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DIRECCIÓN DE NUEVAS CREACIONES

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Bogotá, D.C.,

Abogado
CARLOS R. OLARTE

ASUNTO Radicación 09 35 919
 Trámite 11
 Evento 378
 Actuación 519
 Oficio
 Folios 19 **1 2 5 8 5**

Patente de Invención	☒	Patente de Modelo de Utilidad
Via Nacional		
Via PCT (Fase Nacional)	☒	☒ Capítulo I ☒ Capítulo II
No. Solicitud Internacional	PCT/EP2007/007913	
Fecha de Presentación Internacional	11/Septiembre/2007	

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

1. Documentos estudiados

Descripción:	Folios 78 a 154	07/Abril/2009
Reivindicaciones:	Folios 155 a 165	07/Abril/2009
	Folios 169 a 178	07/Abril/2009
Dibujos:	Folio 168	07/Abril/2009
Prioridad:	EP 06120576.1	13/Septiembre/2006

2. Análisis de la Prioridad

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

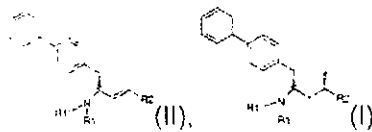
3. Objeto de la invención

Título de la solicitud: "Procedimiento para preparar ácido 4-amino-butírico-biaril-substituido o derivados del mismo y su uso en la producción de inhibidores de endopeptidasa neutra".

El problema planteado en esta solicitud consiste en la necesidad de proporcionar un procedimiento para producir derivados de ácido 4-amino-butírico-biaril-substituido con mayor enantio-selectividad y eficiencia.

Para resolver este problema técnico la solicitud en estudio proporciona un procedimiento para preparar un compuesto de fórmula I que comprende hacer reaccionar un compuesto de acuerdo con la fórmula (ii) con hidrógeno en presencia

de un catalizador de metal de transición y un ligando quiral.



El objeto de la presente solicitud se relaciona con la clasificación internacional de patentes (CIP): C07C227/16//227/32//229/34.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 39 a 43 no es patentable, de acuerdo con el Art 14.

5. De la Solicitud de Patente

Titulo

El título hace alusión a temas excluidos de patentabilidad como es el uso del procedimiento de la invención, por lo cual se sugiere al solicitante hacer la corrección necesaria de tal manera que se ajuste a la categoría de procedimiento.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es clara porque hace referencia a un procedimiento pero este no está definido por las condiciones específicas en que debiera realizarse la reacción. Se sugiere, entonces, definir la invención por sus características esenciales.

La reivindicación 2 no es clara porque menciona un procedimiento pero este no se define mediante características como alguna etapa ó alguna condición específica en que debiera realizarse, sino que define la invención por el mecanismo de reacción, lo cual no es una característica técnica esencial, y no permite distinguir la invención del estado de la técnica. Se sugiere, entonces, definir la invención por sus características esenciales, estructurales o funcionales.

Las reivindicaciones 9 – 11, 13 – 14 y 16 - 18 no son claras porque define la invención términos de los reactivos “Mandypfos”, “Walphos”, “Josiphos”, “Solphos”, entre otros, de los cuales en la descripción se proporciona su estructura y su nombre con nomenclatura IUPAC pero esta característica no se menciona en las reivindicaciones. Se sugiere incluir esta característica esencial en las reivindicaciones.

La reivindicación 20 no es clara porque emplea el término “barias” para referirse a la presión, el cual no es de conocimiento común para la persona del oficio normalmente versada en la materia, además, no se dice en que etapa de la reacción se aplica dicha presión. Se sugiere sustituirlo por el término “bares” y hacer la aclaración correspondiente.

La reivindicación 27 - 29 no son claras porque emplean el término “composición” para referirse a una mezcla de compuestos. Se sugiere reemplazar el término por la palabra “mezcla”.

Las reivindicaciones 35 - 37 no son claras porque emplean el término profármaco, del cual en la descripción señala (fl 130) “describe una sustancia farmacológica que es

administrada en forma inactiva (o menos activa). Una vez administrado el profármaco es metabolizado en el cuerpo in vivo en el compuesto activo", del cual, no se limitan los grupos estructurales que lo pueden conformar. Por lo tanto, se obtendrían un número ilimitado de compuestos que no encuentran soporte en la descripción. Se sugiere al solicitante eliminar este término del alcance del pliego reivindicatorio.

Las reivindicaciones 27-28 y 34 no son claras porque emplean la expresión "en donde la relación molar de los compuestos [...], [...] es de por lo menos" lo cual indica un resultado a alcanzar, no definen al procedimiento porque la invención no queda definida por el resultado a alcanzar, puesto que la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere reemplazarlo por las características esenciales, estructurales o funcionales, que contribuyen a la obtención de ese efecto.

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad 13 de septiembre de 2006 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	US 5.217.996	Biaryl substituted 4-amino-butyric acid amides	08/Junio/1993
D2	Artículo ¹	Dicarboxylic acid dipeptide neutral endopeptidase inhibitors	1995
D2	Artículo ²	Modular chiral ligands: the profiling of the Mandyphos and Taniaphos ligand families	2004

D1

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=5217996A&KC=A&FT=D&ND=&date=19930608&DB=&locale=en_EP, divulga (col. 20, ln 35 – col. 21, ln 68) la obtención de éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico a partir de éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutenoico, y éster etílico del ácido N-(3-carboxi-1-oxipropil)-(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico a partir de éster etílico del ácido N-(3-carboxi-1-oxipropil)-(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutenoico mediante una hidrogenación catalítica en presencia de paladio y carbón.

D2 (folios 213 – 218) divulga (pg. 1691, fl 214, esquema 3, paso g, pg. 1689, fl 213, col. 2) la obtención de éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico a partir de éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutenoico mediante una hidrogenación catalítica en presencia de paladio y carbón.

D3 (folios 219 - 226) divulga (figura 2, pg. 2300, fl 220, figura 4, pg. 2301, fl 221, tablas 2 y 3, pg. 2303, fl 223) la hidrogenación de diversos sustratos en presencia de un catalizador de metal de transición y Mandyphos o Taniaphos como ligandos quirales

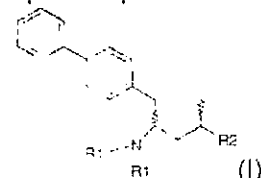
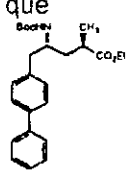
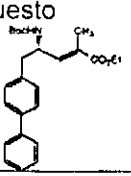
¹ Ksander G., et al; Dicarboxylic acid dipeptide neutral endopeptidase inhibitors; J. Med. Chem.; Vol. 38; No. 10; 1995; pg. 1689-1700; fls 213-218.

² Spindler F., et al; Modular chiral ligands: the profiling of the Mandyphos and Taniaphos ligand families; Tetrahedron: Asymmetry; 2004, Vol. 15, pg. 2299-2306; fls 213-220.

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un procedimiento para preparar un compuesto de fórmula I que comprende hacer reaccionar un compuesto de acuerdo con la fórmula (ii) con hidrógeno en presencia de un catalizador de metal de transición y un ligando quiral.

Comparación de las características técnicas esenciales, con las del estado de la técnica:			
Características esenciales	D1	D2	D3
Procedimiento para preparar un compuesto de fórmula I que comprende:  (I)	Procedimiento para preparar el compuesto éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico que comprende (col. 20, lns 35-43):	Procedimiento para preparar el compuesto, que  comprende: (pg. 1691, fl 214, esquema 3, paso g)	Hidrogenación (introducción, pg. 2299, fl 219)
Hacer reaccionar un compuesto de acuerdo con la fórmula (ii)  (II)	Hacer reaccionar el compuesto éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico	Hacer reaccionar el compuesto 	Diversos sustratos, como olefinas que contienen un grupo amino (figura 2, pg. 2300, fl 220, figura 4, pg. 2301, fl 221)
con hidrógeno	con hidrógeno	con hidrógeno	con hidrógeno
En presencia de: - un catalizador de metal de transición (del grupo 7, 8, o 9 de la tabla periódica), y	En presencia de: - paladio, y	En presencia de; - paladio, y	En presencia de: - un catalizador de metal de transición ([Rh(nbd) ₂]BF ₄ ; [Ru] ₂ (p-cimeno)] ₂)
- un ligando quiral	- carbón	- carbón	- un ligando quiral (Mandyphos, Taniaphos) (tablas 2 y 3, pg. 2303, fl 223)

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan la obtención de éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico a partir de éster etílico del ácido N-t-butoxicarbonil(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico, y éster etílico del ácido N-(3-carboxi-1-oxipropil)-(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico a partir de éster etílico del ácido N-(3-carboxi-1-oxipropil)-(4S)-(p-fenilfenilmetil)-4-amino-2-metilbutanoico mediante una hidrogenación catalítica en presencia de paladio y carbón (D1, col. 20, lns 35-43; D2, pg. 1691, fl 214, esquema 3, paso g, pg. 1689, fl 213, col. 2).

La diferencia entre la invención, definida en la reivindicación 1 y el procedimiento de D1 y D2 consiste en la hidrogenación se realiza en presencia de un ligando quiral.

El efecto que logra el incluir esta característica es que proporciona los compuestos con mayor enantio-selectividad y eficiencia.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular como la necesidad de modificar el procedimiento conocido en D1 y en

D2 para producir derivados de ácido 4-amino-butírico-biaril-sustituido con mayor enantio-selectividad y eficiencia.

Sin embargo, la utilización de ligandos quirales para aumentar la enantio-selectividad y eficiencia en reacciones de hidrogenación catalítica de oleofinas ya está divulgada en el documento D3 que se refiere a la hidrogenación de diversos sustratos (figura 2, pg. 2300, fl 220, figura 4, pg. 2301, fl 221) en presencia de un catalizador de metal de transición y Mandyphos o Taniaphos como ligandos quirales (tablas 2 y 3, pg. 2303, fl 223).

En consecuencia, la persona del oficio normalmente versada en la materia, se vería suficientemente motivada a utilizar un ligando quiral, como mandyphos o taniaphos, divulgados en D3 en el procedimiento de D1 o de D2 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Por lo tanto, la reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18) según en lo divulgado en los documentos D3 con D1 o D3 con D2.

Además, D1 da a conocer que los compuestos obtenidos se separan por cristalización (col. 19), y, que la reacción se puede llevar a 5 bar de presión (pg. 2302, fl 216).

Puesto que las reivindicaciones dependientes 2 – 38 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

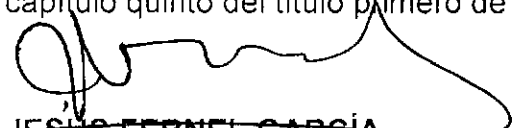
8. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5.217.996	1 - 38	Nivel Inventivo
D2	Artículo	1 - 38	Nivel Inventivo
D3	Artículo	1 - 38	Nivel Inventivo

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

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


JESÚS FERNEL GARCÍA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 11 8 JUL 2012

Elaborado por: Rubiela Pacanchique Vargas
Revisado por: Ana Delia Pinzón García

Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors

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Received August 19, 1994*

The synthesis of three series of dicarboxylic acid dipeptide neutral endopeptidase 24.11 (NEP) inhibitors is described. In particular, the amino butyramide 21a exhibited potent NEP inhibitory activity ($IC_{50} = 5.0$ nM) *in vitro* and *in vivo*. Blood levels of 21a were determined using an *ex vivo* method by measuring plasma inhibitory activity in conscious rats, mongrel dogs, and cynomolgus monkeys. Free drug concentrations were 10–1500 times greater than the inhibitory constant for NEP over the course of a 6 h experiment. A good correlation of free drug concentrations was obtained when comparing values determined by the *ex vivo* analysis to those calculated from direct HPLC measurements. Plasma atrial natriuretic factor (exogenous) levels were elevated in rats and dogs after oral administration of 19a. Urinary volume and urinary sodium excretion were also potentiated in anesthetized dogs treated with 21a.

Atrial natriuretic factor (ANF) is a potent diuretic, natriuretic, and vasorelaxant hormone. These properties have led many investigators to speculate that this peptide might be effective for treating hypertension, congestive heart failure, and renal disease.² To circumvent the inherent problems with the development of a peptide as a therapeutic agent, several approaches can be taken including the identification of nonpeptidic agonists or agents that affect the clearance of the peptide. It is generally accepted that there are two mechanisms responsible for the clearance of ANF. These are receptor-mediated internalization and degradation by so-called C-receptors³ and enzymatic hydrolysis.⁴ Numerous groups have independently demonstrated that kidney membrane preparations degrade ANF enzymatically. Furthermore, inactivation and the loss of biological activity *in vivo*⁵ as well as in part, occur via cleavage of the Cys²–Pro³ peptide bond by neutral endopeptidase 24.11 (NEP; EC 3.4.24.11). Although the relative importance of NEP in the metabolism of endogenous ANF remains to be determined conclusively, NEP inhibitors have been shown to elicit ANF-like responses in animal models.^{6–8} Despite these encouraging experimental results, recent clinical trials have shown, at best, moderate pharmacologic activity. In these clinical studies,^{9–12} several NEP inhibitors including amorphin, SCH34826, and cendoxatriol have produced no or modest antihypertensive effects. Somewhat superior, albeit moderate, effects of these agents have been observed in patients with congestive heart failure. Since these poor clinical outcomes may arise from inferior pharmacokinetics or potency, we have sought to identify novel NEP inhibitors with superior pharmacologic properties.

Chemistry

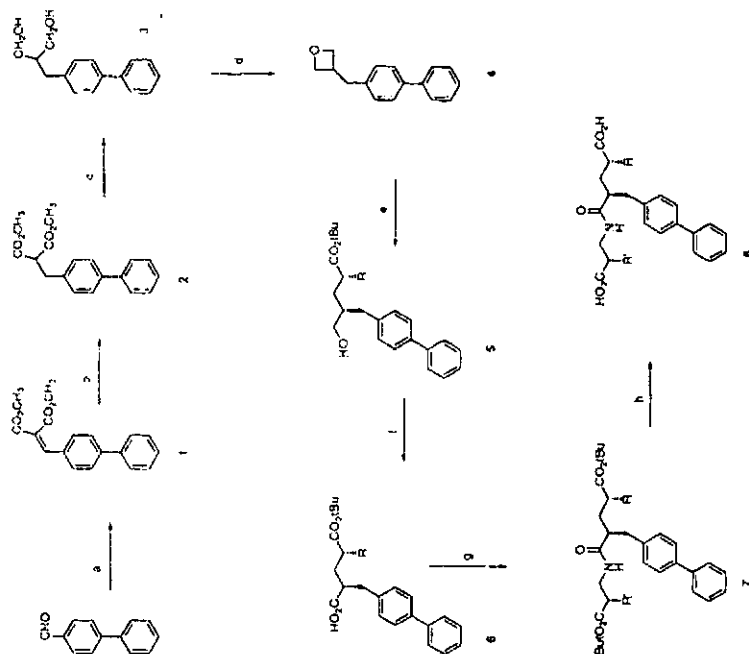
The preparation of racemic unsymmetrical glutaric acids, Table 1, is outlined in Scheme 1. *p*-Phenylbenzaldehyde was converted in successive steps to the oxlactone 4 by condensation with dimethyl malonate/NaOMe, hydrogenation, and LAH reduction to the diol

followed by monosilylation and cyclization with *n*-butyllithium. The oxlactone can be converted to a 2,4-alkyl-substituted, γ -hydroxy ester (5) after boron trifluoride etherate-catalyzed condensation with various *tert*-butyl ester enolates at 75 to 90°C. A variety of aliphatic, aryl-substituted, and heterosubstituted ester enolates¹³ as well as phosphates readily react with 2-methylene biphenyl oxlactone 4 to give diastereomeric mixtures separable by flash chromatography. However, separation at compound 7 was less tedious. The γ -hydroxy ester 6 was oxidized with pyridinium dichromate to give the 2,4-disubstituted mixed glutaric acid ester 8. Activation of the carboxylic acid and coupling with a protected amino acid ester followed by sodium hydride and/or TFA hydrolysis gave the diacids 8.

The symmetrical glutaramides 10, Table 2, were prepared¹⁴ by heating β -alanine or *cis*-4-aminocyclohexanecarboxylic acid in a mixture of methylene chloride/pyridine with the appropriate *trans*-2,4-disubstituted glutaric acid anhydrides, Scheme 2. Preparation of the chiral amino butyramides 20 (Table 3) is outlined in Scheme 3. *N*-Boc-D-tyrosine methyl ester is converted to the triflate 11 which undergoes Suzuki coupling reaction with phenylboronic acid to give 12 in good yield. Conversion of the acid to the hydroxamate followed by lithium aluminum hydride reduction gave the aldehyde 13. Wittig condensation of aldehyde 13 with (carboethoxymethylene)triphenylphosphorane gave the olefin 18 as one geometric isomer. In the analogous series, aldehyde 15 was condensed with (carboethoxymethylene)triphenylphosphine leading to compound 21. Palladium-catalyzed hydrogenation of 18 gave a 6:1 diastereomeric mixture 17. The Boc protecting group was removed with HCl and condensed with succinic anhydride affording the mixed acid ester 19. The diastereomers are readily separated by flash chromatography after treatment of 19 with *N,N*-dimethylformamide di-*tert*-butyl acetal to give the mixed *tert*-butylester 20. Removal of the *tert*-butyl group with TFA gave the chiral products 19 which are readily converted to the chiral diacids 21 with base treatment. Compounds 21e,f were obtained fol-

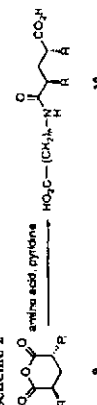
* Abstract published in *Abstracts ACS Medicines*, April 1, 1995.

Scheme 1*



* (a) Dimethyl malonate, n-pyridine; (b) H_2 , Pd/C; (c) LiAlH₄; (d) TeCl₄, nBuLi; (e) ester enolate, BF₃OEt₂; (f) pyridinium dichromate; (g) β -alanine *tert*-butyl ester, HOBT, EDCI; (h) TFA.

Scheme 2



lowing the same sequence of reactions except glutamic and adipic anhydride were substituted for succinic anhydride.

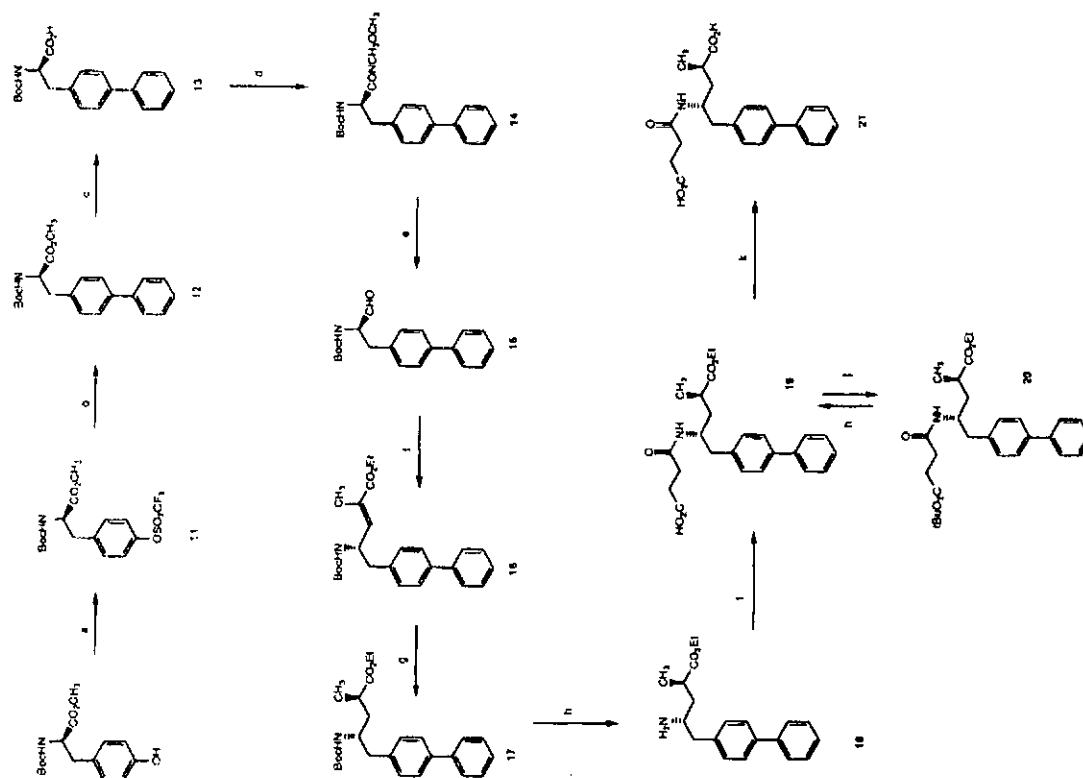
In Vitro Structure-Activity Discussion

A series of glutaramides¹⁵ were published several years ago describing very potent compounds as assessed by an *in vitro* assay using Leu enkephalin as substrate. Changing to our present assay using the synthetic substrate GAAP, we discovered that the previously potent compounds 10a and 21f were no longer active in the nanomolar concentrations, 8 and 2 nM, respectively, but displayed activity in micromolar concentra-

tions. The weak *in vitro* activity was consistent with the poor pharmacology observed with these compounds; however, many factors could lead to this observation. Therefore it was felt that this class of compounds should be reinvestigated.

Table 1 lists the series of racemic unsymmetrical glutaramides. The activity of other series of carboxy-alkyl dipeptides/glutaric acids inhibitors^{16,17} has been reported previously. The *P*₂ substituent, biphenylmethyl, remained constant while the *P*₁ substituent (*R*) was interchanged between β -alanine and isoserine. The *P*₁ substituent was modified with alkyl, aralkyl, alkoxy, and aryl groups. Potency improved by a modest 3–5-fold by changing β -alanine to isoserine (8a–d). When β -alanine and biphenylmethyl were kept constant, very little change in inhibitory activity was observed between alkyl, aralkyl, alkoxy, and aryl *P*₁ modifications. However, in the absence of a *P*₁ substituent (8f), the activity was decreased approximately 4-fold. The stereochemistry is predictably important. Comparing the two pairs of phenoxyl (8e,f) and methoxy

Scheme 3^a



^a (a) NaOH ; (b) NaOH ; (c) NaOH ; (d) NaOH ; (e) NaOH ; (f) NaOH ; (g) NaOH ; (h) NaOH ; (i) NaOH ; (j) NaOH ; (k) NaOH .

Table 1. *In Vitro* NEP Inhibition of Unsymmetrical Chiralities

compd	R	IC ₅₀ (nM)
1a	CH ₃	54
1b	CH ₃	11
1c	CH ₃	46
1d	CH ₃	21
1e	CH ₃	34
1f	CH ₃	> 1000
1g	CH ₃	42
1h	CH ₃	> 1000
1i	CH ₃	19
1j	CH ₃	46
1k	CH ₃	54
1l	CH ₃	155
1m	CH ₃	41

Table 2. *In Vitro* NEP Inhibition of Symmetrical Chiralities

compd	R	IC ₅₀ (nM)
10a	CH ₃	1200
10b	CH ₃	49
10c	CH ₃	36
10d	CH ₃	> 1000 (45% at 10 μM)
10e	CH ₃	489
10f	CH ₃	203
10g	CH ₃	515
10h	CH ₃	52% at 10 μM

(Sg) diastereomers, greater than a 100-fold difference in activity was observed.

Table 2 lists a series of racemic symmetrical diastereomers. The bulky derivatives 10b,c (IC₅₀ = 49, 36 nM, respectively) were the most potent. This effect is governed entirely by the aryl-aryl P₁ substituent. The chiral β-alanine derivative 10a is a relatively weak inhibitor in the CAAP assay with an IC₅₀ of 1.2 μM. Substituting the monophenyl derivative in the para position with an isopropyl group (10e) or a phenoxy substituent (10f) improves activity as compared to the parent unsubstituted phenyl derivative 10a. However, a 2–3-fold decrease in activity is observed when comparing these derivatives to the biphenylmethyl compound 10b. The phenylalanine 10d, theoretically sterically compatible with the P₁ pocket on the basis of the

Table 3. *In Vitro* NEP Inhibition of Amino Butyramides

compd	R	R'	R''	IC ₅₀ (nM)
21a (R,S isomer)	COCH ₂ CO ₂ H	Ph	CH ₃	5
21b (S,R isomer)	COCH ₂ CO ₂ H	Ph	CH ₃	190
21c (R,R isomer)	COCH ₂ CO ₂ H	Ph	CH ₃	700
21d (S,S isomer)	COCH ₂ CO ₂ H	Ph	CH ₃	27
21e	COCH ₂ CO ₂ H	Ph	CH ₃	90
21f	COCH ₂ CO ₂ H	Ph	CH ₃	324
21g	COCH ₂ CO ₂ H	Ph	CH ₃	92
21h	COCH ₂ CO ₂ H	Ph	CH ₃	49
21i	COCH ₂ CO ₂ H	Ph	H	60
21j ^a	COCH ₂ CO ₂ H	H	CH ₃ ₂₉	4000

inhibitory activity of 10h,c, was considerably weaker than other aryl-aryl derivatives. Comparison of 8f, Table 1 (19 nM), with 10d (> 1 μM) implies that one of the heterotations, possibly the nitrogen, is adversely affecting the enzyme interaction in the P₁ pocket.

The inhibitory activities of the aminobutyramides are compiled in Table 3. On the basis of the data generated in the two previous series (Tables 1 and 2), we assumed aliphatic or aralkyl modifications at the P₁ site would not significantly alter the inhibitory activity. In addition, the P₁ biphenylmethyl substituent should be nearly optimum for this series. Therefore, a limited number of compounds were prepared (Table 3) with P₁ substituents being methyl and methoxy and P₂ substituents as biphenylmethyl, while the P₃ functionality was varied from malonyl to succinyl to butyryl to glutaryl to adipyl acids.

The most active compound was 21a, IC₅₀ = 5 nM. All four diastereomers, R,S-21a, R,R-21b, R,R-21c, and S,S-21d, were prepared, and IC₅₀ values of 5, 190, 270, and 27 nM were determined, respectively. The succinic acid in the P₂ site appears to be optimal since extension of the carboxylic acid chain by one (21e) and two (21f) methylene units decreased activity 18- and 65-fold. In addition, decreasing the chain length by one methylene (21g) also showed an 18-fold decrease in activity. Although in series 1 there was no difference in activity between the P₁ methyl and methoxy substituents, a 10-fold change in activity was observed in the amino-butyramide series (21a,h). As expected the P₁ deaminoethyl derivative 21i was considerably less potent than 21a.

Comparison of the P₁ benzyl substituent 21j with other derivatives in Table 3 demonstrates the effect of a P₁ biphenylmethyl group. The biphenyl effect was also evident in the previous examples, shown in Table 2. This effect has been reported in the amino carboxylic acid⁴⁶ and amino phosphonic acid⁴⁷ series. However, replacement of a benzyl group with the biphenylmethyl does not always result in a potency increase. In the thiol series,⁴⁸ thiophenyl (P₁ = benzyl, IC₅₀ = 4 nM) is similar in potency to the biphenylmethyl compound (P₁ = biphenylmethyl, IC₅₀ = 3 nM). In addition, a 50-fold decrease in activity has been reported for a thiol sulfonamide series⁴⁹ with the same P₁ biphenyl modification.

Table 4. Inhibitory Constants of NEP Inhibitors Determined from Different Substrates

Structure	IC ₅₀ (nM) GAAP	IC ₅₀ (nM) Leu-ENK	IC ₅₀ (nM) ANF
	4.8	1.5	8.3
	1.6	0.81	2.0
	5.0	0.74	5.3
	1390	9	NT
	155	0.7	NT

Selectivity of these compounds for NEP over other Zn metalloproteases, e.g., stromelysin, endothelin converting enzyme, is not known; however, these compounds were inactive (<50% inhibition) in ACE at a concentration of 10 μ M.

In Vitro Assays. Leu-enkephalin, glutaryl-Ala-Ala-Phe- β -naphthylamide, and ANF are used as substrates ($K_{cat}/K_m = 56, 37, \text{ and } 18$, respectively) to identify inhibitors of NEP. We have compared the potencies of three different classes of NEP inhibitors, thiole, amino phosphonic acid, and carboxylic acid, in these three assays. Table 4. The IC₅₀ values determined in these assays for thiorphan (a thiole), an amino phosphonate, and 21a (a carboxylic acid) were similar, although the Leu-ENK assay gave somewhat lower values, and the predictive of functional potency *in vivo*. However, the correlation of inhibitory activity between assays was not always constant. Specifically within the dicarboxylic acid series of compounds, for example, 10a and 81 gave differences in potencies of greater than 2 orders of magnitude when tested against GAAP and Leu-ENK as substrates. A possible explanation could be differ-

ences in the kinetics of individual compounds in each assay. Needless to say, the IC₅₀ values for the dicarboxylic acid series of compounds vary significantly depending upon the assay used in determining these values and may not be predictive of *in vivo* functional responses.

Pharmacokinetic Profile

A pharmacokinetic profile was determined for each compound with adequate *in vivo* potency. Since pharmacokinetic measurements using HPLC techniques are labor intensive. The plasma concentrations of NEP inhibitors unbound to plasma proteins were determined by *ex vivo* analysis. This method measures the inhibitory activity in plasma and assumes that all activity is produced by the administered substance or from the active substance released via a suitable prodrug. This method does not measure total plasma levels of active substance but only the concentration of free inhibitor (i.e., not bound to plasma proteins). The total plasma concentration of compound can be calculated after the plasma protein binding is determined.

The pharmacokinetic profile of 19a, the ethyl ester prodrug of 21a, was determined using the *ex vivo* method by measuring plasma inhibitory activity of 21a in conscious rats, anesthetized mongrel dogs, and conscious cynomolgus monkeys (Figure 1). In conscious rats, administration of 19a at 30 mg/kg po produced free plasma levels of the active NEP inhibitor 21a ranging from 0.64 to 0.65 μ M over the course of the 6 h experiment. These values are 10–100 times greater than the inhibitory constant of 21a (IC₅₀ = 5 nM) for NEP. Intraduodenal administration of 19a at 30 mg/kg in anesthetized mongrel dogs produced plasma levels of 21a which ranged from 2.8 to 0.08 μ M at 90 min and 6 h postdosing. In cynomolgus monkeys, dosing at 30 mg/kg po gave concentration values of 8.51 and 0.21 μ M at 1 and 6 h, respectively. These concentrations of free inhibitor 21a were 1500 and 38 times higher than its IC₅₀ value for NEP. The apparent elimination half-life of 21a was 4.6 ± 0.4 h in cynomolgus monkeys.

The accuracy of the *ex vivo* method was next examined using the monkey blood samples. Total drug levels of the active inhibitor 21a were determined by HPLC. The values obtained at 30, 60, 120, 180, 240, 300, 360, and 1440 min were 41, 98, 50, 21, 9, 0, 4, 3, 2, and 0.2 μ M, respectively. The diacid 21a was determined to be 94% plasma protein bound, and the free plasma concentrations of 21a calculated from the HPLC data were in good agreement with those determined by *ex vivo* analysis (Figure 2).

ANF Potentiating Assay. Plasma ANF concentrations were determined in animals infused with exogenous ANF before and after administration of NEP inhibitors. Figure 3 shows the effects of 19a and (+)-candosaril¹⁸ administered at 10 mg/kg po on plasma ANF levels in conscious rats. Plasma ANF levels are expressed as a percent of those measured in vehicle-treated animals which received the infusion of exogenous ANF. ANF levels were increased significantly at all time points (30–240 min) after the administration of 19a. In contrast, the same dose of (+)-candosaril produced a marked increase in plasma ANF levels initially, but this effect progressively diminished and was not significant 3 h after dosing. 19a produced dose-

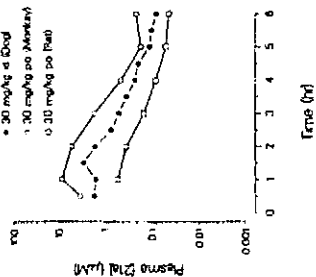


Figure 1.

The pharmacokinetics of 21a after oral administration of 19a (30 mg/kg po) in conscious DOXA and rats, anesthetized dogs, and conscious monkeys (left panel). Plasma levels of 21a shown in the figure were determined by the *ex vivo* method which measures NEP inhibitor activity and does not directly detect 21a. The ratio of plasma 21a concentration/IC₅₀ over the course of the experiment is also shown (right panel).

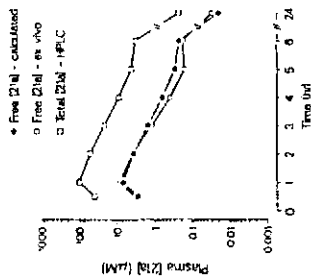


Figure 2. Comparison of free plasma concentrations of 21a determined by the indirect *ex vivo* method and the value calculated from the total concentration obtained from HPLC measurements. The data were obtained from four cynomolgus monkeys.

dependent increases in plasma ANF concentrations after intraduodenal administration in anesthetized dogs (Figure 4). At 30 mg/kg id, 19a increased ANF levels by a maximum of 107%; this effect diminished to 55% by 5 h after dosing. Substantial, albeit smaller, effects of 19a on plasma ANF levels were observed at lower doses.

ANF-Induced Diuretics and Natriuretics. In anesthetized rats intraduodenally administered 19a (30 mg/kg) significantly increased ANF-induced natriuresis without affecting diuresis. Prior to the administration of ANF, there were no significant differences in mean arterial pressure, urine flow, or urinary sodium excretion when rats treated with 19a were compared to controls. In vehicle-treated rats, ANF increased urinary sodium excretion from 0.72 ± 0.25 to 3.26 ± 0.63 μ equiv/kg/min. This effect was potentiated in animals which received 19a (0.63 ± 0.22)–(8.84 ± 2.13) μ equiv/kg/min).

The effects of 21a (10 mg/kg iv) on ANF-induced diuretics and natriuretics in mongrel dogs is shown in

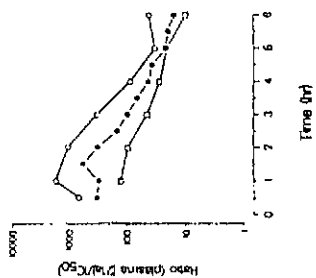


Figure 3.

Effect of 19a and (+)-candosaril administered orally at 10 mg/kg on plasma ANF concentrations in conscious rats infused with exogenous ANF. Values are the mean $\pm$ SEM for six and three rats treated with 19a and (+)-candosaril, respectively.

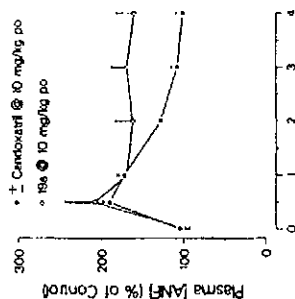


Figure 5. In vehicle-treated dogs, ANF increased urinary sodium excretion from 1.73 ± 3.6 to 1.95 ± 13.4 μ equiv/kg/min. This effect was potentiated significantly in animals which received 21a (20.8 ± 4.2)–(28.2 ± 28.8) μ equiv/kg/min. Urinary volume was also potentiated in animals which received an iv administration of 21a (control: 0.09 ± 0.01)–(1.07 ± 0.09) mL; 21a potentiation, 0.10 ± 0.01)–(1.59 ± 0.21) mL.

In summary, *in vivo* data are presented for three series of NEP inhibitors. The pharmacokinetic profile of 19a/21a was also shown to increase exogenous levels of ANF and enhance ANF's natriuretic and diuretic activity. Although these experiments do not prove 21a will enhance endogenous ANF levels and natriuretic and diuretic activity, it does demonstrate the potential to elicit these activities.

Experimental Section

General Procedures. ¹H NMR spectra were recorded on a Varian XL 400 MHz, Varian VR 500 MHz, and/or Bruker

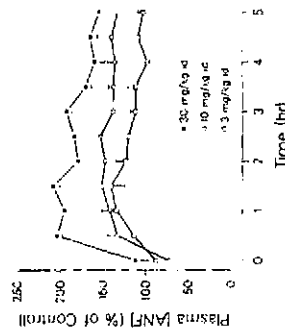


Figure 4. Effect of 21a on plasma ANP concentrations in anesthetized dogs following intraduodenal administration at 3 (n = 2), 10 (n = 3), and 30 (n = 2) mg/kg. Values are the mean $\pm$ SEM.

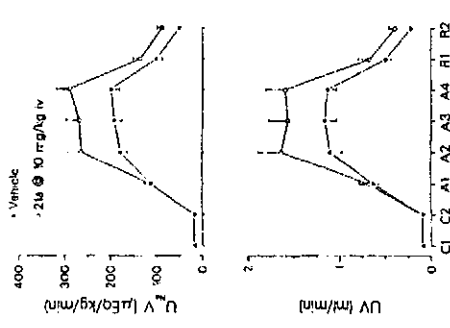


Figure 5. Effect of 21a administered at 10 mg/kg iv on ANP-induced diuresis and natriuresis in anesthetized mongrel dogs. Values are the mean $\pm$ SEM for 11 and 10 dogs treated with 21a and vehicle, respectively. The experiment consisted of two control periods (C₁, C₂), a period of intravenous ANP infusion without 21a (A₁–A₃), and three points of ANP infusion with or without 21a (A₁–A₃) followed by two periods of recovery (termination of ANP infusion; R₁, R₂). Urine volume (UV) and urinary sodium excretion were determined for each of these collection periods.

AC 250 MHz spectrometer with tetramethylsilane as internal standard. Infrared spectra were recorded on a Nicolet 560 FTIR spectrometer. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Dimethyl 2-(1,1'-Biphenyl)-4-ylmethyl-1,3-propanediolate (11). A solution of dimethyl malonate (34.7 g, 0.26 mol), 4-phenylphenol (34 g, 0.16 mol), benzoic acid (2.0 g, 0.02 mol), and pyridine (2.5 mL) was added to a refluxing mixture of 21a (2.1 g, 0.26 mmol) in 25 mL of THF. The mixture was stirred for 1 h. The reaction mixture was cooled, diluted with ethyl ether, washed with 1 N HCl (pH 2), dried (MgSO₄), and concentrated. The mixture was washed with 3 x 1 N

HCl, 1 x 1 N HCl, and brine, dried (MgSO₄), filtered, and concentrated to give 80 g of 1 as a yellow oil. The crude product which contained excess dimethyl malonate was used as is in the next step.

Dimethyl 2-(1,1'-Biphenyl)-4-ylmethyl-1,3-propanediolate (11). Crude 1 (80 g) was dissolved in 200 mL of THF and cooled, and 2 g of 5% NaOH was added. The mixture was hydrogenated at room temperature and pressure for 20 h. The mixture was filtered through a pad of Celite, concentrated, and distilled using a Kugelrohr apparatus. The dimethyl malonate was removed between 100–150 °C, while the product was collected at 180–220 °C. The product was redistilled which solidified upon standing to a sticky solid. The solid was heated; hexanes were added and cooled to 0 °C. The product was collected and dried to give 19.5 g of 2, mp 72–73 °C. ¹H NMR (CDCl₃, δ 7.58 (d, 2H), 7.60 (d, 2H), 7.40 (t, 2H), 7.30 (t, 1H), 7.27 (d, 2H), 3.70 (t, 1H), 3.69 (s, 6H), 3.34 (d, 2H).

2-(1,1'-Biphenyl)-4-ylmethyl-1,3-propanediolate (13). To a solution of 2 (29 g, 97 mmol) in 70 mL of THF was added 68 mL of 2.0 M sodium borohydride. TLC indicated the presence of 3 after refluxing for 5 h. Therefore, an additional 20 mL of lithium borohydride was added and refluxing continued another 2 h. The mixture was cooled, poured into ice-water, extracted three times with ether/EtOAc, dried (MgSO₄), filtered, concentrated, and slurried with ether. The solid was collected affording 13.9 g of 3 melting at 97–99 °C. ¹H NMR (CDCl₃, δ 7.8–7.2 (m, 9H), 3.3 (m, 2H), 3.7 (m, 2H), 2.68 (d, 2H), 2.4 (s, 2H), 2.1 (m, 1H).

3-(1,1'-Biphenyl)-4-ylmethyl-1,3-propanediolate (14). To a solution of 3 (19.5 g, 81 mmol) in 600 mL of THF was added 32.4 mL of 2.5 M NaOH. The thick suspension was kept at 0 °C and stirred for 30 min. To this suspension was added toluene (15.4 mL, 91.0 mmol) in 75 mL of THF. The mixture was stirred for 1 h followed by the addition of a second equivalent of NaOH (32.4 mL, 81.0 mmol). The mixture was heated to 60 °C for 4 h, cooled, poured into ice-water, and extracted three times with ether. The organic extract was washed with brine, dried (MgSO₄), concentrated, and chromatographed on silica gel eluting with ether/hexane (1:4) to give 10.1 g of 4 melting at 78–80 °C. ¹H NMR (CDCl₃, δ 7.57 (d, 2H), 7.52 (d, 2H), 7.42 (t, 2H), 7.34 (t, 1H), 7.2 (d, 2H), 4.82 (dd, 2H), 4.5 (t, 2H), 3.35 (septet, 1H), 3.06 (d, 2H).

1,1-Dimethyl-1-(1,1'-biphenyl)-4-ylmethyl-1,3-propanediolate (15). A solution of 1,1'-biphenyl-4-ylmethyl-1,3-propanediolate (14) (10.1 g, 33.3 mmol) in 20 mL of THF was added to a -78 °C solution of LDA (21.4 mmol) in 20 mL of THF and stirred for 1 h. The mixture was cooled to -110 °C to which the octane (4.0 mL, 33.3 mmol) in 20 mL of THF was added. To this mixture was added boron trifluoride etherate (2.91 g, 21 mmol) in 20 mL of THF. The reaction temperature was raised to 40 °C and the mixture stirred for an additional 90 min. The reaction was quenched with Et₂O and washed with 2 x H₂O, 2 x 1 N HCl, 2 x NaHCO₃, and brine. The organic layer was dried (MgSO₄), filtered, concentrated, and chromatographed eluting with ether/hexane (1:4) to give 1.4 g of 5 as a mixture of diastereomers. The diastereomers can be separated by chromatography. However, the separation was less tedious at a larger scale (compound 7).

1,1-Dimethyl-1-(1,1'-biphenyl)-4-ylmethyl-1,3-propanediolate (15). To a solution of pyridine (1.9 g, 4.79 mmol) in 25 mL of DMF, and the mixture was stirred for 28 h. The reaction mixture was poured into 500 mL of water and extracted with ether. The organic layer was washed with 4 x H₂O, 2 x NaHCO₃, and brine, dried (MgSO₄), filtered, and concentrated to give 1.3 g of 6 as a brown oil.

1,1-Dimethyl-1-(1,1'-biphenyl)-4-ylmethyl-1,3-propanediolate (15). To a solution of 6 (0.67 g, 1.85 mmol), 4-phenylphenol (0.67 g, 0.34 mmol), benzoic acid (0.02 g, 0.002 mmol), and pyridine (2.5 mL) was added to a refluxing mixture of 21a (2.1 g, 0.26 mmol) in 25 mL of THF. The mixture was stirred for 1 h. The reaction mixture was cooled, diluted with ethyl ether, washed with 1 N HCl (pH 2), dried (MgSO₄), and concentrated. The mixture was washed with 3 x 1 N

graphed on silica gel eluting with hexane/ethyl acetate (9:1) in 5% Et₂O in the desired diastereomer 7a as a yellow oil. The crude product which contained excess dimethyl malonate was used as is in the next step.

Dimethyl 2-(1,1'-Biphenyl)-4-ylmethyl-1,3-propanediolate (11). Crude 1 (80 g) was dissolved in 200 mL of THF and cooled, and 2 g of 5% NaOH was added. The mixture was hydrogenated at room temperature and pressure for 20 h. The mixture was filtered through a pad of Celite, concentrated, and distilled using a Kugelrohr apparatus. The dimethyl malonate was removed between 100–150 °C, while the product was collected at 180–220 °C. The product was redistilled which solidified upon standing to a sticky solid. The solid was heated; hexanes were added and cooled to 0 °C. The product was collected and dried to give 19.5 g of 2, mp 72–73 °C. ¹H NMR (CDCl₃, δ 7.58 (d, 2H), 7.60 (d, 2H), 7.40 (t, 2H), 7.30 (t, 1H), 7.27 (d, 2H), 3.70 (t, 1H), 3.69 (s, 6H), 3.34 (d, 2H).

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1,1-Dimethyl-1-(1,1'-biphenyl)-4-ylmethyl-1,3-propanediolate (15). To a solution of 6 (0.67 g, 1.85 mmol), 4-phenylphenol (0.67 g, 0.34 mmol), benzoic acid (0.02 g, 0.002 mmol), and pyridine (2.5 mL) was added to a refluxing mixture of 21a (2.1 g, 0.26 mmol) in 25 mL of THF. The mixture was stirred for 1 h. The reaction mixture was cooled, diluted with ethyl ether, washed with 1 N HCl (pH 2), dried (MgSO₄), and concentrated. The mixture was washed with 3 x 1 N

graphed on silica gel eluting with hexane/ethyl acetate (9:1) in 5% Et₂O in the desired diastereomer 7a as a yellow oil. The crude product which contained excess dimethyl malonate was used as is in the next step.

Compound 8b. mp 105–107 °C. ¹H NMR (DMSO-*d*₆) δ 12.9 (br, 2H), 7.92 (t, 1H), 7.89 (d, 2H), 7.60 (d, 2H), 7.40 (t, 2H), 7.41 (t, 1H), 7.20 (d, 2H), 3.20 (dd, 2H), 2.9 (m, 1H), 2.6 (m, 1H), 2.45 (m, 1H), 2.28 (t, 2H), 2.0 (t, 2H), 1.6 (m, 2H). Anal. (C₂₄H₂₀N₂O₅·0.5H₂O·C₂H₅N) C, 61.5%; H, 4.5%; N, 11.0%. ¹³C NMR (DMSO-*d*₆) δ 171.3, 169.3, 167.3, 165.3, 163.3, 161.3, 159.3, 157.3, 155.3, 153.3, 151.3, 149.3, 147.3, 145.3, 143.3, 141.3, 139.3, 137.3, 135.3, 133.3, 131.3, 129.3, 127.3, 125.3, 123.3, 121.3, 119.3, 117.3, 115.3, 113.3, 111.3, 109.3, 107.3, 105.3, 103.3, 101.3, 99.3, 97.3, 95.3, 93.3, 91.3, 89.3, 87.3, 85.3, 83.3, 81.3, 79.3, 77.3, 75.3, 73.3, 71.3, 69.3, 67.3, 65.3, 63.3, 61.3, 59.3, 57.3, 55.3, 53.3, 51.3, 49.3, 47.3, 45.3, 43.3, 41.3, 39.3, 37.3, 35.3, 33.3, 31.3, 29.3, 27.3, 25.3, 23.3, 21.3, 19.3, 17.3, 15.3, 13.3, 11.3, 9.3, 7.3, 5.3, 3.3, 1.3, -0.3, -2.3, -4.3, -6.3, -8.3, -10.3, -12.3, -14.3, -16.3, -18.3, -20.3, -22.3, -24.3, -26.3, -28.3, -30.3, -32.3, -34.3, -36.3, -38.3, -40.3, -42.3, -44.3, -46.3, -48.3, -50.3, -52.3, -54.3, -56.3, -58.3, -60.3, -62.3, -64.3, -66.3, -68.3, -70.3, -72.3, -74.3, -76.3, -78.3, -80.3, -82.3, -84.3, -86.3, -88.3, -90.3, -92.3, -94.3, -96.3, -98.3, -100.3, -102.3, -104.3, -106.3, 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Modular chiral ligands: the profiling of the Mandyphos and Taniaphos ligand families

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Abstract—A set of 11 ferrocenyl based diphosphine ligands (eight Mandyphos and three Taniaphos) was tested in more than 150 experiments using 20 test reactions. For the assessment of new ligands, a two-pronged strategy was developed consisting of a basic and an extended profiling. The basic profiling showed that the choice of the substituents at the P atoms has a significant effect on the catalyst performance. In the extended profiling it was confirmed that the Mandyphos ligands, in particular **M4** with two bis(3,5-dimethyl-4-methoxyphenyl)phosphino groups, and the Taniaphos ligands, especially the all-phenyl derivative **T1**, showed good to outstanding performances in the hydrogenation of selected α - and β -enamides, acrylic acid derivatives, itaconates, β -ketoesters and 1,3-diketones yielding the corresponding products with up to 99% ee and at substrate/catalyst ratios up to 25,000.

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1. Introduction

The most effective enantioselective catalysts are complexes consisting of a central metal ion and one or more chiral ligands (see Fig. 1).¹ There is no doubt that the choice of a specific metal–ligand combination essentially determines what transformation a complex is able to catalyze selectively. For hydrogenation reactions, the most active and versatile catalysts are low valent Rh, Ru and Ir complexes with tertiary phosphorus ligands in which the chiral element is either the backbone or sometimes the coordinating phosphine.^{2,3} An analysis of the results reported so far shows two somewhat contradictory tendencies. On the one hand, relatively high catalyst specificity is observed, that is, a small change in either ligand or substrate structure often has a strong effect on the catalytic performance (ee, ton, tof). On the other hand, there are a number of ligand families, which are more likely to give better performances than others. For these, Jacobsen has coined the term ‘privileged ligands’ (for selected examples see Fig. 1).

If we want to make catalytic enantioselective hydrogenation a valuable tool for the synthetic chemist, these observations have two consequences: (i) a large variety of ligands has to be designed and prepared, and (ii) their catalytic profiles, that is, the suitability to catalyze specific transformations, should be well known. Even if one applies certain restricting design principles there is still an almost unlimited number of potential ligands, which should be tested for interesting reactions. Obviously, a compromise has to be reached between the benefits of structural diversity and the costs and time involved preparing and testing a large number of ligands. Solvias decided on the following concept: Concentrate on a relatively small number of privileged ligands families, which are highly modular and easily tuned both sterically and electronically with a reasonable amount of synthetic effort. For each ligand family we synthesized various members with a sufficient electronic and steric diversity and tested each in a number of test reactions to obtain a good performance profile for each ligand. This concept has already been implemented successfully for the Josiphos ligand family, albeit with a limited number of test reactions.⁴

Herein we report on a systematic investigation of the catalytic properties of the Mandyphos and Taniaphos ligand families (see Fig. 2) first prepared by Knochel

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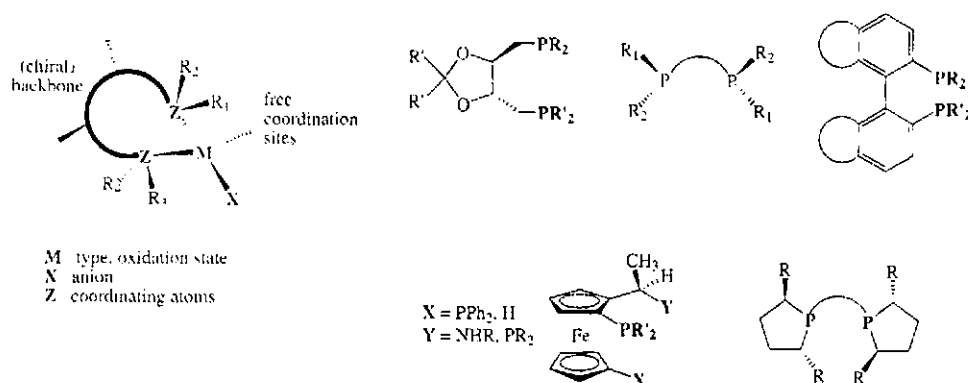


Figure 1. Design elements for chiral metal complexes and selected privileged ligand backbones for enantioselective hydrogenation.

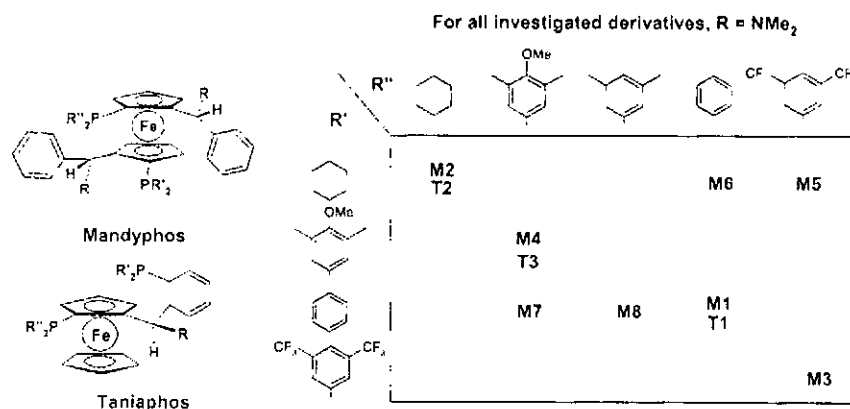


Figure 2. Generic structures of the Mandyphos[®] M and Taniaphos[®] T ligand families and abbreviations used for tested ligands. As a general rule, ligand basicity decreases going to the right and down.

in collaboration with Degussa^{5,6} and now being commercialized by Solvias for Umicore. The Mandyphos diposphines⁵ have a C₂-symmetrical backbone with structural motifs related to ppfa⁷ (see Fig. 3). Herein, several C₁ (or pseudo C₂)-symmetrical derivatives (R' ≠ R'') were also prepared (M5–M8). The Taniaphos family⁶ has a C₁-symmetrical backbone and forms eight-membered metallacycles similar to the Walphos ligands (Fig. 3), independently developed around the same time by Weissensteiner et al.⁸ In the original publications, it was shown that for both ligand types, varying the R substituent on the side chain had a strong effect on the ee, whereas the effect of R' and R'' on phosphorus was not investigated systematically. Herein we show that the nature of R' and R'' has also a very strong effect on the catalytic performance and that this can be used to tailor the ligand to a particular transformation with relatively little synthetic effort.

2. Results and discussion

2.1. Basic ligand profiling

The profiling of a new ligand is the most important aspect when assessing its usefulness for practical applications. To do this as effectively as possible we have developed a two-pronged strategy. For the first assessment of a ligand's potential and for comparisons with literature results, we carried out several standard test reactions with C=C, C=N and C=O double bonds² (see Fig. 4) under standard reaction conditions (see Table 1). Depending on the results of this so-called *basic profiling* some or all ligands would then be tested either on additional, more demanding test substrates or under more demanding reaction conditions in order to assess the potential of the ligand for industrial problems (this we call *extended profiling*).

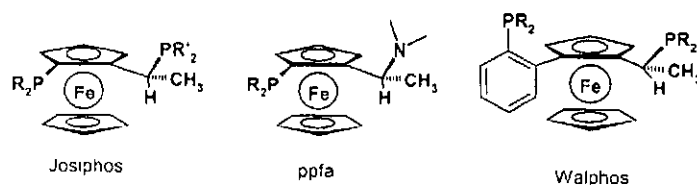


Figure 3. Ferrocene based phosphine ligands with similar structural motifs.

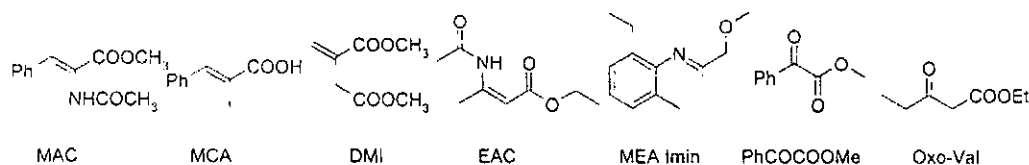


Figure 4. Structures and abbreviations of standard test substrates used in the basic profiling.

Table 1. Standard reaction conditions for basic profiling

Substrate (mmol)	Precursor	Solvent (mL)	<i>s/c</i>	<i>p</i> (bar)	<i>T</i> (°C)	<i>t</i> (h)	Additive
MAC, MCA, DMI (2.53)	[Rh(nbd) ₃]BF ₄	MeOH (10)	200	1 ^a	25	1	
EAC (1.265)	[Rh(nbd) ₃]BF ₄	EtOH (9.5)	100	1	25	1	CF ₃ CH ₂ OH (0.5 mL)
MEA-Imine (12.65)	[Ir(COD)Cl] ₂	Toluene (10)	100	80	25	16	TBAI (4.8 mg), CF ₃ COOH (30 μL)
PhCOCOOME (2.53)	[Rh(nbd)Cl] ₂	Toluene (10)	200	80	25	16	
Oxo-Val (2.53)	[Ru] ₂ (<i>p</i> -cymene) ₂	EtOH (10)	200	80	80	16	1 M HCl (60 μL)

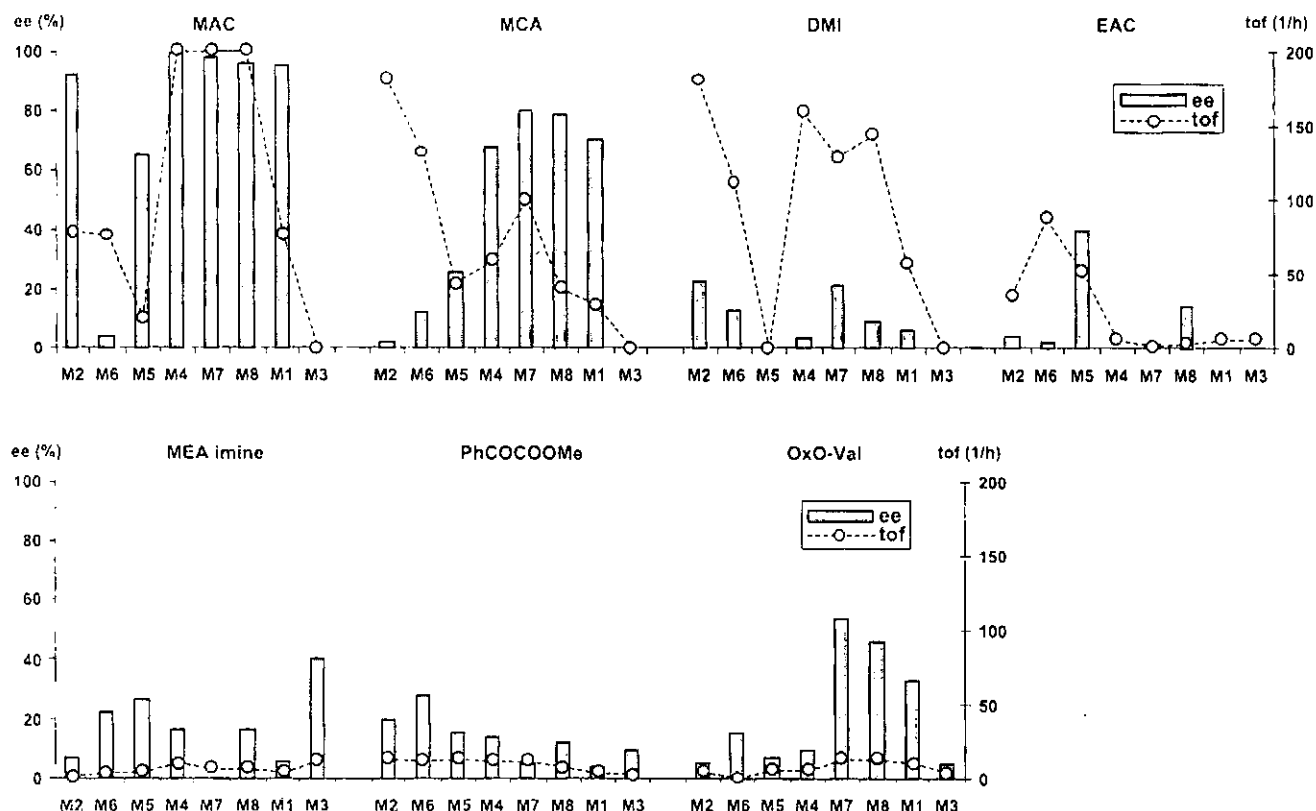
MCA at 5 bar

The results for the basic profiling of the Mandypfos and Taniaphos families are summarized in Figures 5–7. As already observed in the initial publications,^{5,6} the two ligand families have quite different performance profiles. Without going into detail, the following trends merit comments:

- Most Mandypfos ligands showed good to excellent ees and low to good tofs for MAC and MCA but low to mediocre ees for all other test substrates. In particular, catalyst Rh-M14 hydrogenated MAC with >99.5% ee and a very high rate. While the good per-

formance for MAC were expected because of already known results,⁵ it is not clear why DMI is hydrogenated with such low ees.

- Taniaphos exhibited good to very good ees for MAC, DMI, EAC and Oxo-Val and low to mediocre ees for all other test substrates. T3 deserves special mention with ees between 92% and >99.5%. Activities were high for the first two and medium to low for the other substrates. While good ees for MAC and DMI have already been described,⁶ the good enantioselectivity of Taniaphos for EAC and especially for the Ru catalyzed hydrogenation of Oxo-Val was unexpected.

Figure 5. Basic profiling of Mandypfos: ee and tof for eight ligands and eight test substrates. Ligands ordered according to decreasing basicity ($C_3 > MeOXy > Xyl > Ph > CF_3Xyl$).

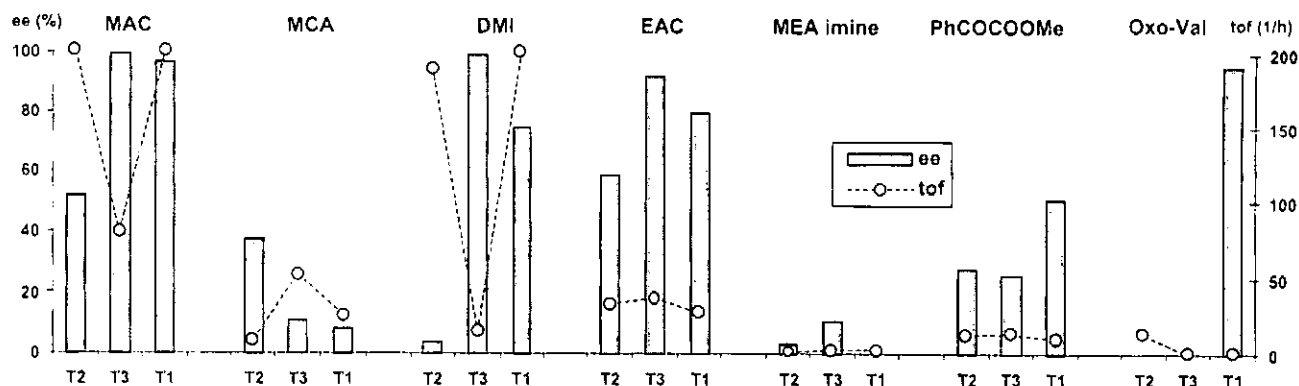


Figure 6. Basic profiling of Taniaphos: ee and tof for three ligands and eight test substrates. Ligands ordered according to decreasing basicity (Cy > MeOXyl > Ph).

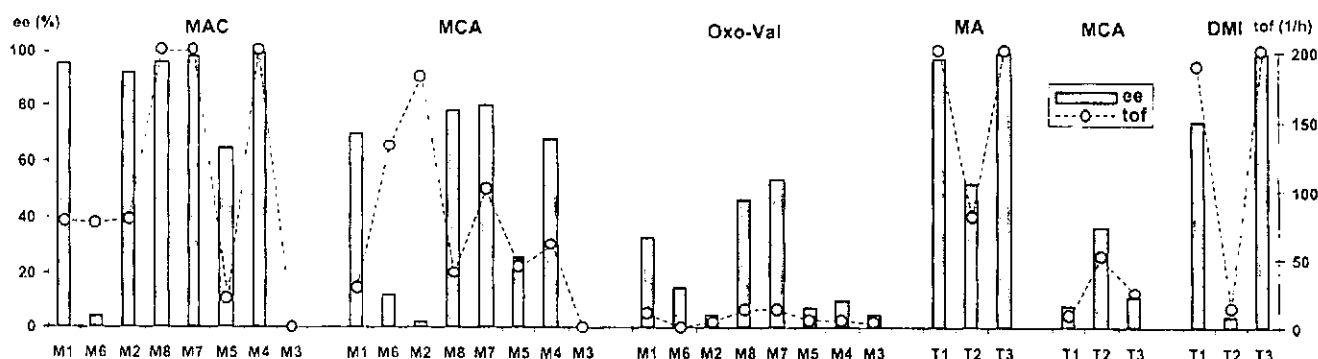


Figure 7. ee and tof for Mandyphos and Taniaphos for selected test substrates. Ligands ordered according to increasing size (Ph < Cy < Xyl < MeO-Xyl < CF₃Xyl).

- For all test substrates and for both ligand families, the nature of the PR₂ groups had a significant influence on both the ee and tof. While there is no unequivocal correlation, a comparison of the selectivity patterns depicted in Figures 5–7 shows that it is the electronic property of the phosphine group (see Figs. 5 and 6) rather than its size (see Fig. 7), which has a systematic effect on the catalytic properties of the resulting complexes.
- With very few exceptions, relatively electron rich all-aryl substituted derivatives (Ph, Xyl, MeOXyl) gave the best performances for both ligand families. Ligands containing PCy₂ and P(CF₃Xyl)₂ groups in general gave moderate to very low ees and tofs. Except for MCA, EAC and Oxo-Val (low ees), symmetrically substituted Mandyphos derivatives usually showed a somewhat better performance than comparable unsymmetrical derivatives.

2.2. Extended ligand profiling

Based on these screening results, it was decided to select **M4** and **T1** for extended profiling with the following goals:

M4 *Technical performance*: Optimize the catalytic performance (ee, ton, tof) for MAC.

Scope: Study the effect of structural variations of MAC and MCA and investigate the hydrogenation of selected α -keto esters (see Fig. 8 and Table 2).

T1 *Scope*: Study the effect of structural variations of MAC, EAC and Oxo-Val and investigate the hydrogenation of selected α -keto esters, unsaturated acids and a hydrazone (see Fig. 8 and Table 3).

Furthermore, in some cases, pressure effects were investigated and for several substrates, both Rh and Ru catalysts were tested.

Comments on the performance of **M4** listed in Table 2

- MAC can be hydrogenated with industrially useful results: At 1 bar ee > 98%, tofs > 7500 h⁻¹ and tons > 20,000 were achieved. The ee slightly dropped at higher *s/c* ratios and values > 20,000 led to incomplete conversions (here the purity of the starting material starts becoming a critical issue). Increasing the temperature to 35 °C or the pressure to 5 bar led to a decrease in ee of ca. 1%. Compared to parent ligand **M1**, modified **M4** clearly has superior enantioselectivity and activity.
- The hydrogenation of dehydroamino acid derivatives with Rh-**M4** turned out to be quite sensitive to substrate structure. While ACA, the correspond-

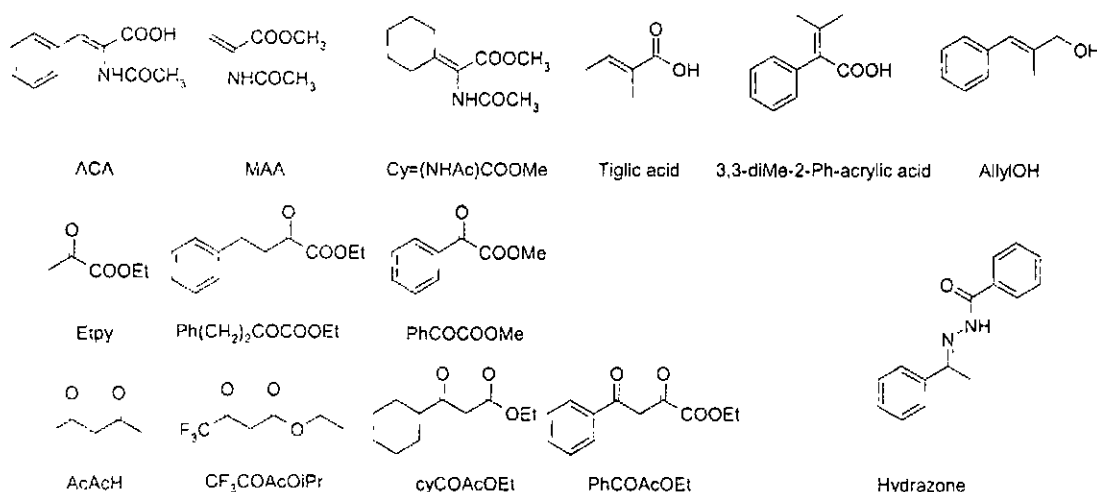


Figure 8. Structures and abbreviations of test substrates used in the extended profiling: dehydroamino acid derivatives, unsaturated acids, allylic alcohol, α -keto esters, β -functionalized ketones, hydrazone.

Table 2. Best results for enamides, activated olefins and α -keto esters with Mandyphos **M4** in the extended profiling

Substrate	Metal ^a	<i>p</i> (bar)	<i>t</i> (h)	Ee (%)	Tof (h ⁻¹)	Comments
MAC	Rh	1	20	97.6	50	ligand M1, <i>s/c</i> 1000
MAC	Rh	1	1.3	98	7692	<i>s/c</i> 10,000, 35°C; ee 99% at 25°C
MAC	Rh	1	7	98.6	2857	<i>s/c</i> 20,000
ACA	Rh	5	17.5	95	11	Ee 59% for Ru
MAA	Rh	1	1	95	200	
Cy=(NHAc)COOMe	Rh	1	20	37	10	
MCA	Rh	50	94	80	2	Ee 72% for Ru
Tiglic acid	Ru	5	18	97	11	Ee 76% for Rh
DiMe-Ph-acrylic acid	Rh	5	17	58	9 ^b	No reaction with Ru
AllylOH	Rh	5	18	72	10 ^b	No reaction with Ru
Etpy	Ru	50	21	69	5.2 ^b	Solvent EtOH
Ph(CH ₂) ₂ COCOOEt	Ru	50	18	88	10 ^b	Solvent EtOH
PhCOCOOMe	Ru	50	22	66	5.4 ^b	

Reaction conditions: *s/c* 200, 25°C.

^a Rh [Rh(nbd)₂]BF₄; Ru [Ru]₂(*p*-cymene)]₂.

^b Incomplete conversion.

Table 3. Best results for enamides, activated olefins, α - and β -keto esters and a hydrazone with Taniaphos **T1** in the extended profiling

Substrate	Metal ^a	<i>p</i> (bar)	<i>t</i> (h)	Ee (%)	Tof (h ⁻¹)	Comments
MAC	Rh	5	22	96	9	Ee 97% at 1 bar
MAA	Rh	1	20	98	10	
Cy=(NHAc)COOMe	Rh	5	20	0.5	10	
MCA	Rh	50	20	10	10	
Tiglic acid	Ru	50	18	38	8 ^b	Ee 32% at 5 bar
DiMe-Ph-acrylic acid	Rh	5	17	66	8 ^b	
AllylOH	Rh	5	18	55	10 ^b	
Ph(CH ₂) ₂ COCOOEt	Ru	50	20	41	9	Solvent EtOH
AcAcH	Ru	80	16	99.5	13	Additive 1 M HCl; dl/meso 97
CF ₃ COAcOiPr	Ru	10	20	84	10	Solvent <i>i</i> -PrOH, 1 M HCl
cyCOAcOEI	Ru	80	18	81	11	Solvent EtOH, 1 M HCl
PhCOAcOEI	Ru	80	16	94	13	Solvent EtOH, 1 M HCl
AcAcOEI ^c	Ru	80	20	79	1200	Solvent EtOH, 1 M HCl
Hydrazone	Rh	5	20	33	1	Conversion 11%

Reaction conditions: MeOH, *s/c* 200, 25°C.

^a Rh [Rh(nbd)₂]BF₄; Ru [Ru]₂(*p*-cymene)]₂.

^b Incomplete conversion.

^c *s/c* 25,000.

ing free acid, and MAA (no phenyl group) were hydrogenated with significantly lower but still very good enantioselectivities, the tetra substituted $\text{Cy}=(\text{NHAc})\text{COOMe}$ only gave 37% ee. This is in contrast to the Rh-Duphos catalysts, which are less sensitive to the degree of substitution and configuration of the C=C bond.²

- An even stronger structure sensitivity was found for α,β -unsaturated olefins. An unprecedented performance was observed for the Ru catalyzed hydrogenation of tiglic acid (ee 97%, full conversion). The best results for MCA and 3,3-dimethyl- 2-phenyl-acrylic acid were obtained with Rh catalysts with ees of 80% and 58%, respectively, and allylOH reduced with 72% ee.
- Acceptable results were also obtained for α -keto esters. The best enantiomeric excess was obtained for the hydrogenation of the commercially interesting HPB-keto ester ($\text{Ph}(\text{CH}_2)_2\text{COCOEt}$, 88% ee) while ees of up to 69% ee and 66% ee were achieved for etpy and PhCOCOEt , respectively.

Comments on the performance of T1 listed in Table 3

- Taniaphos ligand T1 is suitable for the Rh catalyzed hydrogenation of selected enamides and is very efficient for the Ru catalyzed hydrogenation of β -diketones and β -keto esters. The results for the other tested substrate classes confirm the initial tests and are not useful for preparative application.
- The most outstanding result was obtained in the hydrogenation of acetylacetone yielding (2*R*,4*R*)-pentanediol with 99.5% ee with an excellent diastereoselectivity of 97.4:1 (dl:meso). At this small scale, Ru-SI is an alternative for the Ru-Binap or R-MeObiphep catalysts: the potential for large scale application has yet to be investigated.
- AcAcOEt could be hydrogenated with Ru-T1 on a 154mmol scale with an *s/c* ratio of 25,000 with complete conversion after 20h, but with only 78.8% ee: significantly lower than the 96% ee obtained at *s/c* 100.⁵ The reasons for this drop in enantioselectivity is not clear and should be studied in more detail.

- Other β -keto esters were also hydrogenated with good to high ees, whereas α -keto esters or hydrazones seemed to be unsuitable substrates for this Ru catalyst.
- A broad selection of alkenes was studied but only di and trisubstituted α -enamides gave high enantioselectivities. All other tested C=C substrates were hydrogenated with medium to very low ees. The performance of this catalyst for α -enamides is strongly dependent on the degree of substitution at the C=C bond.

3. Conclusions

The results summarized in Table 4 show that Mandyphep and Taniaphos are versatile ligands with very good catalytic performances for a variety of substrate classes. For acrylic acid derivatives, itaconates and β -diketones, the performance was equal to or better than that known for leading commercial ligands. The basic profiling has shown that the choice of the substituents at the P atoms has a significant effect on the catalyst performance. Interestingly, for both ligand families, relatively electron rich aromatic substituents are most suitable for transformations with high enantioselectivity, whereas cyclohexyl (exception MAC) and CF_3 -substituted aryl groups have a negative influence on ee and often the activity as well. This is in contrast to the Josiphos ligands with which several cases are known where these substituents are essential for good performance.⁴

4. Experimental

All ligands were prepared in analogy to the procedures published by Knochel and co-workers^{5,6} and were fully characterized. All ligands can be obtained from Solvias and the derivatives listed in Table 5 are also available from Strem.

The hydrogenation experiments were carried out with the test substrates listed in Figures 4 and 8 in analogy as described in detail for two selected substrates below. The screening experiments were carried out in parallel in 10mL glass vials. Selected single experiments were carried in larger glass vessels or stainless steel autoclaves.

Table 4. Comparison of the best ees of the Mandyphep and Taniaphos ligands with other ligand classes

Substrate class	Umicore ligand (not optimized)	Other commercial ferrocenyl ligands	Other commercial state of the art ligands
Disubstituted α -Enamides	M4 (95%) T1 (>98%)	Josiphos (98%)	Rophos, Duphos Butiphane (99%)
Trisubstituted α -Enamides	M4 (>98%) T1 (>96%)	Josiphos, Taniaphos ⁶ (99%)	Rophos, Duphos Butiphane (99%)
β -Enamides	T1, T3 (up to 92%)	Josiphos (>95%)	Duphos, Bicp, Tangphos (99%)
Acrylic acids	M4 (97%)	Walphos (>92%) Josiphos (98%)	MeObiphep (>90%)
Itaconates	T3 (>99%)	Josiphos (99%) Rophos (>95%)	Butiphane, Duphos, FerroTANE (>95%)
α -Keto esters	M4 (88%) M1 (95%) ⁹	Josiphos (60%)	MeObiphep (94%)
β -Keto esters	T1 (95%)	Taniaphos (99%), Walphos (96%)	Binap, MeObiphep, Segphos (>99%)
β -Diketones	T1 (>99%)	Walphos (96%)	Binap, MeObiphep, Segphos (>99%)

Table 5. Mandypfos and Taniaphos ligands available from Strem

Abbreviation	Solvias no Strem no CAS Reg. no	Name of ligand Acronym Molecular formula, MW	$[\alpha]_D^{20}$ Chemical purity Enantiomeric excess
M1	SL-M001-1 26-0252 [210842-74-3]	(<i>αR,αR</i>)-2,2'-Bis(<i>α-N,N</i> -dimethylaminophenylmethyl)- (<i>S,S</i>)-1,1'-bis(diphenylphosphino)ferrocene (<i>R</i>)-(S)-NMe ₂ -PPh ₂ -Mandypfos C ₃₂ H ₃₀ FeN ₂ P ₂ , 820.28	>−320 >97% >99% ee
M2	SL-M002-1 26-0240 [494227-35-9]	(<i>αR,αR</i>)-2,2'-Bis(<i>α-N,N</i> -dimethylaminophenylmethyl)- (<i>S,S</i>)-1,1'-bis(dicyclohexylphosphino)ferrocene (<i>R</i>)-(S)-NMe ₂ -PCy ₂ -Mandypfos C ₅₂ H ₇₄ FeN ₂ P ₂ , 844.97	>+54 >97% >99% ee
M3	SL-M003-1 26-0244 [494227-36-0]	(<i>αR,αR</i>)-2,2'-Bis(<i>α-N,N</i> -dimethylaminophenylmethyl)-(<i>S,S</i>)-1,1'- bis[di(bis-(3,5-trifluoromethyl)phenyl)phosphino]ferrocene (<i>R</i>)-(S)-NMe ₂ -P(3,5-CF ₃ Ph) ₂ -Mandypfos C ₆₀ H ₄₂ F ₂₄ FeN ₂ P ₂ , 1364.75	>−250 >97% >99% ee
M4	SL-M004-1 26-0248 [494227-37-1]	(<i>αR,αR</i>)-2,2'-Bis(<i>α-N,N</i> -dimethylaminophenylmethyl)-(<i>S,S</i>)-1,1'- bis[di(3,5-dimethyl-4-methoxyphenyl)phosphino]ferrocene (<i>R</i>)-(S)-NMe ₂ -P(3,5-Me-4-MeOPh) ₂ -Mandypfos C ₆₄ H ₇₄ FeN ₂ O ₄ P ₂ , 1053.09	>−61 >97% >99% ee
T1	SL-T001-1 26-1155 [255884-98-1]	(1 <i>S</i>)-Diphenylphosphino-2-[(<i>R</i>)- <i>α</i> -(<i>N,N</i> -dimethylamino)- <i>o</i> - diphenylphosphinophenyl)methyl]ferrocene (<i>R</i>)-(S)-Ph ₂ PPhCHNMe ₂ -T-PPh ₂ C ₄₃ H ₃₈ FeNP ₂ , 687.56	>+312 >97% >99% ee
I2	SL-T002-1 26-0955 [494227-38-2]	(1 <i>S</i>)-Dicyclohexylphosphino-2-[(<i>R</i>)- <i>α</i> -(<i>N,N</i> -dimethylamino)- <i>o</i> - dicyclohexylphosphinophenyl)methyl]ferrocene (<i>R</i>)-(S)-Cy ₂ PPhCHNMe ₂ -T-PCy ₂ C ₄₃ H ₆₃ FeNP ₂ , 711.79	>+110 >97% >99% ee

The reaction mixtures were analyzed by GC and HPLC methods using literature methods.

4.1. Ru catalyzed hydrogenation of acetylacetone (small scale single experiment)

The autoclave was purged with argon by setting the pressure to 40 bar and releasing it. This operation was repeated four times. The starting material acetylacetone (0.254 g, 2.53 mmol) and 5 mL of degassed methanol were placed in a 10 mL Schlenk flask with a stirring bar and a sequence high vacuum/argon-filling repeated six times. 60 μ L of 1 M methanolic HCl was carefully added. In a 10 mL Schlenk flask (also under argon, same procedure as above) [RuI₂(*p*-cymene)]₂ (6.2 mg; 0.0063 mmol) and T1 (9.1 mg; 0.0133 mmol) were placed, and dissolved in methanol (5 mL). These solutions were stirred at room temperature for 10 min and then transferred via cannula to the autoclave with a gentle argon flow. The autoclave was purged with hydrogen (40 bar, four times), set at 60 bar. The autoclave was then heated up to 80 °C, and after 30 min, the hydrogen pressure set to 80 °C. After 16 h reaction time, the pressure was released. The clear reaction mixture was carefully evaporated to dryness under reduced pressure.

2,4-Pentanediol was quantitatively obtained (determined by GC and ¹H NMR). The predominant stereoisomer was (2*R*,4*R*)-pentanediol with a dl/meso ratio

of 97.4:1.0 and an enantiomeric purity of 99.5% [determined after derivatization with trifluoroacetic anhydride using GC (column: Lipodex E, 50 m $\times$ 0.25 mm, 80 °C, isothermic; carrier gas: H₂ 120 kPa)].

4.2. Rh catalyzed hydrogenation of *Z*-acetamidocinnamate (scale up experiment)

The glass reactor was set under an atmosphere of argon by repeated sequences of high vacuum/argon-filling (four times). The starting material, methyl *Z*-acetamidocinnamate (13.18 g, 63.0 mmol), and 40 mL of degassed methanol were placed in a 100 mL Schlenk flask with a stirring bar and a sequence of high vacuum/argon-filling repeated six times. In a 100 mL Schlenk flask (also under argon, same procedure as above) [Rh(nbd)₂]BF₄ (1.2 mg; 0.0032 mmol) and M4 (3.74 mg; 0.0036 mmol) were placed, and dissolved in methanol (40 mL). These solutions were stirred at room temperature for 10 min and then transferred via cannula to the glass reactor with a gentle argon flow. The reactor was purged with hydrogen/vacuum (1.2 bar/0.4 bar, six times), set at 1.05 bar hydrogen, the temperature maintained at 25 °C and stirring then started. After 7 h reaction time, the hydrogen was replaced by argon. The clear reaction mixture was evaporated to dryness under reduced pressure.

Conversion and enantiomeric purity were determined by using GC [Chirasil-L-Val: 30 m; 150 °C, 40, 10 min,

190 °C, 20 min; carrier gas: He (200 kPa)]. The conversion was quantitative and the enantiomeric excess of *N*-acetyl phenylalanine methyl ester determined to be 98.6% (*R*).

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