogencarbonate.

Als Base ganz besonders bevorzugt sind Alkalimetallhydroxide, z.B. Natriumhydroxid und Kaliumhydroxid, sowie Alkalimetallcarbonate und Alkalimetallhydrogencarbonate, z.B. Lithiumcarbonat, Natriumcarbonat und Kaliumcarbonat.

Die Base wird im erfindungsgemäßen Verfahren vorzugsweise mit einem Anteil von 100 bis 500, besonders bevorzugt 150 bis 400 Mol-%, bezogen auf die Borverbindung III, eingesetzt.

Geeignete Palladium-Katalysatoren sind Palladium-Ligandenkomplexe mit Palladium in der Oxydationsstufe Null, Salze des Palladiums in Gegenwart von Komplexliganden oder gegebenenfalls auf Träger aufgezogenes metallisches Palladium, vorzugsweise in Gegenwart von Komplexliganden.

Geeignete Komplexliganden sind neutrale Liganden wie Triarylphosphane, welche in den Arylringen gegebenenfalls substituiert sein können. Die Wasserlöslichkeit der Palladium-Komplexe läßt sich durch folgenden Substituenten verbessern: Sulfonsäuresalzgruppen, Sulfonsäuregruppen, Carbonsäuresalzgruppen, Carbonsäuregruppen, Phosphonsäuresalzgruppen, Phosphonsäuregruppen, Phosphoniumgruppen, Peralkylammoniumgruppen, Hydroxygruppen und Polyethergruppen.

Aus den Palladium-Ligandenkomplexen mit Palladium in der Oxidationsstufe 0 verwendet man vorzugsweise Tetrakis(triphenylphosphan)palladium und daneben Tetrakis[tri(o-tolyl)phosphan]palladium.

In den Salzen des Palladiums, welche in Gegenwart von Komplexliganden verwendet werden, liegt das Palladium normalerweise in der zweifach positiven Oxydationsstufe vor. Bevorzugt verwendet man Palladiumacetat oder Palladiumchlorid.

In der Regel werden 2 bis 6 Äquivalente der vorstehend genannten Komplexliganden, insbesondere Triphenylphosphan, mit einem Äquivalent des Palladiumsalzes kombiniert (vgl. z.B. J. Org. Chem. 49, Seite 5240 (1984)).

Im übrigen sind derartige lösliche Palladium-Komplexe allgemein bekannt (vgl. z.B. Angew. Chem. 105, Seite 1589 (1993)), so daß sich weitere Ausführungen hierzu erübrigen.

Metallisches Palladium verwendet man vorzugsweise in pulverisierter Form oder auf einem Trägermaterial, z.B. als Palladium auf Aktivkohle, Palladium auf Aluminiumoxid, Palladium auf Bariumcarbonat, Palladium auf Bariumsulfat, Palladium auf Calciumcarbonat, Palladium auf Aluminiumsilikaten wie Montmorillonit, Palladium auf SiO_2 und Palladium auf Calciumcarbonat, jeweils mit einem Palladiumgehalt von 0,5 bis 12 Gew.-%. Diese Katalysatoren können neben Palladium und dem Trägermaterial weitere Dotierstoffe, z.B. Blei, enthalten.

Besonders bevorzugt ist bei der Verwendung von gegebenenfalls auf Träger aufgezogenem, metallischem Palladium die Mitverwendung der vorstehend genannten Komplexliganden, insbesondere die Verwendung von Palladium auf Aktivkohle in Gegenwart von Triphenylphosphan als Komplexligand, wobei die Phenylgruppen im Triphenylphosphan vorzugsweise mit insgesamt ein bis drei Sulfonatgruppen substituiert sind.

In der Regel werden 2 bis 3 Äquivalente der vorstehend genannten Komplexliganden pro Äquivalent des Palladiummetalls verwendet.

Der Palladium-Katalysator wird im erfindungsgemäßen Verfahren mit einem Anteil von 0,01 bis 10, vorzugsweise 0,05 bis 5 und insbesondere 0,1 bis 3 Mol-% bezogen auf die Verbindung II eingesetzt.

Das erfindungsgemäße Verfahren kann in einem Zweiphasensystem aus wäßriger Phase und fester Phase, d.h. dem Katalysator, durchgeführt werden. Die wäßrige Phase kann dabei neben Wasser auch ein wasserlösliches organisches Lösungsmittel enthalten.

Für das erfindungsgemäße Verfahren geeignete organische Lösungsmittel sind beispielsweise Ether, z.B. Dimethoxyethan, Diethylenglykoldimethylether, Tetrahydrofuran, Dioxan und tert.-Butylme-

thylether, Kohlenwasserstoffe, z.B. Hexan, Heptan, Cyclohexan, Benzol, Toluol und Xylol, Alkohole, z.B. Methanol, Ethanol, 1-Propanol, 2-Propanol, Ethylenglykol, 1-Butanol, 2-Butanol und tert.-Butanol, Ketone, z.B. Aceton, Ethylmethylketon und iso-Butylmethylketon, Amide, z.B. Dimethylformamid, Dimethylacetamid und N-Methylpyrrolidon, jeweils einzeln oder im Gemisch.

Bevorzugte Lösungsmittel sind Ether, z.B. Dimethoxyethan und Tetrahydrofuran, Kohlenwasserstoffe, z.B. Cyclohexan, Toluol und Xylol, Alkohole, z.B. Ethanol, 1-Propanol, 2-Propanol, 1-Butanol und tert.-Butanol, jeweils einzeln oder im Gemisch.

In einer besonders bevorzugten Variante werden im erfindungsgemäßen Verfahren Wasser, ein oder mehrere in Wasser unlösliche und ein oder mehrere in Wasser lösliche Lösungsmittel eingesetzt, beispielsweise Mischungen aus Wasser, Toluol und Ethanol oder Wasser, Toluol und Tetrahydrofuran, vorzugsweise jeweils im Volumenverhältnis 1:2:1.

Die Gesamtmenge an Lösungsmittel liegt normalerweise bei 3000 bis 500 und vorzugsweise bei 2000 bis 700 g pro Mol der Verbindung II.

Zweckmäßigerweise werden zur Durchführung des Verfahrens die Verbindung II, die Borverbindung III, die Base sowie die katalytische Menge des Palladium-Katalysators in eine Mischung aus Wasser und einem oder mehreren inerten organischen Lösungsmitteln gegeben und bei einer Temperatur von 0 bis 150, vorzugsweise 30 bis 120 °C für einen Zeitraum von 1 bis 50, vorzugsweise 2 bis 24 Stunden gerührt.

Die Durchführung kann in üblichen für derartige Verfahren geeigneten Apparaturen erfolgen, so daß sich weitere Ausführungen hierzu erübrigen.

Nach beendeter Umsetzung wird als Feststoff anfallender Palladium-Katalysator beispielsweise durch Filtration abgetrennt und das Rohprodukt vom Lösungsmittel bzw. den Lösungsmitteln befreit.

Bei nicht völlig wasserlöslichen Produkten werden wasserlösliche Palladium-Katalysatoren oder Komplexliganden bei der Trennung der Wasserphase vom Rohprodukt vollständig abgetrennt.

Anschließend kann nach dem Fachmann bekannten und dem jeweiligen Produkt angemessenen Methoden, z.B. durch Umkristallisation, Destillation, Sublimation, Zonenschmelzen, Schmelzkristallisation oder Chromatographie weiter aufgereinigt werden.

Bei Reaktionsende als Feststoff vorliegender Katalysator läßt sich in der Regel leicht abtrennen, regenerieren und wieder dem Prozeß zuführen, wodurch eine Senkung der Verfahrenskosten und eine Entlastung der Abfallprodukte von Palladium erreicht wird.

Mit dem erfindungsgemäßen Verfahren lassen sich beispielsweise herstellen:

4'-Fluor-2-nitrobiphenyl
4'-Methyl-2-nitrobiphenyl
4'-Methoxy-2-nitrobiphenyl
4'-Brom-2-nitrobiphenyl
3'-Fluor-2-nitrobiphenyl
3'-Chlor-2-nitrobiphenyl
3'-Brom-2-nitrobiphenyl
3'-Methyl-2-nitrobiphenyl
3'-Methoxy-2-nitrobiphenyl
4'-Phenyl-2-nitrobiphenyl
4'-Trifluormethyl-2-nitrobiphenyl
4'-Fluor-4-nitrobiphenyl
4'-Chlor-4-nitrobiphenyl
4'-Brom-4-nitrobiphenyl
4'-Methyl-4-nitrobiphenyl
4'-Cyano-4-nitrobiphenyl
2-Nitrobiphenyl
4-Nitrobiphenyl

Das erfindungsgemäße Verfahren liefert die Verbindungen I in hohen Ausbeuten bei sehr guter Reinheit.

Die mit dem erfindungsgemäßen Verfahren erhältlichen Nitrobiphenyle eignen sich als Vorprodukte für Biphenylamine, welche ihrerseits Zwischenprodukte sind für fungizide Pflanzenschutz-Wirkstoffe (vgl. EP-A 545 099).

Synthese von 4'-Chlor-2-nitrobiphenyl

Beispiel 1

Zu einer Lösung von 9,45 g 2-Nitrochlorbenzol und 10,3 g 4-Chlorphenylboronsäure in 60 ml Tetrahydrofuran gab man eine Lösung von 9,6 g Natriumhydroxid in 60 ml Wasser unter Rühren und unter

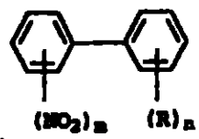
Stickstoffatmosphäre. Anschließend versetzte man die Mischung mit 70 mg Palladium(II)acetat und 370 mg Triphenylphosphan. Die Mischung wurde unter Rühren solange am Rückfluß gekocht (70 °C), bis das 2-Nitrochlorbenzol umgesetzt war (ca. 8 Stunden). Nach dem Abkühlen wurde der Ansatz mit 80 ml Wasser und 80 ml tert.-Butylmethylether versetzt und die organische Phase abgetrennt. Nach Filtration über 10 g Kieselgel und Verdampfen des Lösungsmittels erhielt man 13,95 g der Titelverbindung in einer Reinheit von 95 % (GC).

Beispiel 2

Zu einer Lösung von 4,7 g 2-Nitrochlorbenzol und 5,6 g 4-Chlorphenylboronsäure in 30 ml 1,2-Dimethoxyethan gab man eine Lösung von 8 g Natriumcarbonat in 30 ml Wasser unter Rühren und unter Stickstoffatmosphäre. Anschließend versetzte man die Mischung mit 320 mg Palladium auf Aktivkohle (10 Gew.-%) und 320 mg Triphenylphosphan. Die Mischung wurde unter Rühren solange am Rückfluß gekocht, bis das 2-Nitrochlorbenzol umgesetzt war (ca. 22 Stunden). Nach dem Abkühlen wurde der Ansatz mit 50 ml Wasser und 50 ml tert.-Butylmethylether versetzt und die organische Phase abgetrennt. Nach Filtration und Verdampfen des Lösungsmittels erhielt man 6,7 g der Titelverbindung in einer Reinheit von 92,7 % (GC).

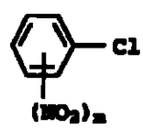
Patentansprüche

1. Verfahren zur Herstellung von Nitrobiphenylen der Formel I



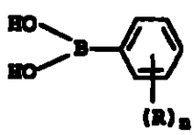
(I)

in der m für 1 oder 2 steht, R Halogen, R' oder OR' bedeutet, wobei R' ein C-organischer Rest ist, welcher unter den Reaktionsbedingungen inerte Gruppen tragen kann, wobei n für 0, 1, 2 oder 3 steht und im Falle, daß n 2 oder 3 ist, die Reste R auch verschieden sein können, dadurch gekennzeichnet, daß man ein Chlornitrobenzol der Formel II

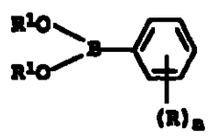


(II)

in Gegenwart eines Palladium-Katalysators und einer Base in einem Lösungsmittel mit einer Phenylboronsäure (IIIa)



(IIIa)



(IIIb)

einem ihrer Alkylester der Formel IIIb, wobei R^1 die Bedeutung C_1-C_6-Alkyl hat, oder einem ihrer Anhydride umsetzt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man als Verbindung II 2-Nitrochlorbenzol einsetzt.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man von einer Phenylboronsäure, welche nur in der 4-Position substituiert ist, als Verbindung IIIa und 2-Chlornitrobenzol als Verbindung II ausgeht.

4. Verfahren nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß man eine Phenylboronsäure IIIa einsetzt, welche als einzigen Substituenten in der 4-Position Fluor, Chlor oder eine Methylgruppe trägt.

5. Verfahren nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß man von 4-Chlorphenylboronsäure als Verbindung IIIa ausgeht.

6. Verfahren nach den Ansprüchen 1 bis 5, dadurch gekennzeichnet, daß man als Palladium-Katalysator Tetrakis(triphenylphosphan)palladium verwendet.

7. Verfahren nach den Ansprüchen 1 bis 5, dadurch gekennzeichnet, daß man als Palladium-Katalysator ein Palladiumsalz in Gegenwart von Triphenylphosphan verwendet.

8. Verfahren nach den Ansprüchen 1 bis 5, dadurch gekennzeichnet, daß man als Palladium-Katalysator metallisches Palladium auf Aktivkohle in Gegenwart von Triphenylphosphan verwendet, dessen Phenylgruppen mit insgesamt 1 bis 3 Sulfonatgruppen substituiert sind.

Highly Efficient and Accelerated Suzuki Aryl Couplings Mediated by Phosphine-Free Palladium Sources

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Suzuki aryl cross-couplings employing aryl bromides and aryl iodides proceed under mild conditions (65 °C) with high efficiency (substrate-to-catalyst ratios in excess of 500) in the presence of phosphine-free palladium catalysts derived from palladium acetate, $Pd_2(dba)_3C_6H_6$ (dba = dibenzylideneacetone), and $[(\eta^3\text{-}C_3H_5)PdCl]_2$. Phosphine inhibition is shown to play a key role in limiting catalytic efficiency; qualitative comparison studies show that the phosphine-free systems are 1–2 orders of magnitude more active than phosphine-supported catalytic systems. $Pd[P(Ph)_3]_4$ proved to be the least active of the catalytic species screened. The phosphine-free methodology appears to be generally applicable; cross-couplings of aryl iodides yielding biaryls **6** and **7** proceed without noticeable steric or electronic effects. Cross-couplings employing aryl bromides are insensitive to electronic effects in the synthesis of **6** but are slowed by steric hindrance in the synthesis of **7**. Acceleration of cross-coupling is observed in the presence of polar cosolvents and at high pH.

Introduction

Palladium-mediated cross-coupling reactions of aryl halides and aryl sulfonates with arylmetal reagents,[1] particularly arylstannanes (Stille coupling)[2] and arylboronic acids (Suzuki coupling),[3] are versatile methods for synthesizing unsymmetrical biaryls. Both couplings employ accessible substrates and proceed under mild conditions; Suzuki couplings offer the additional advantages of being largely unaffected by the presence of water, tolerating a broad range of functionality, and yielding nontoxic byproducts. As a consequence, they have been used extensively in the synthesis of natural products, nucleoside analogs, and pharmaceuticals.

Our principal interest in Suzuki aryl couplings is their application in poly(arylene) synthesis.[4] Step-growth polymerizations of this type are notoriously sensitive to any process which generates endcaps or other imperfections in the growing polymer.[5] For this reason, side reactions in Pd-mediated couplings which have only a limited impact on the synthesis of small molecules (*vide infra*) become vitally important in polymerization because they both result in endcaps[6] and dramatically affect macromolecular architecture.[7] In order to synthesize high molecular weight linear poly(arylenes) we required a catalytic system with significantly greater activity, efficiency, and specificity than the widely employed Suzuki protocol.[8]

In this paper, we demonstrate that phosphine inhibition plays a key role in limiting catalytic efficiency in Suzuki aryl couplings and show that extraordinarily mild, efficient, and clean catalysis occurs in the complete absence of phosphines. These findings expand on extensive development of "ligandless" catalysis for a variety of Pd-mediated reactions by Beletskaya *et al.*[9] Indeed, the first reported example of an aqueous Suzuki aryl coupling describes the production of phenylbenzoates from iodobenzoates and phenylboric acid in the presence of "ligandless" palladium acetate.[10] In addition, we present a series of solvent, pH, and substituent studies which explore optimal conditions for Suzuki aryl couplings and the generality of the phosphine-free method.

Results and Discussion

Phosphine Inhibition. To examine phosphine inhibition, we chose to study the cross-coupling of 4-halonitrobenzenes with phenylboric acid to yield 4-nitrobiphenyl (Table 1). Similar trends in catalytic activity hold for 4-iodo- and 4-bromonitrobenzene with the latter being slightly less reactive than the former. $Pd[P(Ph)_3]_4$ (**1**), $ArPd(PPh_3)_2I$ (Ar = 4-$NO_2C_6H_4$ or 4-$CF_3C_6H_4$) complexes **2**, palladium acetate (**3**), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (**4**), and $Pd_2(dba)_3C_6H_6$ (**5**) (dba = dibenzylideneacetone) were examined as catalyst precursors. Phosphine-free precursors **3**–**5** are approximately 1 order of magnitude more active than **2** (entries 2 and 7, Table 1), which are in turn markedly more active than **1**.[11] The role of phosphines as inhibitors was confirmed further by spiking both **2** and **5** with 2 additional equiv per metal of triphenylphosphine; reactivity identical to **1** and **2**, respectively, was

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Table 1. Effect of Catalyst Precursor on Cross-Coupling To Yield 4-Nitrobiphenyl[a]

entry	precursor	time (h)	% conv[b] (% yield)[c]
	4-Iodonitrobenzene		
1	1	8.0	23
2	2	0.33	83
3	2	8.0	>98 (91)
4	2 + 2PPh_3	8.0	21
5	3	0.75	>98 (97)
6	4	1.0	>98 (99)
7	5	0.33	98
8	5	0.75	>98 (98)
9	5 + 2PPh_3	8.0[d]	>98 (97)
10	6 (0.02%)	6.0	>98 (99)
	4-Bromonitrobenzene		
11	1	12.0	89
12	2	12.0	>98 (94)
13	3	2.5	>98 (96)
14	4	2.0	79
15	5	2.0	>98 (97)

[a] All couplings were carried out at 65 °C in aqueous acetone in the presence of 0.2% catalyst precursor and 2.5 equiv of K_2CO_3 unless noted otherwise. [b] Percent conversion is defined as [(biaryl)/(biaryl + aryl halide)]100 and was determined by ^1H NMR of the crude reaction extract. [c] Percent yield refers to isolated sublimate (≥99% pure as determined by GC/MS of selected runs). [d] Shorter reaction times resulted in incomplete reaction.

Table 2. Cosolvent Effects on Cross-Coupling[a]

cosolvent	time (h)	% conv (% yield)[b]
acetone	8.0	>98 (91)
THF	8.0	>98 (96)
DME	8.0	97
CH_3CN	8.0	94
toluene	8.0	89
benzene	8.0	81

[a] All couplings were carried out using 0.2% catalyst precursor 2 and 4-iodonitrobenzene. [b] Percent conversion and percent yield are defined as in Table 1.

observed (entries 4 and 9, Table 1). Couplings employing 2-5 can be routinely conducted at substrate-to-catalyst ratios of 500. Quantitative coupling at a substrate-to-catalyst ratio of 5000 demonstrates the efficiency attainable with phosphine-free precursors (entry 10, Table 1).

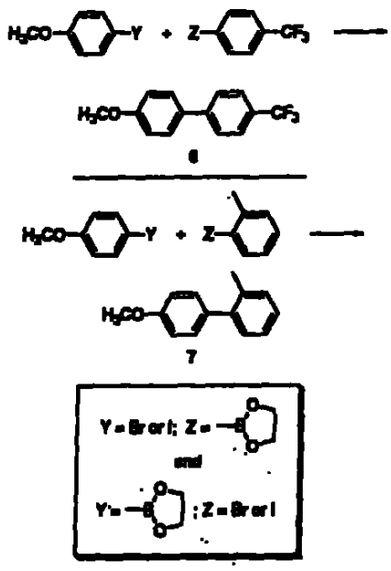
Optimization Studies. Additional studies demonstrated that water-miscible, polar, weakly coordinating cosolvents such as acetone or THF are optimal; DME and acetonitrile inhibit cross-coupling mildly, and nonpolar cosolvents slow the reaction markedly (Table 2).[13] Attempts to accelerate cross-couplings in nonpolar solvents by use of phase-transfer catalysts met with uniform failure. pH plays a role in cross-coupling as well (Table 3). Reactions carried out in the presence of a bicarbonate:carbonic acid buffer (pH = 7–8.5) are retarded relative to cross-couplings buffered with a carbonate:bicarbonate buffer (pH = 9.5–11). Changes in solvent and catalyst do not alter this effect. The pK_A of phenylboric acid is 8.8,[13] suggesting the possibility of two active species with different reactivities: the hydroxyboronate anion at pH > pK_A and the free boronic acid at pH < pK_A. Alternatively, the reaction may proceed *via* equilibrium concentrations of the hydroxyboronate anion at pH < pK_A. The

Table 3. pH and Substrate Effects on Cross-Coupling[a]

base	cosolvent	precursor	time (h)	% conv (% yield)[b]
$KHCO_3$	acetone	2	8.0	57
$KHCO_3$	acetone	3	0.75	59
$KHCO_3$	THF[c]	2	15.0	70
K_2CO_3	acetone	2	8.0	>98 (98)[d]

[a] All couplings were carried out using 0.2% catalyst precursor, 4-iodonitrobenzene, and 4 equiv of $KHCO_3$ unless noted otherwise. [b] Percent conversion and percent yield are defined as in Table 1. [c] Carried out in 70:30 THF:H_2O. [d] 2-Phenyl-1,3,2-dioxaborolane employed. (Compare entry 3 in Table 1.)

Scheme 1



facilitation of Suzuki coupling with strong bases has been noted;[14] faster reaction of the hydroxyboronate anion is consistent with the characteristic electrophilic reactivity of aryliboronates.[15] Under these conditions, 2-phenyl-1,3,2-dioxaborolane was found to be as reactive as phenylboric acid, presumably due to rapid hydrolysis of the boronate ester (entry 4, Table 3).

Generality Studies. In order to explore the generality of the phosphine-free methodology, several permutations of the synthesis of 4-methoxy-4'-(trifluoromethyl)-biphenyl (6) and 4-methoxy-2'-methylbiphenyl (7) were conducted (Scheme 1 and Table 4). Cross-coupling yielded both products quantitatively and proceeded without noticeable electronic or steric effects when aryl iodides were used.[16] Aryl bromides coupled smoothly to yield 6 but demonstrated some sensitivity to steric hindrance in the synthesis of 7. When 2-(2-methylphenyl)-1,3,2-dioxaborolane was employed (entry 8, Table 4), reactions using 0.2% 3 reproducibly attained approximately 50% conversion for reaction times ranging from 3 to 16 h. Raising the amount of 3 to 0.5 and 1.0% increased the conversion to 60 and 81%, respectively. It

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Table 4. Electronic and Steric Permutations of Phosphine-Free Cross-Couplings[a]

entry	Y	Z	time (h)	% conva (% yield)[b]
		Biaryl 6		
1	I	$B(OCH_2)_2$	0.67	[c](97)
2	Br	$B(OCH_2)_2$	4.0	>98 (98)
3	$B(OCH_2)_2$	I	0.67	>98 (99)
4	$B(OCH_2)_2$	Br	4.0	[c](97)
		Biaryl 7		
5	I	$B(OCH_2)_2$	0.67	>98 (98)
6	Br	$B(OCH_2)_2$[d]	16.0	98 (92)
7	$B(OCH_2)_2$	I	0.67	>98 (97)
8	$B(OCH_2)_2$	Br	3.0–16.0	50–81[e]

[a] All couplings were carried out using 0.2% catalyst precursor 3 in aqueous acetone. [b] Percent conversion and percent yield are defined as in Table 1; for 7, percent yield refers to isolated distillate. [c] Not determined. [d] 1.2 equiv of boronate. [e] See text.

is unclear whether poor results in this coupling arise because of catalyst deactivation or due to accelerated deboronation of the *ortho*-substituted boronate.[17] Slower coupling was also observed when the functionality of the aryl substrates was reversed (entry 6, Table 4). In this case, however, quantitative consumption of aryl bromide was attained by employing 1.2 equiv of boronate and longer reaction times.

Catalytic Species. Whereas reactions carried out using 1 and 2 most likely proceed by the catalytic pathway generally invoked for Suzuki couplings,[18] the nature of the catalytic species generated from precursors 3, 4 and 5 is unclear. Zero-valent Pd is not known to exist as a molecular species in solution in the absence of strong donor or acceptor ligands.[19] Ligand-free ArPdX complexes (Ar = C_6H_5) have been prepared by metal-vapor deposition and are stable at −116 °C; at higher temperatures, rapid disproportionation and reductive coupling occur, yielding Pd, PdX_2, and biphenyl.[20] In the absence of credible molecular intermediates on the catalytic pathway, we cannot discount the possibility that phosphine-free cross-couplings are heterogeneous processes.[21] Reactions carried out with 3–5 darken immediately on addition of the catalyst precursor and precipitate metal particles even at 0 °C, yet remain highly active. Regardless of the identity of the active species, phosphine-free couplings can be routinely carried out at substrate-to-catalyst ratios 1–2 orders of magnitude greater than standard Pd-mediated coupling reactions.

It has been shown that 3 mediates the stoichiometric reductive coupling of aryl boronates.[22] This process and accompanying side reactions appear to be responsible for converting 3 to a catalytically active Pd(0) species. Reaction of 3 with 2 equiv of 2-[4-(trifluoromethyl)-phenyl]-1,3,2-dioxaborolane in basic aqueous acetone yielded 4,4'-bis(trifluoromethyl)biphenyl, 4-(trifluoromethyl)phenol, and unconsumed 4-(trifluoromethyl)-phenylboronic acid in addition to Pd black.

Side Reactions in Cross-Couplings. Protodeboronation. The mild hydrolytic instability of arylboronic acids has been extensively documented. Protodeboronation occurs *via* an electrophilic *ipso*- substitution and proceeds by acid-, base-, and metal-ion-catalyzed pathways.[16,17] Since deboronation can be expected to occur with a rate constant independent of aryl coupling, some loss of reagent due to this process is inevitable.[23] In most standard cases, addition of a 10% excess of boronate ensures quantitative consumption of the aryl halide. In situations where expensive or rare boronates are employed or where careful matching of reactive functional groups is necessary, such as in step-growth polymerization, the use of excess boronate may not be desirable. Accelerated cross-coupling should minimize deboronation and thus facilitate higher reaction efficiency in these instances.

Aryl Scrambling (Homocoupling). Traces of homocoupled materials are frequently observed in Pd-mediated cross-couplings.[24] We find that homocoupled byproducts are undetectable by GC/MS analysis of the products obtained from cross-couplings employing 3.[25]

Phosphine-Related Side Reactions. Exchange of metal-bound aryls and phosphine-bound aryls occurs reversibly in Pd complexes analogous to 2 at 50 °C.[26] Since these compounds are key intermediates in the proposed cross-coupling pathway, aryl exchange allows ligand-bound phenyl groups to enter the cross-coupling cycle *in lieu* of the desired aryl halide-derived aryl moieties and hence to contaminate reaction products.[27] Tetraarylphosphonium salts can be synthesized by the Pd-catalyzed reaction of iodoarenes and triarylphosphines.[28] To the degree that phosphine arylation occurs during cross-coupling, it represents a nonproductive consumption of aryl halides. Both of these phosphine related side reactions can be eliminated by employing catalyst precursors such as 3–5.

Further studies exploring the nature of the active catalyst in these couplings and the applicability of phosphine-free catalysis to related cross-coupling reactions are underway.[29] We will present the details of an ongoing mechanistic investigation of catalysis in aqueous Suzuki couplings in the near future.

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Experimental Section

General. Schlenk-line techniques were used for all manipulations. ^{1}H NMR spectra were acquired at 300, 400, or 500 MHz using Bruker AM-series and AMX-series spectrometers; ^{13}C and ^{19}F spectra were obtained at corresponding frequencies. Mass spectrometric analyses were performed by the University of California, Berkeley Mass Spectrometry Laboratory, or with a Hewlett-Packard 5890A gas chromatograph equipped with a 5970 mass-selective detector. Melting points are uncorrected.

Reagents. Solvents were purified by standard methods, deoxygenated by four freeze–pump–thaw cycles, and stored under argon. Water was obtained from a Millipore Milli-Q Water System and was deoxygenated in a similar manner. Palladium acetate was obtained from Aldrich Chemical Co. Complexes 1,[20] 4,[21] and 5[22] were synthesized by standard methods. $ArPd(PPh_3)_2I$ compounds 2 (Ar = 4-$NO_2C_6H_4$,[23] 4-$CF_3C_6H_4$[24]) were synthesized by reaction of 1 equiv of (Pd) 5 with 2 equiv PPh_3 in the presence of 1 equiv of the appropriate aryl iodide in THF at ambient temperature and were recrystallized from THF/hexanes. Aryl halides were obtained commercially, purified by sublimation or distillation at reduced pressure, and stored under argon at −20 °C prior to use. Phenylboric anhydride was prepared from recrystallized phenylboric acid by dehydration *in vacuo* followed by sublimation. Substituted 2-aryl-1,3,2-dioxaborolanes were prepared from the corresponding aryl bromides by standard methods.[25]

Cross-Couplings. Scrupulous care must be used to exclude atmospheric oxygen from these reactions. We observed irreproducible results upon deviating significantly from the representative protocol outlined below.

4-Nitrobiphenyl (92–93–3) (registry numbers supplied by author). To a thick-walled glass tube equipped with a sidearm and Teflon stopcock were added a stir-bar, 0.248 g of 4-iodonitrobenzene (1.00 mmol), 0.106 g of phenylboric anhydride (0.38 mmol, 1.05 equiv as phenylboric acid), and 0.346 g of K_2CO_3 (2.5 mmol). The tube was flushed with argon and equipped with a rubber septum. Acetone (2.0 mL) and 2.5 mL of water were added with a gas-tight syringe. The septum was replaced by a Teflon stopcock, and two freeze–pump–thaw cycles were performed. A 4.0 mM solution of 2 in acetone (0.5 mL, 0.002 mmol) was then introduced under an argon backflow. Two additional freeze–pump–thaw cycles were performed, and the flask was capped with argon, sealed, and heated at 65 °C for 45 min. The contents were extracted with ether (4 × 10 mL), pooled, back-extracted with 10 mL of water, and concentrated *in vacuo*. This crude isolate contained no starting materials detectable by ^{1}H NMR. Sublimation (80 °C, 10 mTorr) gave 0.194 g (97% yield) of 4-nitrobiphenyl. No contamination by 4,4′-dinitrobiphenyl or biphenyl was detectable by GC/MS analysis of the sublimate: mp 113–115 °C (CH_3OH) (lit.[26] mp 112–114 °C); ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 1H), 7.49 (m, 2H), 7.62 (m, 2H), 7.73 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 124.1, 127.4, 127.8, 128.9, 129.1, 138.8, 147.1, 147.6; MS (*m*/*z*) 199.

4-Methoxy-4′-(trifluoromethyl)biphenyl (6) (10355–12–1). An identical procedure employing 0.187 g (1.00 mmol) of 4-bromoanisole and 0.227 g of 2-[4-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (1.05 mmol) yielded, after 4.0 h at 65 °C, 0.244 g of sublimed 6 (97%). No contamination by 4,4′-bis(trifluoromethyl)biphenyl or 4,4′-dimethoxybiphenyl was detectable by GC/MS: mp 122–124 °C (CH_3OH) (lit.[27] mp 124–126 °C); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H); 6.99 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.64 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 55.2, 114.4, 124.4 (q, $^1J_{CF}$ = 270.8 Hz), 125.7 (q, $^3J_{CF}$ = 3.8 Hz), 128.8, 128.3, 128.7 (q, $^2J_{CF}$ = 32.5 Hz), 132.2, 144.3, 159.9; ^{19}F NMR ($CDCl_3$) δ −62.3; MS (*m*/*z*) 252.

4-Methoxy-2′-methylbiphenyl (7) (92495–54–0). An identical procedure employing 0.234 g (1.00 mmol) of 4-iodoanisole and 0.172 g of 2-(2-methylphenyl-1,3,2-dioxaborolane (1.05 mmol) yielded, after 40 min at 65 °C, 0.193 g of 7 (97%) as a colorless distillate[28b] (Kugelrohr, ot 80–85 °C, 10 mTorr). No contamination by 2,2′-dimethylbiphenyl or 4,4′-dimethoxybiphenyl was detectable by GC/MS: ^{1}H NMR ($CDCl_3$) identical to spectrum reported in ref 24b; ^{13}C NMR ($CDCl_3$) δ 20.5, 55.3, 113.5, 125.7, 126.9, 129.9, 130.2, 134.4, 135.5, 141.5, 158.5; MS (*m*/*z*) 198.

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Supplementary Material Available: Appropriate ^{1}H, ^{13}C, and ^{19}F NMR spectral tabulations and other characterization data for the 2-aryl-1,3,2-dioxaborolanes (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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122

The Suzuki Reaction in Biaryl Synthesis

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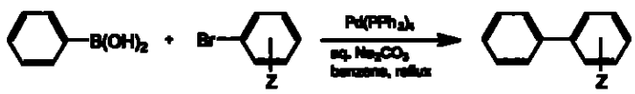
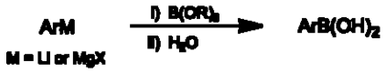
Biaryls and their homologues are an important class of organic compounds because several types of interesting compounds such as natural products, polymers, advanced materials, liquid crystals, supermolecules, and pharmaceuticals, include the biaryl unit. Therefore, a great number of studies in regard to the biaryl synthesis have been carried out. Particularly, development in cross-coupling reactions using organometallic catalysts has been rapid.

In 1981, Suzuki and Miyaura *et al.* reported that the cross-coupling reaction of phenylboronic acid with aryl bromide in the presence of palladium catalysts and base provides corresponding biaryls in good yields[1]. The Suzuki reaction is tolerant of a wide variety of functional groups, so that various substituted aromatic rings can be used. By-products from homocoupling are limited because of the selective reaction involved. Arylboronic acids are stable and they are easily treated. Furthermore, they have lower toxicity in comparison with other organometallic reagents. Therefore, the Suzuki reaction has been used for biaryl synthesis in various fields. It is an important reaction in organic synthesis.



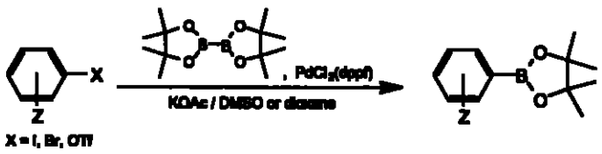
1. Preparation of arylboronic acids

Arylboronic acids are prepared from aryllithiums or Grignard reagents and trialkyl borates. They are normally stable in air and heat, and can be recrystallized from water or alcohol. Arylboronic acids are easily dehydrated to produce a trimer, a boroxine ($ArBO_3$), and exist as mixtures of arylboronic acid and boroxine, which can be used in the Suzuki reaction as they are.



Various arylboronic acids are prepared relatively easily by functionalization reactions of the parent arylboronic acid since the boronic acid group is inert to many chemical reactions.

The convenient method for the preparation of arylboronate from aryl halides or triflates using bis(pinacolate)diboron which is thermally stable and easily handled in air was recently reported[2]. It is possible to prepared the substituted arylboronic acid derivatives directly due to be tolerant of involved functional groups.



2. Mechanism

The general catalytic cycle for the cross-coupling of organometallics with organic halides catalyzed by transition metals, which involves (a) oxidative addition, (b) transmetallation, (c) reductive elimination sequences, is widely accepted (Figure 1). Although a similar catalytic cycle has also been suggested for the Suzuki reaction[3], it differs in that two equivalent bases are required (Figure 2). The coupling reaction of organic boron compounds proceeds only in the presence of bases. This is due to the fact that the organic group on boron is not nucleophilic enough for the transfer from the boron to the palladium in the transmetallation step because of the strong covalent character of the B-C bond in boron compounds. Therefore, it is necessary to increase the carbanion character of organic groups by the formation of an organoborate with a tetravalent boron atom, which utilizes base. Further, it is known that bases substitute for Pd-X to form Pd-OH (or Pd-OR) which has higher activity. Thus, the transmetallation reaction in the Suzuki reaction is favored by the formation of both four-coordinated boron compounds and Pd-OH (or Pd-OR).

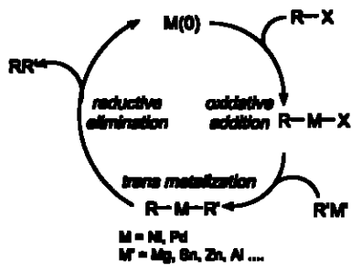


Figure 1

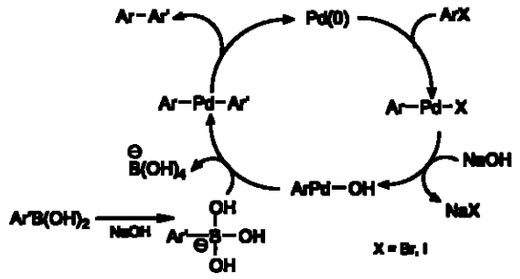
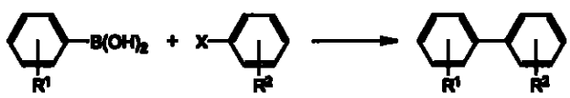


Figure 2

3. Biaryl synthesis

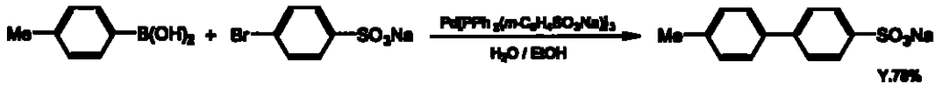
The table lists some representative biaryls which are synthesized by the Suzuki reaction. The tabulated examples show that the biaryls are synthesized in high yields, even if they have functional groups such as hydroxy, carboxy and formyl groups *etc.*



R^1	R^2	X	Catalyst	Base	Yield(%)
H	2-Me	Br	$Pd(PPh_3)_4$	Na_2CO_3	94
H	4-OH	I	$Pd(OAc)_2$	Na_2CO_3	80
H	4-COOH	I	$Pd(OAc)_2$	Na_2CO_3	95
4-F	4-CHO	Br	Pd/C + PPh_3	Na_2CO_3	84
2-CHO	2-NO_2	Br	$Pd(PPh_3)_4$	Et_3N	82
3-NO_2	H	Br	$Pd(PPh_3)_4$	Na_2CO_3	95

Aryl halide and aryl triflate function as electrophiles whose reactivity order is Ar-I > Ar-Br > Ar-OTf >> Ar-Cl. Aryl chlorides are usually not reactive enough, with the exception of those having heteroaromatic rings and electron-withdrawing groups. This is because the oxidative addition of aryl chlorides to palladium complexes is too slow to develop the catalytic cycle. A recent paper showed that the use of nickel catalysts for the cross-coupling reaction with aryl chlorides obtained favorable results[4].

Although the most often used catalyst in the Suzuki reaction is $Pd(PPh_3)_4$, various palladium catalysts are also employed, such as $Pd(dppb)Cl_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$ and $PdCl_2$ *etc.* $PPh_2(m\text{-}C_6H_4SO_3Na)$ is used as phosphine ligand when the reaction is carried out in aqueous solvent. For example, the cross-coupling reaction using the water-soluble palladium complex $Pd[PPh_2(m\text{-}C_6H_4SO_3Na)]_3$ between sodium 4-bromobenzenesulfonate and 4-methylbenzeneboronic acid obtained the corresponding biaryl in good yield[5], compared to using $Pd(PPh_3)_4$ in a two-phase organic solvent.



Bases are always required in the Suzuki reaction as opposed to the coupling reaction using organotin or organozinc reagents. The best results are achieved with the use of a relatively weak base and Na_2CO_3 is a most frequently used. However, the strong bases such as $Ba(OH)_2$ and K_3PO_4 are efficient in reactions involving steric hindrances.

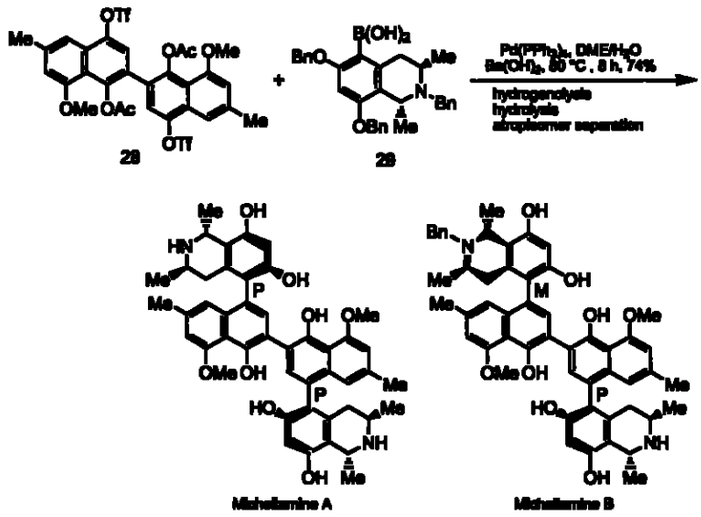
It is also possible to perform a coupling reaction with heterocyclic compounds in the same way. For example, 2,3'-bithiophene is obtained from 2-thiopheneboronic acid and 3-bromothiophene[6].

In addition, 2,2'-functionalized asymmetric biaryls provide a convenient route for the construction of tricyclic aromatics. For example, 2-formylphenylboronic acid is coupled with 2-amidoiodothiophene to give tricyclic heteroaromatic rings in one-pot without isolating the first biaryl generated[7].

4. Application of Suzuki reaction

The Suzuki reaction is widely utilized in the syntheals of biologically active substances, pharmaceuticals, functional materials *etc.*, and a large number of applications are reported. For example, anti-HIV alkaloid, Michellamine, with the expectation of being a drug for AIDS was synthesized using a double Suzuki-type cross-coupling reaction[8]. In addition, with the aim at appearance of new functions, a fully aromatic hyperbranched polyphenylene[9], which was generated by homocoupling of 3,5-dibromophenylboronic acid, and dendrimers[10], having a high number of aromatic chain ends, were synthesized under the Suzuki reaction.

The Suzuki reaction is one of the direct methodologies for the formation of carbon-carbon bonds, so it is a useful method for constructing the carbon skeletal structure of target molecules.



Although in this article only biaryl syntheses using the coupling reaction of arylboronic acids with aryl halides or aryl triflates have been described, it is also possible for the Suzuki reaction to be used for coupling reactions between various organic boron compounds and a variety of organic halides. Further detailed information can be found in the references cited.

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Arylboronic acids

B0857	Phenylboronic Acid	25g JPYen 9,900	5g JPYen 3,400
P1358	1,4-Phenylenediboronic Acid		1g JPYen 13,800
M1313	2-Methylphenylboronic Acid		5g JPYen 12,500
M1314	3-Methylphenylboronic Acid	5g JPYen 29,100	1g JPYen 9,800
M1128	4-Methylphenylboronic Acid		5g JPYen 9,800
V0075	4-Vinylphenylboronic Acid		5g JPYen 12,000