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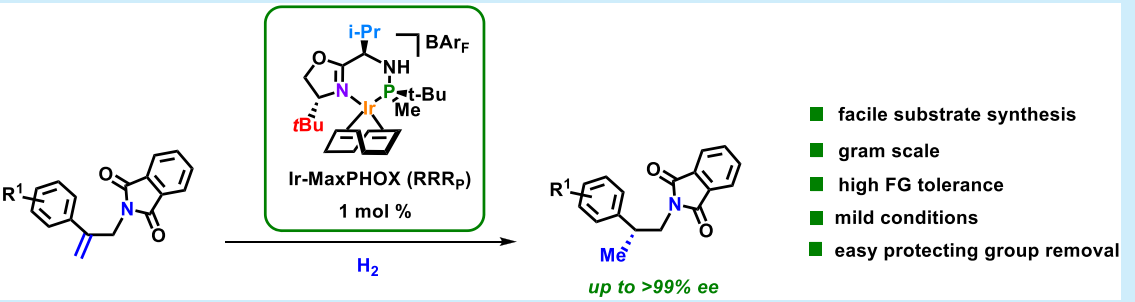
Highly Enantioselective Iridium-Catalyzed Hydrogenation of 2-Aryl Allyl Phthalimides

Albert Cabré,[¥,§] Elia Romagnoli,[¥] Pol Martínez-Balart,[¥] Xavier Verdaguer,*[,¥,§] and Antoni Riera*[,¥,§]

[¥]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology (BIST), Baldiri Reixac 10, 08028 Barcelona, Spain

[§]Departament de Química Inorgànica i Orgànica, Secció Orgànica, Facultat de Química, Universitat de Barcelona, Martí i Franquès 1, Barcelona E-08028, Spain

Supporting Information



ABSTRACT: The iridium-catalyzed asymmetric hydrogenation of 2-aryl allyl phthalimides to afford enantioenriched *β*-aryl-*β*-methyl amines is presented. Recently developed Ir-MaxPHOX catalysts are used for this enantioselective transformation. The mild reaction conditions and the feasible removal of the phthalimido group makes this catalytic method easily scalable and of great interest to afford chiral amines. The importance of this new methodology is exemplified by the formal synthesis of (*R*)-Lorcaserin, OTS514, and enantiomerically enriched 3-methyl indolines.

The biological activity of many pharmaceutical compounds and agrochemicals is intrinsically related to their absolute molecular configuration.[1] The asymmetric synthesis of chiral compounds is, therefore, an essential field in organic chemistry. In particular, chiral *β*-aryl propanamines are extremely interesting candidates as precursors of pharmaceuticals and active molecules:[2] for example, Lorcaserin, an anorectic drug that has been typically synthesized by chiral resolution;[3] OTS514, a marketed inhibitor of a serine-threonine kinase that is often overexpressed and transactivated in several types of cancer;[4] and LY-392098, a potent positive allosteric modulator of 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid (AMPA) receptor.[5] Moreover, we can envision the synthesis of several drug intermediates such as 3-methylindolines in few steps from *β*-aryl propanamines (Figure 1).

Among the strategies to obtain enantioenriched *β*-aryl propanamines, catalytic asymmetric hydrogenation provides one of the most practical and powerful approaches due to its operational simplicity, high reactivity, and atom economy.[6] However, most of the syntheses found in the literature are performed by means of chiral resolution or by using stoichiometric agents.[7] To the best of our knowledge, there are only few examples in which enantioenriched *β*-aryl propanamines can be obtained by metal-catalyzed enantioselective hydrogenation.[8] In 2005, Zhang and co-workers reported the asymmetric hydrogenation of 2-alkyl allyl phthalimides using a Ru−C$_3$−tunephos catalyst.[8a] However, the scope of this reaction was focused on alkyl groups, and the single example of 2-aryl allyl phthalimide gave only 55% ee of the corresponding *β*-methylpropanamine. More recently, our group reported the hydrogenation of *N*-sulfonyl allyl amines using the iridium complex of Pfaltz's catalyst Ubaphox.[8d]

Iridium complexes bearing chiral P,N ligands[9] have been successfully applied in the asymmetric hydrogenation of a wide range of unfunctionalized or minimally functionalized olefins.[10] Our group has developed several P-stereogenic chiral ligands.[11] Recently, we designed a family of P,N-ligands (MaxPHOX) that were coordinated to iridium.[12] These catalysts can be obtained from protected *tert*-butyl methyl phosphinous acid and commercially available amino acids and amino alcohols.

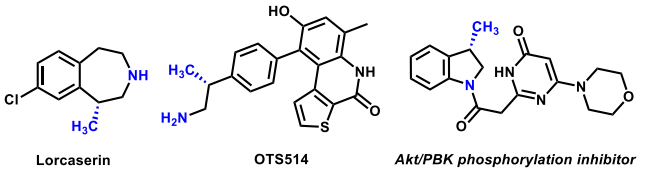


Figure 1. Examples of biologically active compounds containing a chiral *β*-methyl amine.

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These iridium complexes have three chiral centers, so up to four diastereoisomers (catalysts **1**−**4**, Figure 2) can be

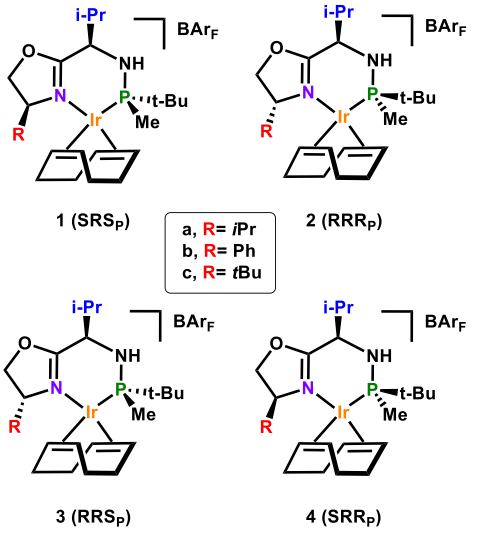


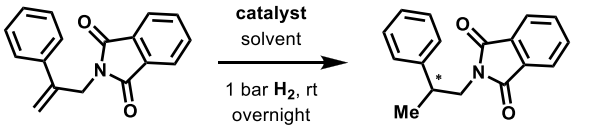
Figure 2. Ir-MaxPHOX family of catalysts.

obtained. Moreover, the substituent of the oxazoline ring can be easily modified. This variety of structures facilitates the fine-tuning of the catalyst. This strategy has allowed us to find an excellent catalyst for the enantioselective hydrogenation of cyclic enamides[12a] and *N*-aryl[12b] and *N*-alkyl[12c] imines. Moreover, these catalysts also proved to be extremely efficient in the isomerization of cyclic allyl carbamates, yielding high levels of enantioselectivity.[12d]

Here, we present the asymmetric hydrogenation of *N*-phthalimido 2-aryl allyl amines using an Ir-MaxPHOX catalyst to obtain chiral β-methyl amines. It is worth noting that, in this occasion, the best catalyst of the family (**2c**) had not been described. To showcase the applicability of this reaction, the formal enantioselective synthesis of several biologically active compounds was performed.

On the basis of our studies, *N*-phthalimido 2-phenyl allyl amine (**5a**), which is easily synthesized in three steps from acetophenone (see Supporting Information), was used as the model substrate. The family of Ir-MaxPHOX catalysts was then used for the asymmetric hydrogenation of **5a** to afford chiral amine **6a** (Table 1). The standard conditions of the reaction were as follows: dichloromethane as solvent, 1 bar of H_2 pressure, and stirring overnight. The Ir-MaxPHOX catalysts with an isopropyl in the oxazoline ring **1**−**4a** were first tested (Table 1, entries 1−4). All of them showed full conversion to **6a**. In particular, catalyst **2a** gave the best ee (64% ee, Table 1, entry 2). Of note is the huge difference between the catalysts in terms of chiral induction achieved by simply modifying the relative configuration of their chiral centers. We then modified the oxazoline substituent of **2** into an aromatic group, such as phenyl (**2b**) or bulkier group such as *tert*-butyl (**2c**). In the first case, the reactivity was not affected, but the enantioselectivity was substantially improved (Table 1, entry 5). With **2c**, the enantiomeric excess was enhanced up to 90% without affecting the conversion (Table 1, entry 6). The synthesis of this ligand is described in the Supporting Information. Then we studied the effect of the hydrogen pressure: when increased to 50 bar^G, the enantioselectivity was not affected (Table 1, entry 7). Finally, catalyst loading was decreased to 1 mol % and a

Table 1. Catalyst Screening and Optimization of the Asymmetric Hydrogenation of 2-(2-Phenylallyl)isoindoline-1,3-dione 5a[a]



5a **6a**

entry	catalyst	loading	solvent	conv. (%)[b]	ee (%)[c]
1	1a	5 mol %	CH_2Cl_2	>99	6 (*S*)
2	2a	5 mol %	CH_2Cl_2	>99	64 (*R*)
3	3a	5 mol %	CH_2Cl_2	>99	20 (*S*)
4	4a	5 mol %	CH_2Cl_2	>99	32 (*R*)
5	2b	5 mol %	CH_2Cl_2	>99	69 (*R*)
6	2c	5 mol %	CH_2Cl_2	>99	90 (*R*)
7[d]	2c	5 mol %	CH_2Cl_2	>99	89 (*R*)
8	2c	1 mol %	CH_2Cl_2	>99	90 (*R*)
9	2c	1 mol %	EtOAc	60	89 (*R*)
10	2c	1 mol %	THF	5	n.d.
11[e]	2c	1 mol %	CH_2Cl_2	>99	**98** (*R*) (96)[f]

[a]See Supporting Information for experimental details. Reactions were run in a pressure reactor at 1 bar^G of H_2 pressure. [b]Determined by ^{1}H NMR. [c]Measured by chiral HPLC. [d]Reaction was performed at 50 bar of H_2. [e]Reaction was performed at- 20 °C. [f]Isolated yield.

solvent screening was performed at 1 bar of H_2. With dichloromethane the conversion after 12 h was still complete (Table 1, entry 8); in contrast, with ethyl acetate or THF, the reactivity decreased to 60% and 5%, respectively (Table 1, entries 9 and 10). Using dichloromethane the reaction temperature could be decreased to −20 °C, affording **6a** with an excellent 98% ee and full conversion (Table 1, entry 11).

A mechanistic study of this reaction using D_2 revealed that the hydrogenation occurred exclusively to the allylic bond and that there was no prior isomerization to the corresponding enamide (see Supporting Information).

With the optimal conditions in hand, we studied the scope of the reaction. As seen in Scheme 1, halide-substituted aryl groups were well-tolerated, with excellent enantioselectivities in all cases (**6b** to **6e**, Scheme 1). The catalyst loading for the substrates with bromine (**5d**) and iodine (**5e**) had to be increased to 2 mol % to ensure full conversion. Electron-donating substituents such as methyl (**6f**) or isobutyl (**6m**) gave 97% and 98% ee, respectively (Scheme 1). We then expanded the substrates to *meta*-substituted aryl groups. Again, and using only 1 mol % of catalyst **2c**, chiral amines **6g** and **6h** were afforded with excellent enantioselectivities. The asymmetric hydrogenation *ortho*-substituted compounds (**5i**−**k**) also gave excellent enantiomeric excesses except in the case of the methoxy substituent (**6i**) that decreased to 83% ee. Finally, an allyl amine with another aryl substituent such as a naphthyl (**5l**) also afforded the corresponding amine **6l** in 97% ee.

To showcase the applicability of our methodology, here we disclose a novel, short, and efficient synthesis of (*R*)-Lorcaserin, **8** (Scheme 2). We performed a gram-scale enantioselective synthesis of **6g** applying our optimal conditions and decreasing the catalyst loading to 0.5 mol %. Compound **6g** was achieved with an excellent 98% ee without recrystallization. Next, we deprotected the phthalimido group with hydrazine in toluene to afford **7** in excellent yield (93%). To the best of our knowledge, this is the most efficient catalytic

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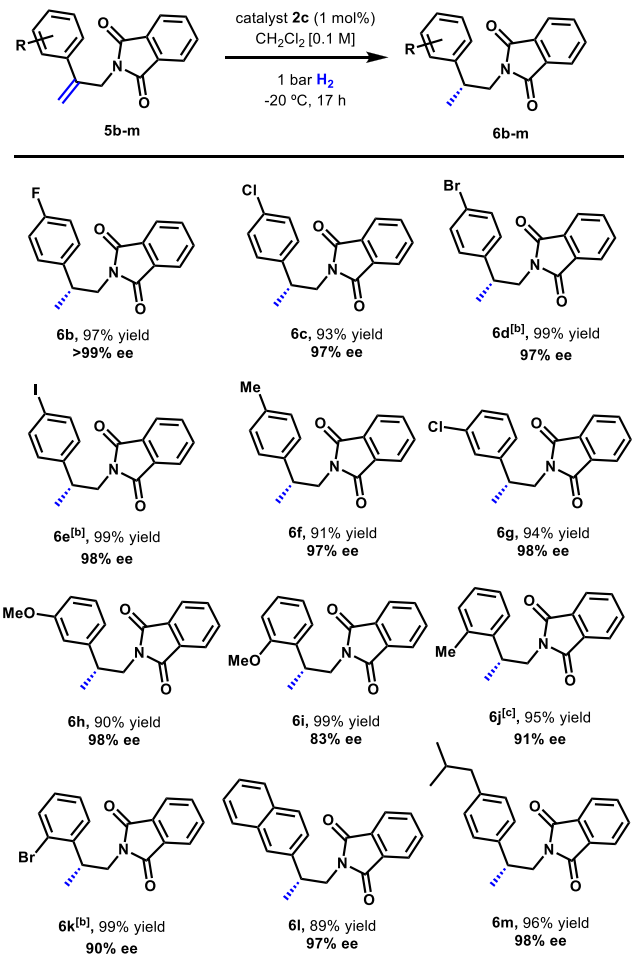
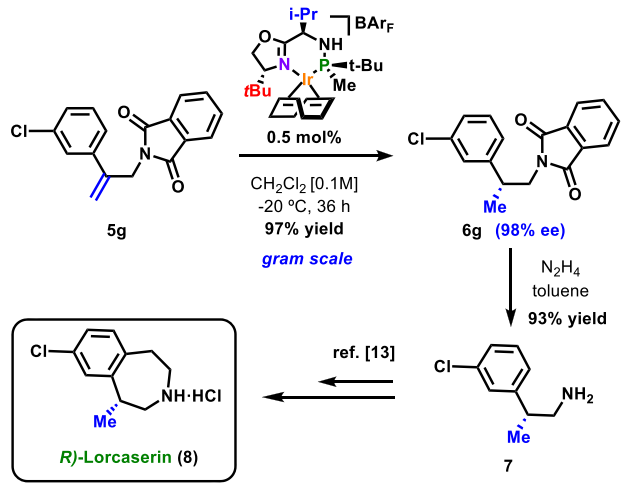
Scheme 1. Scope of the Catalytic Hydrogenation[a]



[a]See Supporting Information for experimental details. Reactions were run in a pressure reactor at 1 bar of H_2 pressure. The reaction showed full conversion for all the examples. Enantiomeric excess was measured by chiral HPLC. [b]Two mol % of catalyst **2c** was used. [c]Three mol % of catalyst **2c** was used.

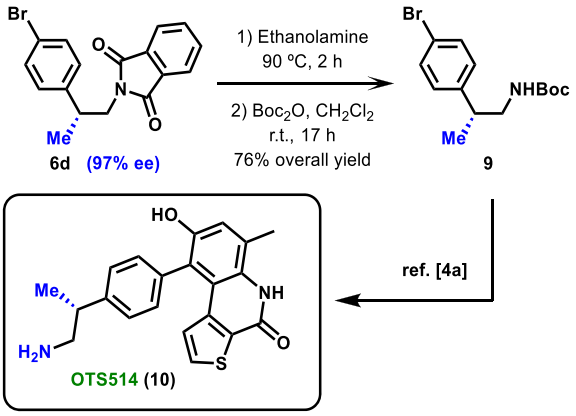
Scheme 2. Formal Synthesis of (*R*)-Lorcaserin, 8



enantioselective synthesis of intermediate **7**, a direct precursor of (*R*)-Lorcaserin (**8**).[13]

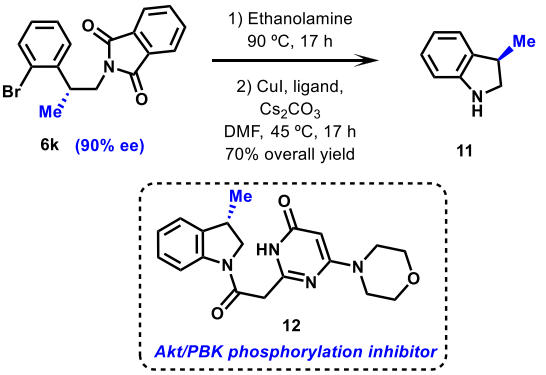
The importance of the methodology developed here can also be appreciated by using **6d** in the formal synthesis of OTS514 (**10**) (Scheme 3). The enantioenriched phathalimide **6d** was deprotected by ethanolamine at reflux and protected as *tert*-butyl carbamate. The resulting *N*-Boc amine **9** is a known precursor of **10**.[4a]

Scheme 3. Formal Synthesis of OTS514, 10



Finally, the chiral amines prepared here can be used in the synthesis of 3-methyl indolines.[14] These compounds are relevant precursors of a number of biologically active compounds and natural products such as Duocarmycins,[14a,15] the potent cytotoxic drug (+)-CC1065,[14a,16] and the Akt/PBK phosphorylation inhibitor **12**,[17] currently in clinical phases. Thus, 3-methyl indoline **11** was readily prepared from amine **6k** (Scheme 4) by phthalimido deprotection followed by copper-catalyzed intramolecular Ullmann-type amination.[18]

Scheme 4. Enantioselective Synthesis of 3-Methyl Indoline 11



In summary, we have described a very efficient enantioselective synthesis of β-aryl propanamines by means of iridium-catalyzed asymmetric hydrogenation of *N*-phthalimido 2-aryl propanamines using the Ir-MaxPHOX complex **2c**. Excellent enantiomeric excess values were obtained for wide range of compounds (up to 13 examples) using low catalyst loading and low hydrogen pressure. Several direct synthetic applications of this novel and effective catalytic method have been disclosed such as a formal synthesis of (*R*)-Lorcaserin and OTS514, as well as a novel approach to enantiomerically enriched 3-methyl indolines.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03865.

Experimental procedure for the preparation of catalyst **2c**; experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: antoni.riera@irbbarcelona.org.
*E-mail: xavier.verdaguer@irbbarcelona.org.

ORCID

Albert Cabré: 0000-0001-5256-8798
Xavier Verdaguer: 0000-0002-9229-969X
Antoni Riera: 0000-0001-7142-7675

Notes

The authors declare no competing financial interest.

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