DIFLUORPHOS and SYNPHOS in asymmetric catalysis: Synthetic applications

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Abstract. Enantiomerically pure diphosphines play an important role in various homogeneous metal-catalyzed asymmetric reactions. Over the last few years, our group has been involved in the design and synthesis of atropisomeric ligands named SYNPHOS and DIFLUORPHOS with complementary stereoelectronic properties. This paper shows the high catalytic performances of DIFLUORPHOS, SYNPHOS and SYNPHOS analogues for some C–H and C–C bond forming processes as well as for the synthesis of biorelevant targets.

Keywords. Hydrogenation; asymmetric catalysis; total synthesis; atropisomeric phosphines.

1. Introduction

Over the last few years, significant research has been directed toward the development of new methods for synthetic efficiency and atom economical processes.¹ Among them, the potential of transition metal catalysed reactions has been steadily demonstrated, as they provide a direct and selective way towards the synthesis of highly valuable products. We have been engaged in a project dedicated to the development of catalytic methods for the synthesis of biorelevant targets. More specifically, we have been interested in hydrogenation reactions² and C–C bond-forming processes which provide important catalytic approaches to fine chemicals. There is no doubt that chiral ligands³ are at the heart of any enantioselective homogeneous process. In this context, our contribution to this field is the development of atropisomeric diphosphanes named SYNPHOS⁴ and DIFLUORPHOS⁵ possessing complementary stereoelectronic properties. In particular, the electrodefficient atropisomeric diphosphane DIFLUORPHOS bearing an original stereoelectronic skeleton based on a bi(difluorobenzodioxole) backbone provided excellent enantioselectivities in asymmetric hydrogenation of fluorinated compounds as a result of an atypical combination of a narrow dihedral angle and an unusual π -acidity. On the other hand, SYNPHOS (bearing a narrow dihedral angle and a stronger basicity) is fully complementary to DIFLUORPHOS in

terms of structural features and selectivity. This study focuses, mainly since 2009, on some significant applications of DIFLUORPHOS, SYNPHOS and SYNPHOS analogues (scheme 1), for C–H and C–C bond-forming processes and for the synthesis of bioactive molecules.

2. Carbon–hydrogen bond-forming processes

2.1 *Ru-catalysed asymmetric hydrogenation of trisubstituted enamides*

The 3-aminochroman moiety is a common structural feature that is present in numerous pharmaceutical drug candidates.⁶ However, only limited progress has been made towards the development of asymmetric synthetic methods for this important structural unit.⁷ In 2011, we reported an atom economical and clean process for the synthesis of 3-aminochroman derivatives through cationic Ru-SYNPHOS-catalysed enantioselective hydrogenation of trisubstituted enamides (scheme 2).⁸ Initial experiments revealed that the nature of the amide moiety and the substitution pattern in the aromatic ring exerted influence on the stereocontrol, while hydrogen pressure and reaction temperature did not significantly affect the stereochemical outcome. For this process, polar solvents tend to provide higher enantioselectivities than non-polar ones, with methanol being the optimum. Under optimized reaction conditions, a wide range of enamides were successfully reduced in moderate to high yields (60–97%) and ees up

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Scheme 1. DIFLUORPHOS, SYNPHOS and SYNPHOS analogues.

to 96% as illustrated by some representative examples depicted in scheme 2.

2.2 Ir-catalysed asymmetric hydrogenation of quinoline derivatives

Transition-metal catalysed asymmetric hydrogenation of readily available heteroaromatic derivatives provided a straightforward route to enantiomerically enriched nitrogen-containing scaffolds which are biorelevant targets in pharmaceutical industry.⁹ Zhou *et al.* described in 2003 the first iridium-catalysed asymmetric hydrogenation of quinoline derivatives using (*R*)-

MeO-BIPHEP with excellent yields up to 94% and enantioselectivities up to 96%.¹⁰ Since this pioneering study, several efficient processes have been reported using electron-deficient or electron-rich atropisomeric ligands.^{11–17} Hydrogenation reactions have been usually performed by mixing [Ir(COD)Cl]₂ and the appropriate diphosphine ligand or by using Ir(III) complexes {[IrH(diphosphine)]₂(μ-X)₃}⁺X[−] (X = Br, Cl, I) as shown in scheme 3.¹⁸

Zhou *et al.* reported strategies based on substrate activation by chloroformates using Ir/(*S*)-SEGPHOS/Li₂CO₃/ClCO₂Bn/THF catalyst system to promote the hydrogenation of 2-alkylquinoline derivatives.^{10b} In collaboration with Mashima and

Note: *p*-cym = *p*-cymene

Scheme 2. Ru-catalysed enantioselective hydrogenation of trisubstituted enamides.

Note: COD = 1,5-cyclooctadiene

Scheme 3. General Ir-catalysed hydrogenation of quinolines.

Ohshima, our group showed that the hydrogenation reaction could be efficiently performed on 2-alkyl- and 2-arylquinolinium chlorhydrate or bromhydrate derivatives using $\{[IrH((S)\text{-diphosphine})]_2(\mu\text{-Y})_3\}^+Y^-$ ($Y = \text{Cl, Br}$) catalysts incorporating atropisomeric diphosphines such as BINAP, *tol*-BINAP, SYNPHOS, SEGPHOS, DTBM-SEGPHOS and DIFLUORPHOS. The corresponding tetrahydroquinolines were synthesized with excellent conversions and enantioselectivities as

high as 95% with better enantiofacial discrimination reached with *para* and *meta*-substituted HCl or HBr arylquinolinium salts compared to the corresponding *ortho*-substituted derivatives.¹⁹ Some representative examples are depicted in scheme 4.

These results demonstrated the unexpected performance of chloro and bromo-iridium dinuclear Ir-DIFLUORPHOS catalysts compared to the corresponding iodo-iridium complexes.

Scheme 4. Ir-catalysed asymmetric hydrogenation of quinolinium salts.

Scheme 5. Ir-catalysed asymmetric hydrogenation of quinoxalines.

2.3 Ir-catalysed asymmetric hydrogenation of quinoxaline derivatives

Enantiomerically enriched tetrahydroquinoxaline derivatives are key building blocks for a range of promising targets for medicinal chemistry studies.²⁰ As previously mentioned for quinoline derivatives, hydrogenation of quinoxalines to access the corresponding tetrahydroquinoxalines can be carried out by mixing $[\text{Ir}(\text{COD})\text{Cl}]_2$ and the chiral ligand or by using pre-formed cationic dinuclear triply halogen-bridged iridium complexes $\{[\text{Ir}(\text{H})(\text{S-diphosphine})]_2(\mu\text{-X})_3\}^+\text{X}^-$ (scheme 5).

Since the pioneering report by Murata in 1987,²¹ most of the hydrogenations have been limited to 2-methylquinoxaline.²² Electronically rich or deficient monodentate or bidentate phosphines,^{23–27} were used in the asymmetric hydrogenation of 2-methylquinoxaline. We demonstrated in 2010 that the cationic dinuclear triply halogen-bridged iridium

complex $\{[\text{IrH}(\text{S-DIFLUORPHOS})]_2(\mu\text{-Cl})_3\}^+\text{Cl}^-$ enabled the hydrogenation of quinoxaline derivatives with no substrate activation allowing the hydrogenation reaction of a series of 2-alkyl and challenging 2-aryl substituted quinoxalines under mild conditions with good yields up to 99% and high levels of enantioselectivities up to 95% (scheme 6).²⁷ The iridium(III)-DIFLUORPHOS catalytic system provided an efficient access to valuable building blocks of synthetic interest. A crucial role of amines was highlighted in 2012 by Mashima *et al.*²⁸

2.4 Ir-catalysed asymmetric hydrogenation of isoquinoline derivatives

Isoquinoline derivatives, widely present in plants and several tissues in mammalian alkaloids, play an important role in the field of medicinal chemistry due to their remarkable pharmacological potential.²⁹ Asymmetric hydrogenation of 1-substituted-3,4-dihy-

Scheme 6. Ir-catalysed asymmetric hydrogenation of quinoxaline derivatives.

Scheme 7. Ir-catalysed asymmetric hydrogenation of isoquinoline derivatives.

droisoquinoline derivatives (DHIQs) provides a practical, convenient and atom-economically efficient route to 1-substituted-tetrahydroisoquinoline (THIQ) scaffolds. To date, only few approaches are based on catalytic asymmetric reactions.³⁰ Since the pioneering studies of Buchwald *et al.*³¹ and Noyori *et al.*,³²

only a few efficient catalytic systems have been described to access 1-alkyl-THIQs in high enantioselectivity; whereas 1-aryl-THIQs were prepared with low to moderate selectivity.³³ Until now, only two reports of catalytic enantioselective reduction of 1-aryl-substituted-3,4-dihydroisoquinolines have been

Scheme 8. Synthesis of α -chloromethylene- γ -butyrolactams.

reported.^{33k} We demonstrated that $[\text{Ir}(\text{COD})\text{Cl}]_2/(\text{R})$ -3,5-diMe-SYNPHOS catalyst is highly efficient for the enantioselective hydrogenation of challenging 1-aryl-3,4-dihydroisoquinolines under mild reaction conditions. This method provides an atom economical and attractive route to pharmaceutically relevant enantiomerically enriched 1-aryl-THIQ compounds in high yields up to 95% and excellent enantioselectivities up to >99%, after a single crystallization (scheme 7).³⁴

Mashima *et al.* reported in 2013 the first efficient asymmetric hydrogenation of 1- and 3-substituted isoquinolinium salts using the new class of cationic dinuclear triply halogen-bridged iridium complexes $\{[\text{Ir}(\text{H})((\text{S})\text{-diphosphine})]_2(\mu\text{-X})_3\}\text{X}$.³⁵

3. Carbon–carbon bond-forming processes

3.1 Rhodium-catalysed asymmetric cycloisomerization of *N*-tethered 1,6-enynes with an intramolecular halogen shift

Metal-catalysed cycloisomerization of 1,*n*-enynes is one of the most efficient methods for the synthesis of a variety of carbocyclic and heterocyclic compounds that contribute to sustainable development and atom economy concepts.³⁶ In 2012, Zhang, Ratovelomanana-Vidal and co-workers reported an efficient rhodium-catalysed enantioselective cycloisomerization of *N*-tethered 1,6-enynes with an intramolecular halogen

shift leading to the corresponding α -chloromethylene- γ -butyrolactams (scheme 8).³⁷ A number of atropisomeric diphosphine ligands including BINAP, SEGPHOS, DIFLUORPHOS, SYNPHOS and SUNPHOS family of ligands were screened for these transformations using various cationic rhodium complexes. As a result of these investigations, it was demonstrated that the stereochemical outcome of the reaction is strongly influenced by the nature of the ligands employed. The SYNPHOS ligand used in combination with either $[\text{Rh}(\text{cod})_2]^+\text{SbF}_6^-$ or $[\text{Rh}(\text{cod})_2]^+\text{OTf}^-$ as rhodium sources turned out to be the ligand of choice for this process, giving the desired cyclized products in moderate to good yields (45–91%) and with enantioselectivities ranging from 67% to 96%. During this screening phase, it was also established that both reactivity and enantioselectivity were influenced by the nature of the *N*-protecting group, the *N*-tosyl derivatives providing higher catalytic activity. As illustrated in scheme 8, both aryl and alkyl substituents are tolerated on the alkyne moiety.

3.2 Rh-catalysed asymmetric conjugate 1,4-addition of arylboronic acids to activated alkenes

Since the initial breakthrough reported by Hayashi, Miyaura *et al.* in 1998,³⁸ the Rh-catalysed enantioselective conjugate 1,4-addition of organoboron reagents to activated alkenes is arguably one of the most

powerful and highly stereoselective synthetic methods for carbon–carbon bond-forming processes.³⁹ Consequently, a large number of catalytic systems have been developed for this useful reaction. However, with the exception of chiral dienes,⁴⁰ most of them operate at elevated temperature to achieve high catalytic activity. In 2009, Sakai and co-workers⁴¹ showed for the first time that the use of electron-poor chiral atropisomeric diphosphine ligands could significantly improve the catalytic activity for Rh-catalysed 1,4-addition of arylboronic acids at room temperature. Inspired by this work, we reported that rhodium complexes bearing new fluorinated 3,5-diCF₃-SYNPHOS and *p*-CF₃-SYNPHOS ligands developed by our group, were also highly effective catalysts for this transformation. Initial investigations were conducted at 20°C using 1.5 mol% of catalyst in the presence of KOH in toluene/H₂O (9/1) for 18 h with cyclohexenone as a model substrate (scheme 9). It was found that a wide range of arylboronic acids were tolerated in this reaction giving the corresponding Michael adducts in good to excellent yields and with excellent enantioselectivity. It should be noted that the use of sterically more hindered arylboronic acids such as 2-tolylboronic acid and 1-naphthylboronic acid gave slightly lower enantioselectivity, probably due to increased steric hindrance. As highlighted in scheme 9, both cyclic and acyclic α,β -unsaturated ketones and lactones were found to be suitable substrates for this process. Under optimized reaction conditions, the corresponding cyclic and acyclic

1,4-adducts were obtained in moderate to excellent yields (62–96%) and with excellent enantioselectivities (93–99%).

Remarkably, the above mentioned Rh-(*R*)-3,5-diCF₃-SYNPHOS catalyst system proved to be also highly efficient for the Rh-catalysed asymmetric conjugate 1,4-addition of arylboronic acids to maleimide derivatives, which are one of the most tricky substrates and for which only a few efficient catalytic systems have been reported (scheme 10).⁴² After intensive experiments, optimized reaction conditions were established using 3 mol% of Rh-(*R*)-3,5-diCF₃-SYNPHOS complex as a catalyst in toluene/H₂O (9/1) in combination with 0.5 equiv. of KOH as base, at 30°C for 3 h. From this screening, it was found that the nature of the *N*-protecting groups of the maleimide had a dramatic impact on the stereochemical outcome of the reaction, the *N*-methyl maleimide being the substrate of choice providing the best results in terms of both yield and selectivity. As illustrated by some representative examples depicted in scheme 10, the reaction conducted with a wide variety of arylboronic acids bearing both electron-withdrawing and electron-donating substituents resulted in the formation of various synthetically and biologically important chiral 3-aryl substituted succinimide derivatives, in high yields (75–90%) and good to excellent enantiomeric excesses (80–94% ee). Interestingly, all the 1,4-addition products could be easily upgraded up to 94–99% ee, after a single crystallization.

Scheme 9. Rh-catalysed conjugate addition of arylboronic acids to activated alkenes.

Scheme 10. Rh-catalysed conjugate addition of arylboronic acids to maleimides.

3.3 Rh-catalysed asymmetric intramolecular Pauson–Khand reaction

Since its discovery in the early 1970s,⁴³ the formal [2 + 2 + 1] cycloaddition reaction of an alkyne and an alkene in the presence of carbon monoxide to produce a cyclopentenone, known as the Pauson–Khand (PK) reaction, has been recognized as one of the best methods in organic synthesis to produce cyclopentenone derivatives or cyclopentane-containing natural products.⁴⁴ In 2007, we have reported an efficient intramolecular enantioselective PK reaction of *O*- and *N*-tethered 1,6-enynes catalysed by cationic Rh catalysts generated *in situ* from $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ in the presence of AgOTf as chloride scavenger and various chiral diphosphines including SYNPHOS, DIFLUORPHOS and BINAP family of ligands (scheme 11). It was found during this ligand screening that product yield and enantioselectivity of the reaction were greatly influenced by both the stereoelectronic properties of the

ligands and the electronic density of the alkyne substrates. SYNPHOS and DIFLUORPHOS, which possess a narrower dihedral angle than BINAP type ligands, give improved catalytic activity for most substrates. As highlighted in scheme 11, under optimized reaction conditions, various 1,6-enynes bearing both alkyl and aryl substituents on the alkyne moiety react smoothly at 80 °C in THF under a low pressure of CO (1 atm) to give the corresponding bicyclic cyclopentenones in moderate to good yields and moderate to excellent enantioselectivities.

3.4 Rh-catalysed asymmetric desymmetrization through Pauson–Khand reaction

Transition metal-catalysed asymmetric desymmetrization is an efficient and powerful tool for synthesizing optically active compounds. This strategy stands out as

Scheme 11. Rh-catalysed asymmetric intramolecular Pauson–Khand reaction.

a synthetically practical method because chiral compounds bearing one or multiple chiral centres can be created in a controlled fashion, through differentiation of two prochiral functional groups on readily prepared meso or achiral substrates.⁴⁵ In 2007, we reported an efficient enantioselective synthesis of biologically relevant cyclopentenone derivatives *via* a one-pot, two-steps sequence involving a Pauson–Khand reaction followed by acidic hydrolysis of the resulting bicyclic

compounds (scheme 12).⁴⁶ In this transformation, a wide variety of bisallenyl propargyl acetals reacted smoothly through a PK reaction to give the cyclized compounds using a neutral Rh(I)-SYNPHOS catalyst prepared *in situ* by mixing 3 mol% of $[\text{Rh}(\text{cod})\text{Cl}]_2$ and 9 mol% of SYNPHOS. Subsequent acidic hydrolysis of the bicyclic compounds afforded the desired chiral cyclopentenones in good yields (77–84%) and moderate to excellent enantiomeric excesses ranging

Scheme 12. Rh-catalysed asymmetric desymmetrization through Pauson–Khand reaction.

Scheme 13. Total synthesis of gymnangiamide.

from 64% to 95%. It should be noted that cinnamaldehyde not only serves as a solvent but also as a source of carbon monoxide by *in situ* Rh(I)-catalysed decarbonylation.

4. Synthetic applications

As part as our ongoing projects directed toward the synthesis of relevant biologically active molecules, we have successfully used both SYNPHOS and DIFLUORPHOS ligands in the hydrogenation of functionalized ketones for the total synthesis of gymnangiamide, symbioramide[®] and SR58611A.

4.1 Synthesis of gymnangiamide

Gymnangiamide⁴⁷ is a cytotoxic pentapeptide isolated in 2004 from the marine hydroid *Gymnangium regae* Jaderholm, which contains three non-standard amino acid residues, namely *N*-desmethyl-Dolaisoleucine (Ddil), *O*-desmethyl-Dolaproine (Ddap) and α -guanidino-*L*-serine (Gser) as well as (2*S*, 3*S*)-isoleucine (Ile) and (2*S*, 3*R*)-phenylserine (Pser). We reported a total synthesis of gymnangiamide relying on Ru-SYNPHOS-mediated asymmetric hydrogenation of α -substituted β -ketoesters through dynamic kinetic resolution for the preparation of the non-proteinogenic chiral amino acids Pser **3** and Ddap **4** (scheme 13). The *syn* α -amino β -hydroxyester and α -methyl β -hydroxy

Scheme 14. Total synthesis of symbioramide.

Scheme 15. Hemisynthesis of taxotere[®].

ester moieties found respectively in **3** and **4** were thus enantio- and diastereomerically prepared using this method. The Ddap, Pser, Ddil, Ile and Gser amino acid residues were then assembled using iterative DEPC-mediated coupling reactions which readily provided the natural gymnangiamide. Moreover, this efficient synthesis allowed a stereochemical reassignment at the C³⁴ stereocenter leading to a stereochemical revision of the natural product.⁴⁸

4.2 Synthesis of symbioramide

A total synthesis of symbioramide,⁴⁹ a naturally occurring bioactive ceramide, has been completed⁵⁰ using a convergent route that involved the dynamic kinetic resolution of an α -amino β -ketoester through ruthenium-SYNPHOS-catalysed hydrogenation and efficient stereoselective reduction of a α -keto- β -yne ester (scheme 14). Thus, α -amino β -hydroxyester **9** was readily obtained in a high enantio- and diastereoselective fashion from the corresponding β -ketoester **8** using [Ru(*R*)-SYNPHOS]Br₂ complex in the hydrogenation step, and subsequent reduction of the ester function followed by acetonide formation provided **10**. On the other hand, carboxylic acid **13** was prepared

from α -keto- β,γ -acetylenic ester **11** through (*S*)-alpine borane reduction of the ketone function followed by stereoselective LiAlH₄ reduction of the resulting propargylic alcohol. Coupling of compounds **10** and **13** proceeded cleanly using HATU/DIPEA, and global deprotection of the hydroxy functions then delivered symbioramide.

4.3 Hemisynthesis of taxotere[®]

Furthermore, we achieved the hemisynthesis of taxotere[®],⁵¹ an analogue of taxol[®],⁵² both remarkable broad spectrum cancer therapeutic agents.⁵³ To this end, dynamic kinetic resolution of α -chloro β -ketoester **14** using the (*R*)-DIFLUORPHOS ligand allowed a highly enantio- and diastereoselective access to the *anti* protected phenylisoserine side chain **18** of taxotere[®] through formation of the enantiomerically enriched α -chloro β -hydroxy ester **15**, followed by conversion into the corresponding epoxide **16** which was regio- and stereoselectively cleaved to afford **17** (scheme 15). Oxazolidine formation and hydrolysis of the ester function then provided the corresponding carboxylic acid **18** which was used for the esterification of the 7,10-bis-trichloroethoxycarbonyl derivative of 10-desacetyl

Scheme 16. Synthesis of SR58611A.

baccatin III **19** under previously reported conditions.⁵⁴ Subsequent cleavage of the oxazolidine moiety and deprotection of the 2,2,2-trichloroethoxycarbonyl (Troc) groups⁵⁵ then afforded taxotere[®].

4.4 Synthesis of SR58611A

SR58611A⁵⁶ is a potent and selective β_3 -adrenergic receptor agonist for the treatment of various diseases including obesity, type 2 diabetes and depression. We reported a practical synthesis⁵⁷ of this compound involving the Ru–SYNPHOS-mediated asymmetric hydrogenation of the trisubstituted *N*-acetyl enamide **21** prepared from the corresponding 2-tetralone (scheme 16). The reduction was carried out under 40 bar of hydrogen pressure in methanol in the presence of 1 mol% of $[\{\text{RuCl}((R)\text{-SYNPHOS})\}_2(\mu\text{-Cl})_3]\text{[NH}_2\text{Me}_2\text{]}$, and delivered the hydrogenated compound in good yield and 95% ee. Deprotection of the amine was performed under mild conditions⁵⁸ and the resulting aminotetralin **22** was reacted with (*R*)-chlorostyrene in refluxing DMSO to afford enantiomerically pure SR58611A after crystallization of the corresponding hydrochloride salt.⁵⁶

5. Conclusion

Some recent applications of DIFLUORPHOS, SYNPHOS and SYNPHOS analogue ligands have been described. These atropisomeric diphosphanes exhibiting complementary stereoelectronic properties proved their efficiency in both C–H and C–C bond-forming processes. Thus, asymmetric hydrogenation of trisubstituted enamides, quinoline, quinoxaline and isoquinoline derivatives catalysed by ruthenium or iridium complexes bearing those ligands provided in high yields and good to excellent selectivity the corresponding enantiomerically enriched oxygen and nitrogen-containing scaffolds which are relevant targets in the pharmaceutical industry. Carbon–carbon bond-forming processes were addressed as well and studies of asymmetric conjugate 1,4-addition of arylboronic acids to activated alkenes, asymmetric intramolecular Pauson–Khand reaction and cycloisomerization of *N*-tethered 1,6-enynes demonstrated the high performance of DIFLUORPHOS, SYNPHOS and SYNPHOS analogues. Finally, application of these C–H and C–C bond-forming processes to the synthesis of several biologically relevant compounds including gymnangiamide, symbioramide, taxotere and SR58611A is also reported.

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