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Design and synthesis of chiral ligands for use in stereoselective atropisomeric biaryl coupling reactions

Mary J. Gresser
University of Wollongong

DESIGN AND SYNTHESIS OF CHIRAL LIGANDS

FOR USE IN

STEREOSELECTIVE ATROPISOMERIC

BIARYL COUPLING REACTIONS

A thesis submitted in fulfilment of the
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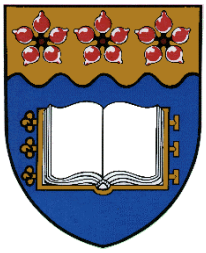

by

Mary J. Gresser, B. Sc. (Adv.) (Hons)

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Certification

I, Mary Jacinta Gresser, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

Mary Jacinta Gresser

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Publications

Gerhard Bringmann, Anne J. Price Mortimer, Paul A. Keller, Mary J. Gresser, James Garner, Matthias Breuning; Atroposelective Synthesis of Axially Chiral Biaryl Compounds, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384-5427.

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Abstract

A new chiral ligand design program was initiated for the stereoselective synthesis of sterically hindered systems, such as atropisomeric biaryls. The concept of helical-sense discrimination was investigated, for use in the Pd-based Suzuki coupling reaction. A new set of design principles was established for chiral ligands for use in these reactions; 1) the ligand must contain a defined helical twist enclosed at each end by donor atoms, 2) the ligand must be bidentate, to best transfer the helical aspect of the ligand to the Pd reaction site, 3) the substituents of the donor atoms should be tied back in ring systems to prevent steric hindrance of the already sterically demanding reaction site and 4) the helical twist should be in close proximity to the Pd reaction site. The first two target scaffolds which would incorporate the above principles were chiral 2,2'-bispyrrolidine and 2,2'-bisindoline.

A new synthetic strategy was devised, which provided both enantiomers of 2,2'-bispyrrolidine and was modified to access 2,2'-bisindoline. The key steps of the synthesis were the metathesis dimerisation and subsequent Sharpless asymmetric dihydroxylation (AD) from achiral starting materials.

(*R*,*R*)-*N*,*N*'-Di-*tert*-butoxycarbonyl-2,2'-bispyrrolidine **92a** was synthesised in 13% yield, over 10 steps, from commercially available 4-penten-1-ol. The metathesis reaction gave the desired benzyl protected alkene as a mixture of geometric isomers (4:1), which were dihydroxylated using AD mix α and standard Sharpless conditions to give the corresponding diol with an *ee* of 80%.

The procedure was repeated using the PMB protected derivatives to give (*R*,*R*)-**92a** in overall 9% yield, with the AD reaction using AD mix α giving the diol in 92% *ee*. The procedure was repeated using AD mix β, which gave the enantiomeric 2,2'-bispyrrolidine (*S*,*S*)-**92b** in 24% overall yield and 88% *ee*.

The synthetic strategy was applied towards the synthesis of chiral 2,2'-bisindoline, for which there is no literature precedent. Benzyl protected 2-allylphenol was dimerised via the metathesis reaction using Grubbs 1st generation catalyst, to give the dimeric aromatic allylic alkene in 81% yield (*E*:*Z* 5.2:1). The geometric ratio could be improved to 9:1 via recrystallisation from DCM/hexanes. Grubbs 2nd generation catalyst was found to increase the geometric ratio, however the alkene could not be separated from the secondary metathesis products. The alkene was dihydroxylated using AD mix α in 15% yield and 64% *ee*. The yield was increased to 60% by using modified Sharpless conditions, however the enantiopurity decreased to 36% *ee*.

The poor outcome of the AD reaction lead to extensive investigations into the Sharpless AD reaction via the modification of the *ortho* substituent of dimeric aromatic allylic alkenes. A variety of dimeric, heterodimeric and monomeric alkenes were synthesised, including seven phenolic based and two nitrogen based dimeric alkenes, via the metathesis reaction using both Grubbs 1st and 2nd generation catalysts. The alkenes were subsequently dihydroxylated using AD mix α and AD mix β. The diols were formed in poor yield (0% to 58%) and poor enantioselectivity (1% to 58%). The AD reaction of the *ortho*-tolyl derivative increased the yield (45-65%) and the *ee* (62-70%) while the unsubstituted derivative gave the corresponding diol in 84-88% yield with excellent stereocontrol (93-95% *ee*).

It was therefore concluded that the presence of *ortho*-substituents in the aromatic rings of dimeric allylic aromatic alkenes prevented access of the substrate to the ligand bound OsO_4, thereby minimising chemical yield and enantioselection.

Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
CI	chemical ionisation
CM	cross-metathesis
COSY	correlation spectroscopy
d	day
DCM	dichloromethane
DHQ	dihydroquinine
DHQD	dihydroquinidine
DMF	*N*,*N*'-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron ionisation
ES	electrospray
h	hour
HMBC	heteronuclear multiple bond correlation experiment
HPLC	high performance liquid chromatography
HR	high resolution
HSQC	heteronuclear single quantum correlation
IR	infrared
min	minute
MHz	megahertz
m/z	mass/charge ratio
MS	mass spectrometry
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
PMB	*p*-methoxybenzyl
ppm	parts per million
RCM	ring-closing metathesis
ROMP	ring-opening polymerization
RT	room temperature
SM	self-metathesis
SMPs	side metathesis products
Tf	trifluoromethanesulfonyl (triflate)
THF	tetrahydrofuran
TLC	thin layer chromatography
TBS	*tert*-butyldimethylsilyl
TMS	trimethylsilane
UV	ultraviolet

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