The Asymmetric Suzuki Coupling Route to Axially Chiral Biaryls

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Axially chiral biaryls are ubiquitous structural motifs in biologically active natural products or ligands for homogeneous catalysis. Their properties relate to the particular spatial arrangement of the two aromatic residues and therefore the control of their absolute configuration constitutes an issue of major importance. The asymmetric Suzuki–Miyaura coupling has recently emerged as an attractive alternative to standard methods for the control of biaryl axial chirality. Recent diastereo- and enantioselective approaches, as well as some applications in target-oriented synthesis, are commented on in this microreview.

1. Introduction

The axial chirality of biaryls arises from the hindered rotation around the biaryl bond (the so-called atropisomerism phenomenon) due to the presence of at least two bulky substituents in the *ortho* position to this bond. Axially chiral biaryls are structural motifs present in a number of natural products from various origins and have a wide range of biological properties.[1] Among these vancomycin (**1**) (Figure 1[2]), a clinically used glycopeptide antibiotic from *Streptomyces orientalis*,[3] steganacin (**2**), a cytotoxic tubulin-binding dibenzocyclooctadiene lignan from *Steganotaelia araliacea*,[4] and michellamine B (**3**), an *anti*-HIV naphthylisoquinoline alkaloid from *Ancistrocladus abbreviatus*,[5] have aroused the interest of many synthetic chemists in the past decades for both structural and biological reasons. Besides biological activity, axially chiral biaryls find many other applications in chemistry. For instance they prove efficient ligands for asymmetric catalysis, as highlighted by the well-known BINAP (**L**^{1}),[6] MOP (**L**^{2})[7] and BINOL (**L**^{3})[8] ligands, which show remarkable enantioselectivities in a number of transition metal catalyzed processes. In many cases the absolute configuration of the biaryl axis is crucial to the property of the molecule, for instance biological activities are often restricted to one atropisomeric form.[4] To date, a large number of synthetic methods have been described in the literature in order to address the issue of the axial chirality control in biaryls, some of which have been successfully applied in targeted syntheses.[9] The most popular methods include: intramolecular oxidative couplings in the presence of a metal oxide or via a biarylcuprate intermediate,[10] the intermolecular (Meyers) Grignard/oxazoline coupling,[11] and the asymmetric ring cleavage of configurationally unstable biaryl lactones (Bringmann lactone method).[12] In the past few years, interesting novel concepts have emerged to complete this synthetic arsenal, such as the asymmetric coupling of phenols or anilines with aryllead triacetates,[13] the enantioselective oxidative homocoupling of naphthols catalyzed by copper(I) and a chiral diamine,[14] as well as various types of stereoselective benzannulations.[15] Today, the Suzuki–Miyaura coupling is certainly the most widely used method for the construction of the biaryl bond due to its great versatility and relatively environmentally friendly nature.[16] Despite this growing success, its asymmetric variant still remains a challenge, probably because of the inherent difficulty in coupling two

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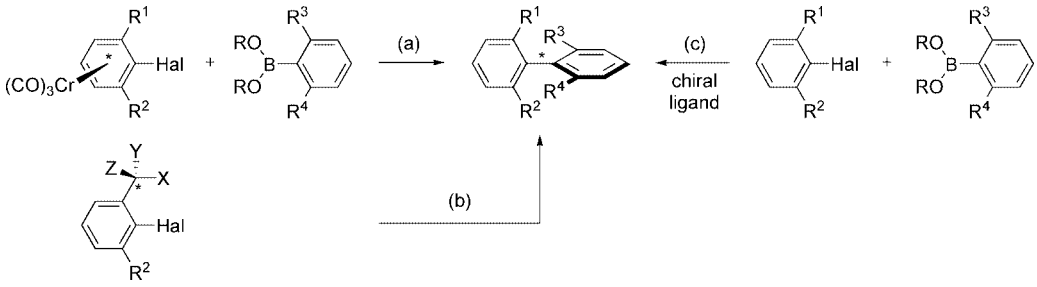


Figure 2. Diastereoselective (a, b) vs. enantioselective (c) Suzuki coupling.

sterically hindered arenes in a transition metal mediated process.[9] The aim of the present review is to summarize recent advances in asymmetric Suzuki coupling, with a particular emphasis on applications to the synthesis of biologically active natural products and analogs. Examples will be classified into diastereoselective or enantioselective methods (Figure 2). Diastereoselective methods consist either of a planar-to-axial (path a) or a central-to-axial (path b) chirality induction, whereas enantioselective methods (path c) involve a chiral palladium ligand as the principal or unique source of chirality.

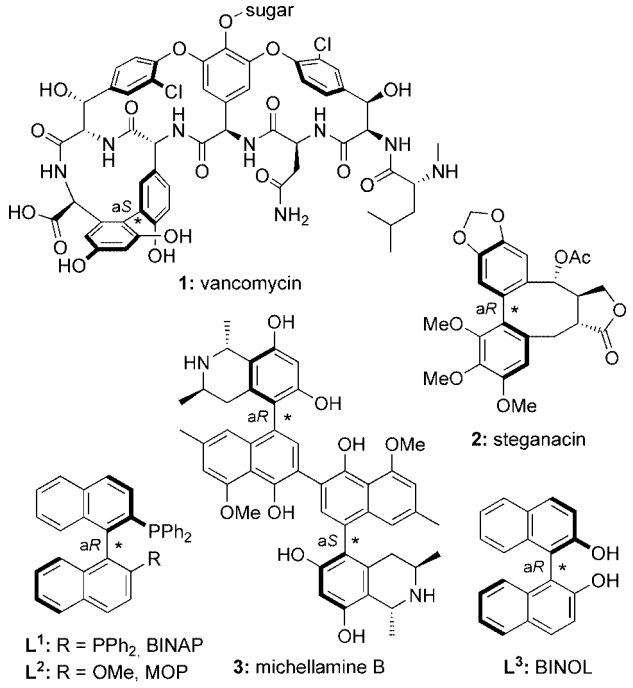
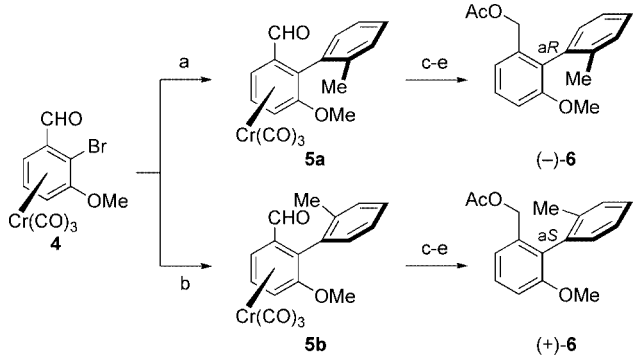


Figure 1. Selected axially chiral natural products and ligands for asymmetric catalysis.[2]

2. Diastereoselective Suzuki Coupling with Achiral Ligands

Planar-to-Axial Chirality Induction

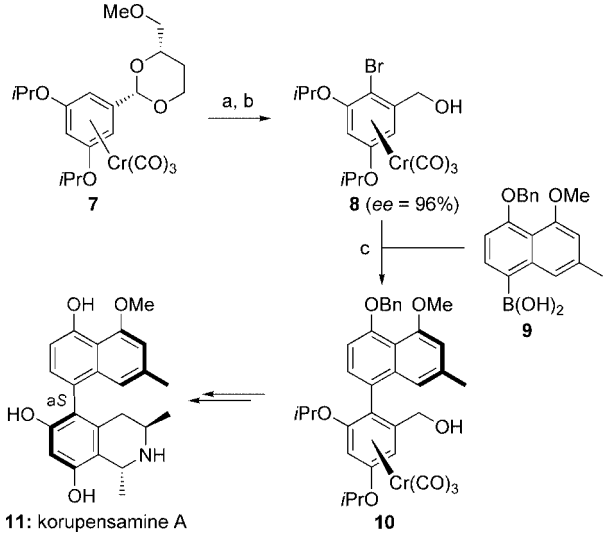
The Suzuki coupling of a chiral (arene)tricarbonylchromium complex (arene = aryl halide) with a boronic acid, developed by Uemura et al., is a powerful diastereoselective method for the synthesis of axially chiral biaryls (Scheme 1).[17] In this approach the biaryl axial chirality is induced by the planar chirality of the (arene)chromium complex. This presents a number of advantages: a) the carbon–halogen bond of the (aryl halide)chromium complex is very electron-deficient, which makes it more reactive in the oxidative addition step of the coupling and generally provides mild reaction conditions; b) the metal complex completely blocks one face of the aryl halide so that high diastereoselectivities are achieved; c) the metal atom can be easily decomplexed by exposure to air and sunlight; d) in principle, the method can furnish both atropisomers from one enantiomer of the chiral (arene)chromium complex. Indeed, when complex **4** was coupled with *o*-tolylboronic acid in refluxing methanol, the kinetically favored *syn*-chromium complex **5a** was exclusively formed, while in refluxing xylene the thermodynamically favored *anti* diastereoisomer **5b** was obtained.[18] After functionalization and decomplexation of **5a** and **5b**, both enantiomers of biaryl **6** could be obtained in optically pure forms. Drawbacks of the (arene) chromium method include: a) the synthesis of required enantiopure (aryl halide)chromium complexes; b) the relative fragility of intermediate (arene)chromium complexes.



Scheme 1. Suzuki coupling with (arene)chromium complexes.[17] Reagents and conditions: a) *o*-tolylboronic acid, $Pd(PPh_3)_4$, aq. Na_2CO_3, MeOH, 75 °C, 30 min (80%); b) *o*-tolylboronic acid, $Pd(PPh_3)_4$, aq. Na_2CO_3, xylene, 140 °C, 30 min (75%); c) $NaBH_4$, MeOH (98%); d) Ac_2O, pyridine (90%); e) *hv*/O_2, Et_2O (52%).

Nevertheless, the efficiency of the method was demonstrated by its successful application to the formal and total syntheses of (–)-steganone,[19] the synthesis of the A–B ring system of vancomycin (**1**),[20] and the total synthesis of korupensamines A and B [the monomeric parts of michellamine B (**3**), having (a*S*) and (a*R*) configurations, respectively].[21] In the last synthesis (Scheme 2), (aryl bromide)

chromium complex **8** was synthesized from chiral acetal **7** in 63% yield and 96% *ee* by diastereoselective lithiation (planar chirality inducing step) followed by quenching with an electrophilic bromine reagent, Lewis acid mediated removal of the chiral auxiliary, and reduction of the aldehyde. Suzuki coupling of **8** with naphthylboronic acid **9** in refluxing methanol provided the kinetically favored *syn* complex **10**, which was further elaborated to korupensamine A (**11**) in sixteen steps.

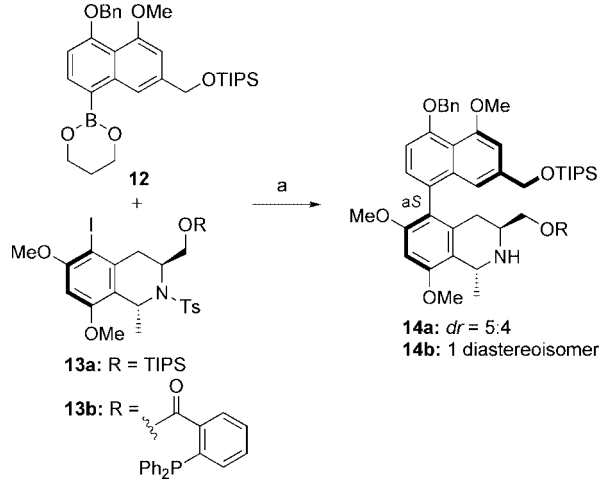


Scheme 2. Total synthesis of korupensamine A.[20] Reagents and conditions: a) *n*BuLi, Et_2O, –78 °C, then $BrCF_2CF_2Br$, then $TiCl_4$ (64%); b) $NaBH_4$, $MeOH/CH_2Cl_2$ (2:1), 0 °C (99%); c) 5 mol-% $Pd(PPh_3)_4$, 1 M aq. Na_2CO_3/MeOH (1:10), 75 °C, 10–30 min (88%); Bn = benzyl.

Central-to-Axial Chirality Induction

Early examples of diastereoselective Suzuki couplings using chirality induction from a stereogenic center with a distance of two (1,3-induction) or three (1,4-induction) atoms from the biaryl axis were described in the total syntheses of the michellamines[22] and vancomycin (**1**).[23] In the syntheses of the michellamines, where the key stereogenic center was too distant from the biaryl axis, poor diastereoselectivities [maximum diastereomeric ratio (*dr*) of 3:2] were observed for the Suzuki coupling step.[22] The lack of stereoselectivity was actually utilized in the stereodivergent synthesis of michellamine B (**3**), which exploited the fact that the natural product has both (a*R*) and (a*S*) configurations at its biaryl axes (Figure 1). Similarly, in the syntheses of vancomycin the best *dr* obtained from the Suzuki coupling was 2:1.[23a,23b] However, in this case Boger et al. circumvented the lack of stereoselectivity by a thermal equilibration of the atropisomeric products, a process which occurred with a 3:1 ratio in favor of the natural (a*S*) atropisomer.[23c] High diastereoselectivites could also be achieved by Nicolaou et al. during synthetic studies related to vancomycin using a chiral ligand. In fact, this process can be better related to enantioselective couplings and will therefore be discussed in the following section.

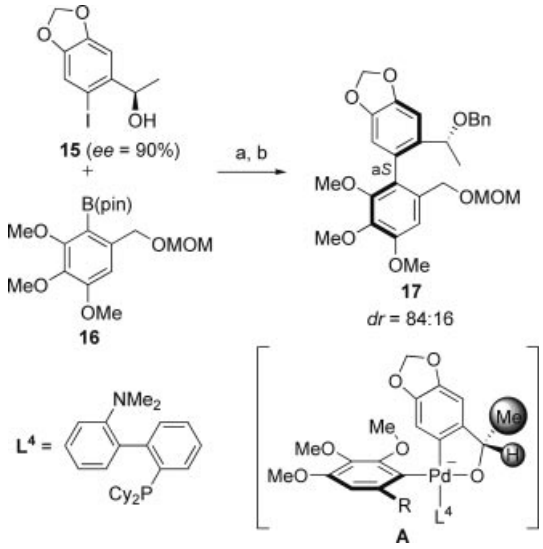
An elegant solution to the Suzuki coupling diastereoselectivity issue was disclosed by Lipshutz et al. in their approach to korupensamine A (Scheme 3).[24] The first attempts of coupling boronate **12** and iodide **13a**, containing a TIPS-protected primary alcohol at the chirality-inducing stereocenter, proved almost nonstereoselective as in previous syntheses.[22] By contrast, the incorporation of a metal-directing phosphane residue [*ortho*-(diphenylphosphanyl)benzoate **13b**][25] instead of the silyl ether allowed a complete control of the axial chirality, with excellent yield. The authors proposed a stereochemical model with coordination of the internal phosphane ligand to the palladium atom in order to account for the observed stereoselectivity.



Scheme 3. Approach to korupensamine A by diastereoselective Suzuki coupling.[24] Reagents and conditions: for **14a**: $Pd(PPh_3)_4$ cat., K_3PO_4, BHT, DMF, 96 °C (81%); for **14b**: 20 mol-% $PdCl_2$(dppf), K_3PO_4, BHT, DMF, 117 °C (81%); TIPS = triisopropylsilyl; BHT = 2,6-di-*tert*-butyl-4-methylphenol.

In 2003, the group of Colobert and our group reported simultaneously similar diastereoselective Suzuki coupling methods (Schemes 4 and 5).[26–27] Our approach relied on a simple 1,3 chirality induction from a stereogenic benzylic alcohol (compound **15**) to the biaryl axis, giving biaryl **17** with a *dr* of 84:16 after Suzuki coupling in the presence of ligand $\mathbf{L^4}$,[28] and aqueous barium hydroxide as the base. Particularly crucial was the combination of ligand $\mathbf{L^4}$, described by Buchwald et al. for Suzuki coupling of hindered substrates,[28] and aqueous barium hydroxide, which accelerated the coupling and limited the formation of hydrolysis byproducts.[29] After benzylation of the alcohol and crystallization, biaryl **17**, which contains the biaryl system of steganes, could be obtained as essentially one diastereomer (*dr* 96:4). The diastereoselectivity could be improved by replacing the MOM protecting group of boronate **16** by the larger triethylsilyl (TES) group, albeit at the expense of the coupling yield.[30] The stereochemical outcome of the coupling was interpreted by the initial formation of an oxapalladacycle from oxidative addition of iodide **15**. In this complex one face would be hindered by the benzylic methyl group, which would direct the orientation of the aromatic ring of **16** in order to minimize steric

interactions with its largest *ortho* substituent (Scheme 4, intermediate **A**). Colobert et al. observed the same chirality induction effect on different coupling substrates.[27] They even reported much better coupling yields and diastereoselectivities upon methylation of the benzylic alcohol and introduction of a chiral sulfoxide β to the methoxy group (Scheme 5). Thus, the coupling of β-hydroxy sulfoxide **18** and naphthylboronic acid **19** afforded biaryl **20** in quantitative yield and as a single diastereomer, using dppf as the palladium ligand and cesium fluoride as the base. A number of other substrates could be coupled with a *dr* from 75:25 to > 99:1. The presence of both chirality centers in the β-hydroxy sulfoxide component proved necessary to obtain high diastereoselectivities, since either the corresponding benzylic ketone or the β-hydroxy sulfone gave a lower *dr*. Besides, there seems to be a matched relative configuration between both chirality centers since the diastereomer of **18**, having the opposite benzylic carbon atom configuration, gave a *dr* of only 55:45. In conclusion, the diastereoselective Suzuki approach by chirality induction from a stereogenic benzylic carbinol appears to be a simple and relatively versatile method for the control of biaryl axial chirality, with a relatively good tolerance to steric factors. Applications to the synthesis of biologically active biaryls such as steganes or vancomycin should follow in the near future.

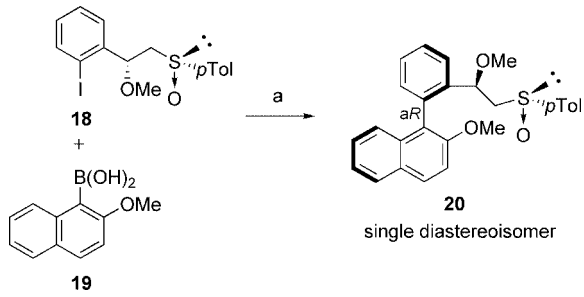


Scheme 4. Approach to the steganacin biaryl system by diastereoselective Suzuki coupling.[26] Reagents and conditions: a) 5 mol-% $Pd(OAc)_2$, 10 mol-% **L⁴**, $Ba(OH)_2{\cdot}8H_2O$, dioxane/H_2O (9:1), 100 °C, 1 h; b) NaH, BnBr, THF, 25 °C, 4 h (63% for two steps); MOM = methoxymethyl.

3. Stereoselective Suzuki Coupling with Chiral Ligands

Diastereoselective Coupling with Chiral Ligands

The use of chiral ligands in asymmetric Suzuki coupling was pioneered by Hayashi et al. who reported the enantioselective nickel-catalyzed biaryl coupling of naphthyl Grignard reagents in the presence of the chiral ferrocenylphosphane ligand PPFOMe (analogous to **L⁵**, Figure 3), with *ee* values up to 95%.[31] Uemura, Hayashi et al. disclosed the utilization of chiral phosphanes such as **L¹** and **L⁵** in the enantioselective desymmetrization of a *meso*-(arene)chromium complex by Stille, Negishi or Suzuki cross-coupling of vinylmetal reagents (with *ee* up to 44%).[32] A third pioneering work by Shibasaki et al. reported an intramolecular enantioselective (non-biaryl) Suzuki coupling using chiral phosphanes, with *ee* values of up to 31% with ligand **L⁵**.[33] Acknowledgments should be given to the early reports, which inspired subsequent work in enantioselective biaryl Suzuki coupling. The first use of a chiral ligand in a *biaryl Suzuki coupling* was reported by Nicolaou et al. during model synthetic studies toward vancomycin (Scheme 6).[34] The coupling of chiral iodide **21** with cyclic boronate **22** afforded biaryl **23** as a 1:1 mixture of atropo-diastereomers in the presence of PPh_3 as the ligand, showing the spectator role of the remote chirality center of **21**. When (a*R*)- or (a*S*)-BINAP (**L¹**) were employed, a *dr* of 3.5:1 was observed in favor of one or the other atropo-diastereomer. When the coupling was repeated with a more functionalized iodoarene, containing the B–C–D ring system of vancomycin, a single atropo-diastereomer was obtained, albeit in moderate yield. Similarly, Bringmann et al. reported that the coupling of iodoarene **24** and boronic acid **25** in the presence of PPh_3 afforded a 45:55 mixture of the naphthylisoquinoline alkaloid ancistroealaine A **26** and its (a*R*) atropo-diastereomer ancistrotanzanine B.[35] The diastereoselectivity was reversed using ligand (a*S*)-**L¹** or (*R*,*S*p)-**L⁵**, with a 75:25 ratio in favor of **26**. In this case a matched-mismatched effect was evidenced since the enantiomeric ligands provided a lower *dr* of 61:39 for (a*R*)-**L¹** and 51:49 for (*S*,*R*p)-**L⁵**. New phenylnaphthyl ligands such as **L¹⁰** (Figure 3) were also evaluated in the coupling of **24** and **25**, which gave improved yields but lower diastereoselectivities compared to **L¹** and **L⁵**.[35b] In this example, contrary to the case of the vancomycin biaryl system, it seems that both the resident stereogenic center and the chiral ligand influence the atroposelectivity of the coupling. At this point, it appears that commercially available ligands such as **L¹** and **L⁵** are clearly not optimal for asymmetric biaryl Suzuki coupling and specific ligands have to be designed for this purpose.



Scheme 5. Diastereoselective Suzuki coupling with β-hydroxy sulfoxides as chiral auxiliaries.[27] Reagents and conditions: 10 mol-% $Pd(OAc)_2$, 15 mol-% dppf, CsF, dioxane, reflux, 1 h; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

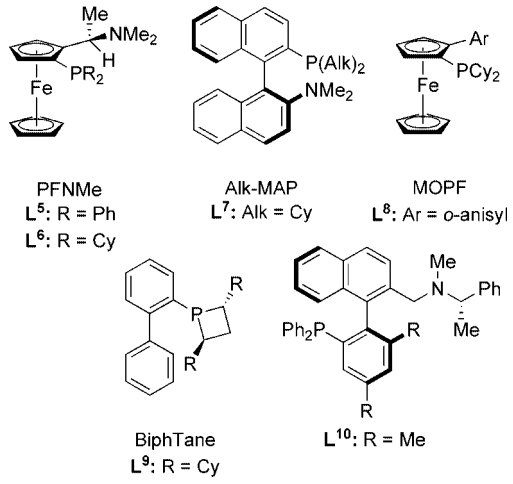
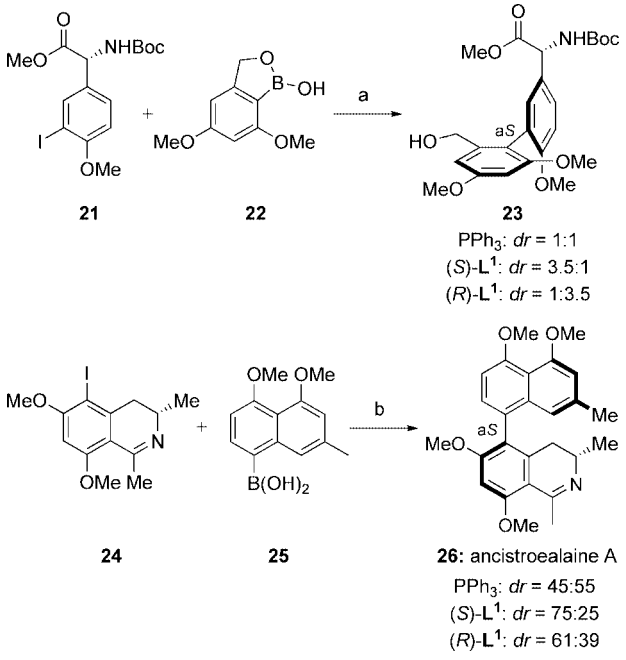


Figure 3. Chiral ligands used in asymmetric Suzuki couplings (see also Figure 1).

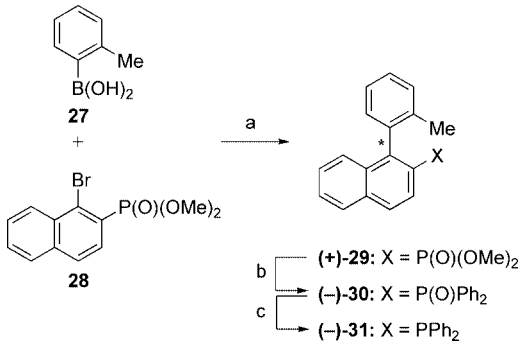


Scheme 6. Diastereoselective Suzuki coupling with chiral ligands for the synthesis of vancomycin biaryl system[34] and naphthylisoquinoline alkaloids.[35] Reagents and conditions: a) 20 mol-% $Pd(OAc)_2$, 0.6 equiv. ligand, aq. Na_2CO_3, toluene or THF, 90 or 60 °C, 2 h [yields: 83% with PPh_3, 75% with (a*R*) and (a*S*)-**L**^{1}]; b) 10 mol-% $Pd(PPh_3)_4$ or 10 mol-% Pd_2dba_3/0.3 equiv. **L**^{1}, aq. $NaHCO_3$, toluene, reflux, 10 h [yields: 50% with PPh_3 and (a*S*)-**L**^{1}, 45% with (a*R*)-**L**^{1}].

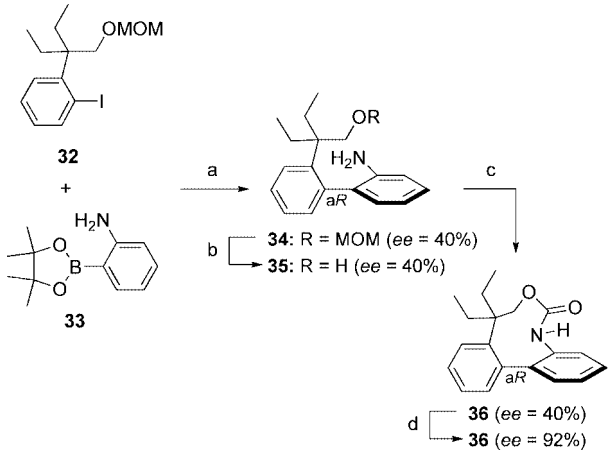
Enantioselective Coupling with Chiral Ligands

The first efficient atropo-enantioselective Suzuki couplings were independently reported by the groups of Cammidge[36] and Buchwald[37] in 2000. The former reported the synthesis of two simple axially chiral binaphthalenes, 2-methyl-1,1′-binaphthyl and 2,2′-dimethyl-1,1′-binaphthyl. A maximum of 85% *ee* with a 60% yield was reached with Hayashi's ferrocenylphosphane **L**^{5} (Figure 3) and cesium fluoride as the base in DME. Interestingly, the use of different boronates resulted in the production of different biaryl enantiomers, which indicates that the reaction may be operating under kinetic control and that the stereo-determining step may be transmetalation. In addition, it was shown later by the group of Colobert, who studied a similar enantioselective biaryl Suzuki coupling giving 2,2′-dimethoxy-1,1′-binaphthyl,[38] that the ligand [in this case BINAP (**L**^{1})]/palladium ratio had a significant impact on the enantioselectivity. It was also shown recently that cationic palladium complexes of BINAP (**L**^{1}) and Cy-BINAP give interesting results in the enantioselective biaryl Suzuki coupling of naphthyl substrates, with *ee* values up to 70%.[39] In 2000 Buchwald et al. reported the synthesis of various axially chiral phenylnaphthyls and binaphthyls using new binaphthyl-monophosphanes such as **L**^{7} (Figure 3).[37] These ligands are chiral analogs of biphenylphosphane ligands such as **L**^{4} (Scheme 4) previously developed for Suzuki coupling of chloroarenes and bulky bromoarenes.[28] Ligand **L**^{7}, bearing two cyclohexylphosphorus substituents, gave the highest enantioselectivities with substrate-dependent *ee* values between 57 and 92% and excellent yields. Contrary to the observation of Colobert et al., different Pd/ligand ratios did not affect the enantioselectivity, suggesting a high degree of ligand acceleration in this case. These results were applied to the synthesis of an enantiopure (phenylnaphthyl)phosphane **31** (Scheme 7). The coupling of *o*-tolylboronic acid **27** and phosphonate **28** with as little as 0.2 mol-% Pd^0 and 0.24 mol-% **L**^{7} gave biarylphosphonate **29** with 95% yield and 86% *ee*. After recrystallization, the optical purity of **29** was improved to 99%. Phosphonate **29** was then elaborated to diphenylphosphane **31** (*ee* = 99%) in two steps. This example shows that axially chiral phosphane ligands, potentially useful for asymmetric catalysis, can be obtained by enantioselective Suzuki coupling. The application of Buchwald's ligand **L**^{7} to the asymmetric synthesis of tricyclic biaryl **36**, a potent analog of the antitubulin natural product (–)-rhazinilam,[40] was reported recently by our group (Scheme 8).[41] Phenyl iodide **32**, obtained in four steps from commercially available material, was coupled with pinacol-derived boronate **33** under conditions previously optimized for the coupling of bulky substrates,[29] in the presence of 5 mol-% Pd^0 and 6 mol-% ligand (a*S*)-**L**^{7}. After deprotection of the primary alcohol, amino alcohol **35** was obtained in good yield along with moderate enantioselectivity (*ee* = 40%). Compounds **34** and **35** bear only two substituents in positions 2 and 2′ and have therefore limited configurational stability. However, under the described conditions, the coupling was sufficiently fast (45–60 min at 80 °C) to avoid thermal epimerization of the product. Cyclization with triphosgene at low temperature gave the target **36** with 40% *ee*. A single crystallization improved the *ee* to 92%, providing compound quantities suitable for further biological evaluation. During this study, other ligands were synthesized and evaluated in the Suzuki coupling step. The ligand design was based on the assumption that (aryl)dialkylphosphanes $P(Ar)(Alk)_2$ give the highest enantioselectivities. From the ligands (**L**^{1}, **L**^{2} and **L**^{5}–**L**^{9}) that were screened (Figures 1

and 3), ligand **L**[7] gave the best yield and *ee*, which was confirmed on another Suzuki coupling system. MOPF ligands such as **L**[8] were also reported by Johannsen et al. to give significant enantioselectivity in biaryl Suzuki coupling, with *ee* values of up to 54% for the model system 2,2′-dimethyl-1,1′-binaphthyl.[42] From our data, it was not clear whether the Suzuki coupling giving biphenyl **34** was under kinetic or thermodynamic control. For instance, the boronate structure had a significant influence on the enantioselectivity but different reaction temperatures gave the same *ee* values. Given the great substrate dependency of the Suzuki coupling, it is possible that different coupling substrates give rise to different mechanisms of stereoselectivity control.



Scheme 7. Enantioselective Suzuki coupling with MAP ligand **L**[7].[37] Reagents and conditions: a) 0.1 mol-% $Pd_2(dba)_3$, 0.24 mol-% (a*S*)-**L**[7], K_3PO_4, toluene, 60 °C, 24 h (95%); b) PhMgBr, DME, 45 °C, 24 h (89%); c) poly(methylhydrosiloxane) (PMHS), $Ti(OiPr)_4$, THF, 70 °C, 24 h (86%).



Scheme 8. Asymmetric synthesis of rhazinilam analog **36**.[41] Reagents and conditions: a) 2.5 mol-% $Pd_2(dba)_3{\cdot}CHCl_3$, 6 mol-% (a*S*)-**L**[7], $Ba(OH)_2{\cdot}8H_2O$, dioxane/water (9:1), 80 °C, 1 h; b) concd. HCl/MeOH (1:4), 35 °C, 1 h (66% for two steps); c) $(Cl_3CO)_2C{=}O$, pyridine, CH_2Cl_2, –78 °C, 30 min (98%); d) crystallization from CH_2Cl_2/heptane (35%).

4. Summary and Outlook

The diastereoselective and enantioselective Suzuki couplings have emerged as efficient tools for the control of the axial chirality of biaryls. An array of methods were developed and applied to the synthesis of bioactive natural products and analogs, such as vancomycin, steganacin and naphthylisoquinoline alkaloids. Diastereoselective methods, and in particular the use of (arene)chromium complexes or benzylic stereocenters, have proven the most selective and versatile so far, but enantioselective couplings have recently emerged as viable and more direct alternatives, thanks to the design of new chiral ligands such as **L**[7]. Inherent difficulties such as elevated reaction temperatures, sensitivity towards steric hindrance and important substrate dependency still limit a broader use of the atropo-selective Suzuki coupling. In particular, biaryls with thermally labile configurations (such as **34**) and those with similar substitution patterns at both aromatic rings (such as symmetrical binaphthyls) have probed the limits of the existing methods. Future directions in the control of biaryl axial chirality might include further ligand design and the development of alternative coupling methods.

Acknowledgments

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