Enantioselective synthesis of biaryl atropisomers using distal ionic interactions

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1 Abstract

Biaryl atropisomers are important in the synthesis of antiviral, antihypertensive and antifungal drugs. While the traditional Suzuki-Miyaura reaction with a neutral ligand is the most widely used method to construct biaryl atropisomers, there remain certain compounds difficult to synthesize with favourable enantiomeric purity. Hence, in this report, we investigated the use of novel chiral anionic ligands in Suzuki-Miyaura reaction to synthesise biaryl atropsiomers with high enantiomeric purity. It was observed that anionic chiral ligands have the potential to display distal ionic substrate-catalyst interactions and direct axial chirality of resulting biaryl compounds. As such, we investigated the use of ionic interactions in Suzuki-Miyaura reactions by changing the substituents of the boronic acid and bromide substrates reacting with a novel anionic chiral ligand. There was a significant increase in enantiomeric excess (ee) of up to 74% when anionic ligand is used instead of neutral ligand. We also managed to optimise a disubstituted diamine biaryl atropisomer reaction by varying bases and found that K_2CO_3 was the superior base affording product in 60% ee. With the use of ionic interactions in Suzuki Miyaura reactions, we were able to improve upon traditional Suzuki Miyaura reactions with neutral ligand to obtain compounds with excellent yield and enantiomeric purity, thereby providing a potentially more efficient method for the enantioselective synthesis of biaryl atropisomers.

Keywords— Biaryl atropisomers, Suzuki-Miyaura reaction, Chiral anionic ligand, Axial chirality, Ionic interactions, Enantiomeric excess

2 Introduction

Biaryl compounds are an important class of aromatic compounds, which are versatile building blocks for the synthesis of antiviral[3], antihypertensive[4], and antifungal[5] drugs. However, the methodology for the enantioselective synthesis of biaryls has been a challenging focus in the field of asymmetric synthesis for decades, with traditional synthesis yielding unfavourable enantiomeric purity for certain compounds. As such, the synthesis of atropisomers turns to modern methods, with one notable method being the usage of distal ionic interactions to direct enantioselectivity. In our current lab, some success has been achieved in using secondary ionic interactions to induce enantioselectivity. In this report, we further investigated using this strategy to expand the scope of asymmetric transformation.

3 Experimental Section

3.1 Scheme 1. Synthesis of Anionic Chiral Ligand

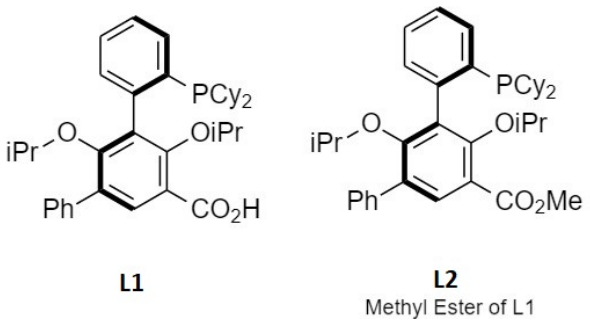

Figure 1: Anionic ligand (L1) and neutral ligand (L2)

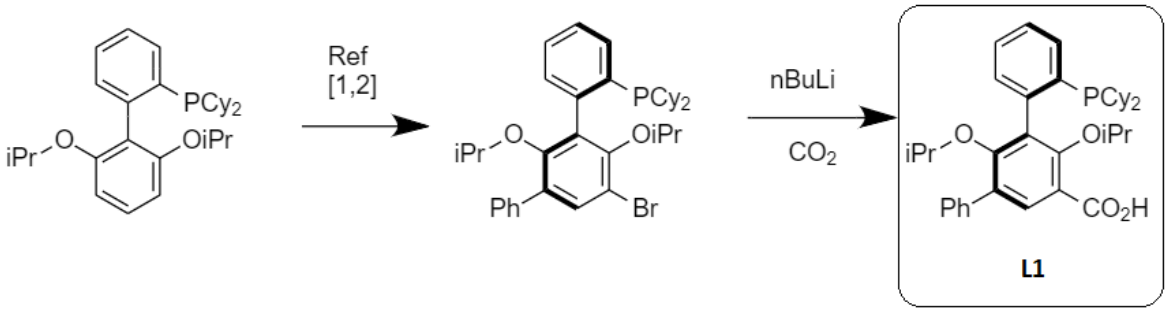

Figure 2: Synthesis of anionic chiral ligand

In this report, 2 main ligands were utilised - L1 is the anionic chiral ligand that is able to establish distal ionic interactions, while L2 is the methyl ester of L1, which is a neutral ligand. With the carboxylic group in L1 deprotonated to carboxylate anion in basic Suzuki - Miyuara reaction conditions, this anionic part of L1 is then able to establish ionic interactions. L2 serves as the control ligand to compare the effects of the ionic interactions of L1. The synthesis steps of L1 is shown in figure 2.

3.2 Scheme 2. Distal ionic interactions direct enantioselectivity

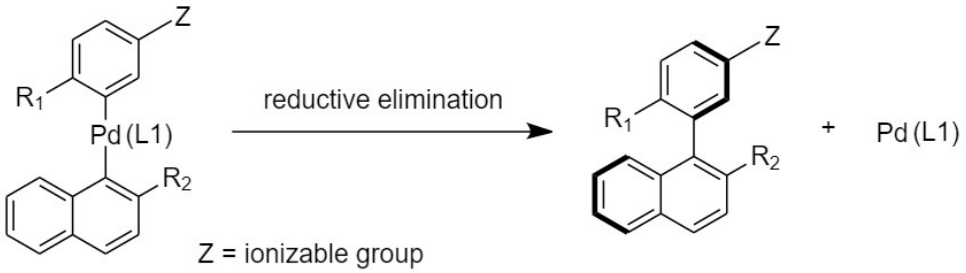

Figure 3: Ionic interactions in reductive elimination step

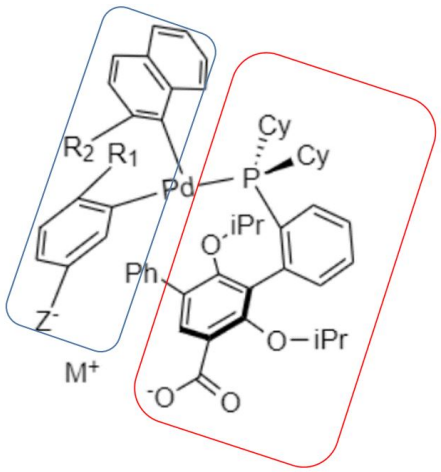

Figure 4: Proposed stereochemical model - left (blue): Pd-substrate complex | right (red): anionic ligand (L1)

We propose that our L1 (figure 1) anionic ligand interacts with the charged substituent (Z^-M^+) of the substrate preferentially as demonstrated in the above stereochemical model (figure 4). Prior to the leaving of the Ligand-Palladium (Pd-L1) complex in the reductive elimination step (figure 3), L1 is joined with the Pd-substrate complex as shown in figure 2. L1 interacts with the anionic group (Z^-) on the substrate via a cation bridge (M^+). The cation bridge, contributed by the base used in the synthesis, forms a charged substituent (Z^-M^+) with the anionic group which interacts with L1. Through this interaction, L1 preferentially directs the axial chirality of the resulting biaryl compound. Here, we conclude that catalyst-controlled electrostatic steering of substrates leads to an enantioselective Suzuki–Miyaura reaction that establishes axial chirality.

3.3 Scheme 3. Effect of Distal Ionic Interactions

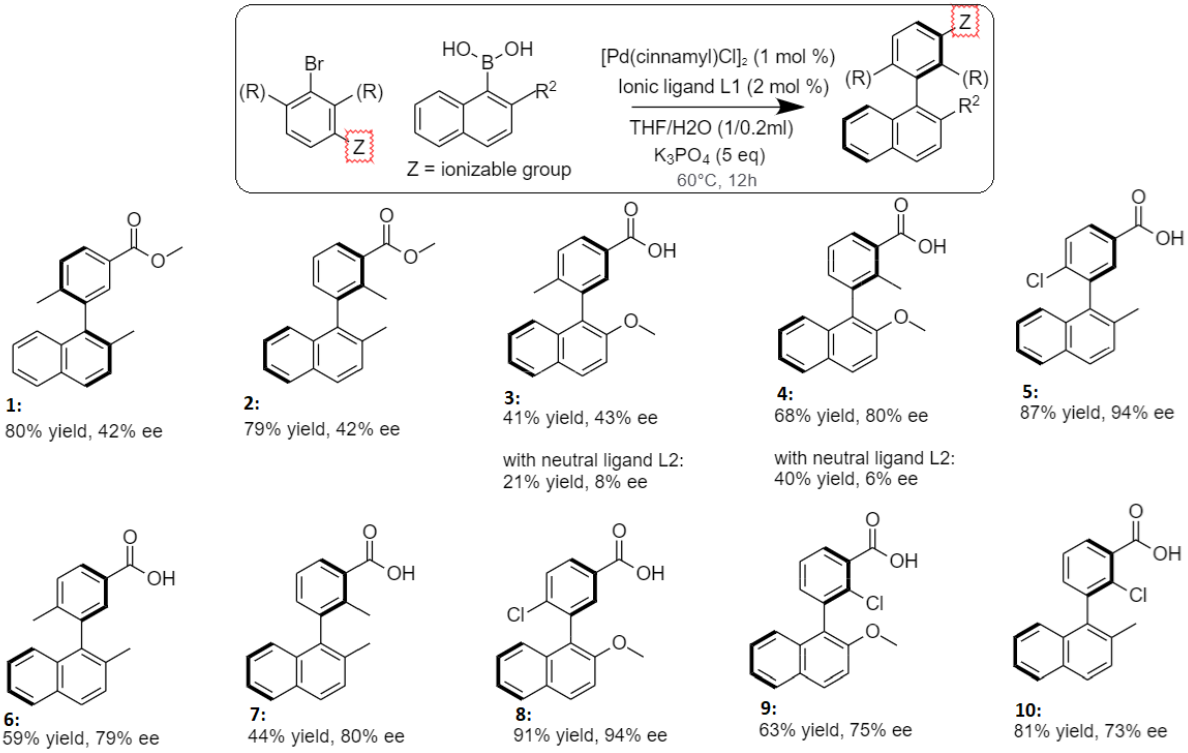

Figure 5: Effect of meta-distal ionic group and its activity on enantioselectivity

By comparing the enantiomeric excess (ee) of compounds **1** with **6** and compounds **2** with **7**, we observe that for the same substituents, the molecule with ionizable groups displayed significantly higher ee. This is consistent with the fact that ionizable groups allow our chiral ionic ligand to direct enantioselectivity, thus improving the ee. Again, this is observed through the significant increase in ee for compounds **3** and **4** when anionic ligand L1 is use instead of neutral ligand L2, implying the huge role that ionic interactions play in improving the ee.

Different substituents for the boronic acid and bromide yield different steric and electrostatic effects. Using the chiral anionic ligand L1, we observe the highest e.e when the chlorine group is para with respect to the ionic group. This may be due to the fact that the chlorine group is ortho, para directing, which helps to stabilise the resonance structures of benzoate anion, thereby allowing greater ionic interactions to take place with the more stabilized benzoate anion.

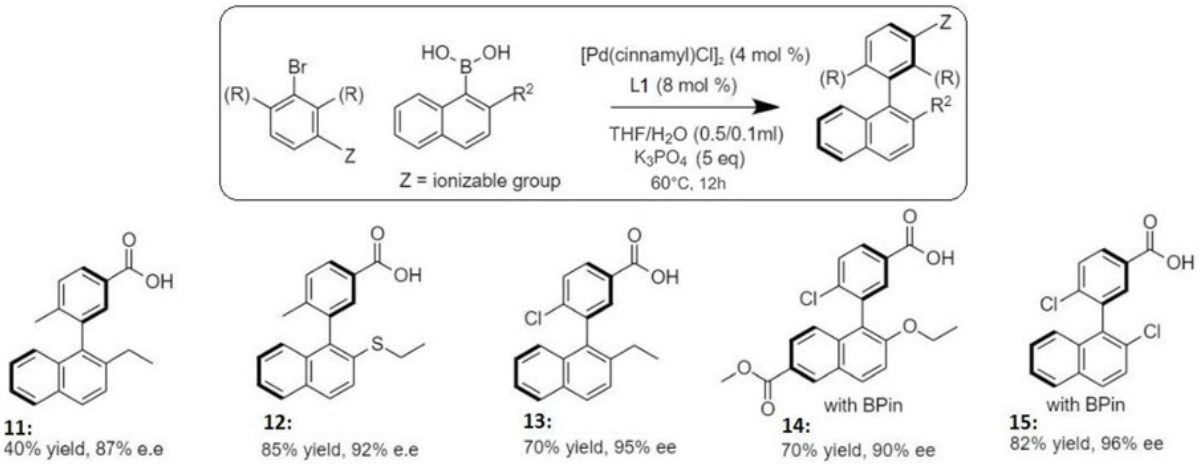

Figure 6: Expanded scope of meta ionizable group on enantioselectivity

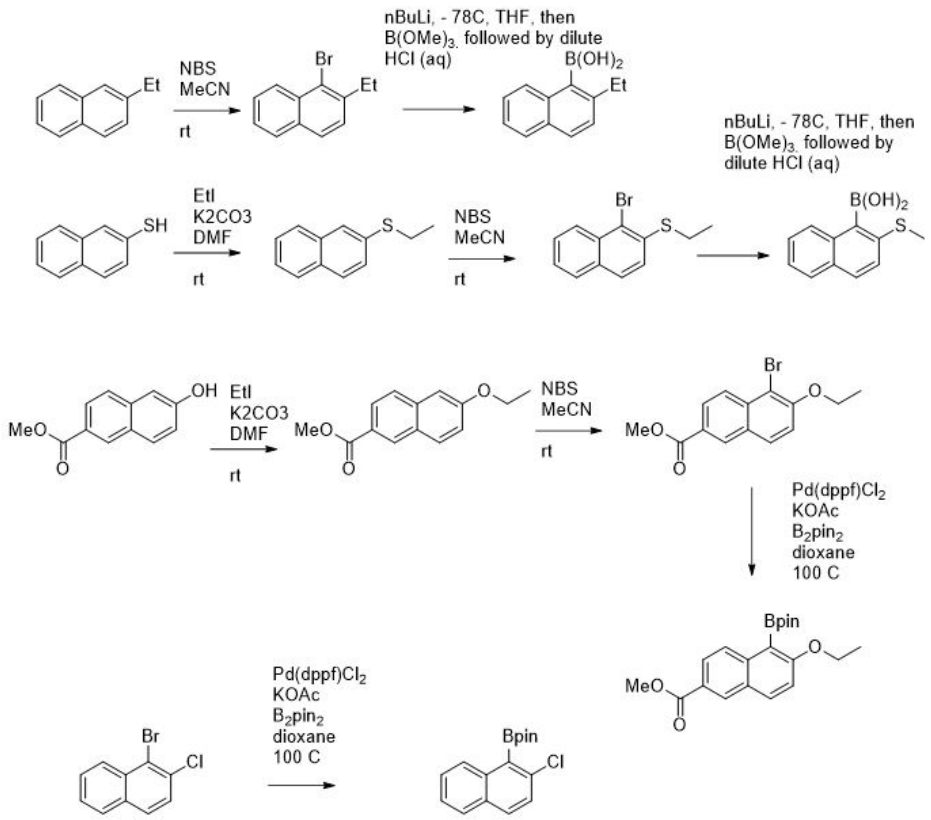

Figure 7: Synthesis scheme for reactants used in expanded scope reaction

Since the enantiomeric excess of compound **3** is unsatisfactory, and we observed that 4-chloro-3-bromobenzoic acid for compound **8** is a competent coupling partner, we sought to expand the substrate scope by changing boronic acid partners, which we were able to synthesise using the scheme in Figure 7. Delightedly, using a bulkier ethyl group improved enantioselectivity and the use of thioester instead of methyl ester has significant beneficial effect, as it can been seen by compounds **1**1 and **12** . We further confirmed 4-chloro-3-bromobenzoic acid to be a competent coupling partner, as reflected by the high ee in compounds 13-15.

3.4 Scheme 4. Optimisation of disubstituted diamine biaryl atropisomers

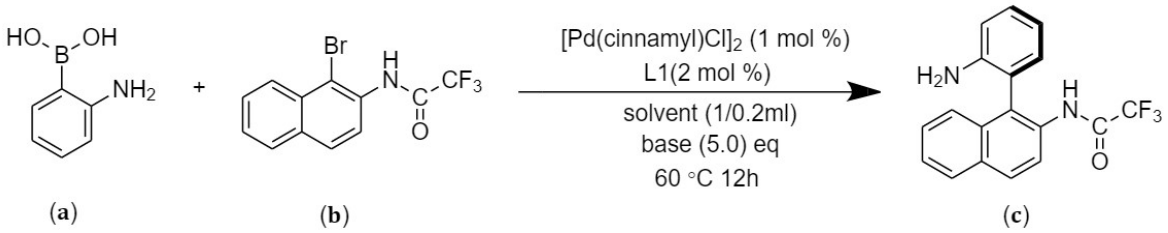

Figure 8: Optimisation via varying base

Entry	Ligand	Solvent	Base	Conversion %	ee %
1	L1	THF/H_2O	K_3PO_4	20	53
2	L1	THF/H_2O	Li_2CO_3	20	57
3	L1	THF/H_2O	Na_2CO_3	20	53
4	L1	THF/H_2O	K_2CO_3	20	60
5	L1	THF/H_2O	Cs_2CO_3	20	59

We commenced the optimisation of disubstitued diamine biaryl atropisomers using **(a)** and **(b)** as substrates for the synthesis of axially chiral biaryl in the presence of palladium at 60°C with THF/H_2O (1/0.2ml) with anionic ligand L1. Through several screenings of base effects, K_2CO_3 was identified as the most effective base affording product in 60% ee and 20% conversion rate. Cs_2CO_3 follows closely, affording product in 59% ee and 20% conversion rate.

4 Conclusion

By comparing the enantiomeric excess (ee) of **1** with **6** and **2** with **7**, we observe that for the same substituents, the molecule with ionizable group displayed significantly higher ee. This is consistent with the fact that ionizable groups allow our chiral ionic ligand to direct enantioselectivity, thus improving the ee. There was a significant increase in ee for substrate **3** from 8% to 43% and substrate **3** from 6% to 80% when anionic ligand L1 is used instead of neutral ligand L2. With bulkier substituents, the ee is expected to be higher due to greater steric demand on its configuration. Our results were consistent with that expectation, with **11** showing a 8% increase in ee as compared to **6**. The substrate with the sulfide substituent (**13**) showed the largest increase with a 49% percent increase in ee as compared to its ether-substituted counterpart (**3**). We also managed to optimise a disubstituted diamine biaryl atropisomer reaction by varying bases and found that K_2CO_3 was the superior base affording product in 60% ee. With the use of ionic interactions in Suzuki Miyaura reactions, we were able to improve upon traditional Suzuki Miyaura reactions with neutral ligands to obtain compounds with more favourable yield and enantiomeric purity

5 Future Work and Application

Further research will be underway to determine the potential for using distal ionic interactions as a widespread and effective means for synthesizing biaryl atropisomers to serve as building blocks for important drugs. To provide a more robust understanding of distal ionic interactions, different substituents on the boronic acid and bromide substrate could be further researched upon, such as amide groups, thiols, aldehyde and ketone. These substituents may be at different positions on the benzene ring. Additionally, further research could be conducted for biaryl diamines, as these compounds are difficult in nature to synthesize, often giving low enantiomeric purity.

6 Acknowledgements

We would like to extend our deepest gratitude towards our professor, Prof. Zhu Ye, and research mentor, Mr Ivan On, for their invaluable patience and guidance along our journey. They have provided us with valuable reference materials and imparted to us practical skills and knowledge which helped us immensely in completing our research. Our endeavor would also not have been possible without the generous support from the Ye Zhu Research Group lab, which provided us with resources and facilities. Dr Maury Jean Pierre has also guided us in the presentation of our findings for our previous competitions and we are grateful for his assistance. We are also grateful for the rest of the researchers in the lab who advised us on the safety and use of the lab equipment and supported us throughout the journey.

7 Declarations

We have submitted this project for the Singapore Science and Engineering Fair (SSEF), in March 2023, where we clinched the bronze medal. We have also submitted this project for the National Stem Talent Search (NSTS) and emerged finalist.

Commitments on Academic Honesty and Integrity

We hereby declare that we

1. are fully committed to the principle of honesty, integrity and fair play throughout the competition.
2. actually perform the research work ourselves and thus truly understand the content of the work.
3. observe the common standard of academic integrity adopted by most journals and degree theses.
4. have declared all the assistance and contribution we have received from any personnel, agency, institution, etc. for the research work.
5. undertake to avoid getting in touch with assessment panel members in a way that may lead to direct or indirect conflict of interest.
6. undertake to avoid any interaction with assessment panel members that would undermine the neutrality of the panel member and fairness of the assessment process.
7. observe the safety regulations of the laboratory(ies) where the we conduct the experiment(s), if applicable.
8. observe all rules and regulations of the competition.
9. agree that the decision of YHSA(Asia) is final in all matters related to the competition.

We understand and agree that failure to honour the above commitments may lead to disqualification from the competition and/or removal of reward, if applicable; that any unethical deeds, if found, will be disclosed to the school principal of team member(s) and relevant parties if deemed necessary; and that the decision of YHSA(Asia) is final and no appeal will be accepted.

(Signatures of full team below)

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Name of team member:

Lim Teck Kong
Name of team member:

NA
Name of team member:

Julien JP MAURY
Name of supervising teacher:

Noted and endorsed by

(signature)

Mr Goh Hock Leong
Deputy Principal (Academic)
NUS High School of Math & Science

Name of school principal: SOH Lai Leng Magdalen

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