

## APPENDIX 5

### *Stereochemical Model and Mechanistic Discussion for Iridium-Catalyzed Allylic Alkylation*

#### **A5.1 INTRODUCTION**

Following the first reports of iridium-catalyzed allylic alkylation<sup>75</sup> and amination<sup>78</sup> nearly two decades ago, myriad studies investigating the underlying mechanism of regio- and enantioselectivity in iridium-catalyzed allylic substitutions, and the nature of role of Ir-phosphoramidite complexes in these processes, have been conducted.<sup>79</sup> Seminal contributions from Hartwig and Helmchen<sup>79</sup> confirmed evidence that active species in Ir-phosphoramidite catalyzed allylic substitution processes are *in situ* generated iridacycles, formed by C–H insertion into the amidite domain of a Feringa type ligand.<sup>79a</sup> Moreover, Hartwig and coworkers went on the show that only the stereocenter  $\beta$  to the metal center is crucial in affecting enantioinduction and that only one such center is requisite for stereocontrol.<sup>79g, 79h</sup>

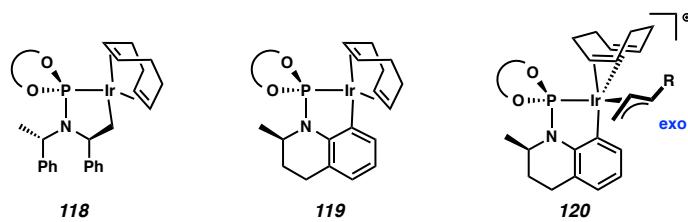
Comparatively less investigation has been undertaken to unearth the source of diastereoselectivity in iridium-catalyzed allylic substitution processes, in part due to the lack of reports describing such findings. Herein, we speculate as to the source of

diastereoselectivity in our iridium catalyzed regio-, diastereo- and enantioselective allylic alkylation, and present a plausible catalytic cycle.

### A5.2 STEREOCHEMICAL MODEL FOR DIASTEREOSELECTIVITY IN IRIDIUM-CATALYZED ALLYLIC ALKYULATION

Feringa-type phosphoramidite ligands have been shown to form iridacycles via iridium(I) insertion into the C(sp<sup>3</sup>)–H bond (**118**, Figure A5.2.1). Investigations by You and coworkers<sup>87</sup> led to the development and N-arylphosphoramidite ligand **L12**, which was then shown to form an active iridacycle via transition metal insertion into the C(sp<sup>2</sup>)–H bond of the aryl group (**119**, Figure A5.2.1). DFT studies and single crystal X-ray diffraction analysis conducted by the You group<sup>87</sup> revealed that the (π-allyl)-Ir complex formed upon oxidative addition of iridium(I) into cinnamyl derived allyl carbonates is predominately the *exo* isomer<sup>104</sup> (**120**, Figure A5.2.1). This is at odds from what is observed with Feringa ligand-derived iridacycles. We speculate that both the ligand structure, in particular the aromatic amine moiety, and the unique allyl orientation may play a role in imparting **L12** its selectivity profile.

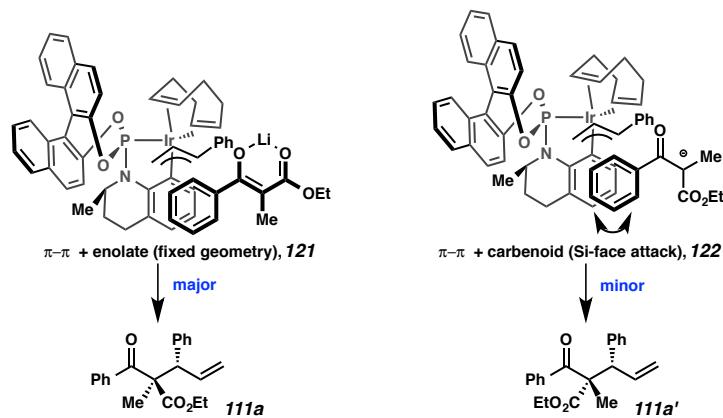
**Figure A5.2.1.** Selected iridium-phosphoramidite complexes: **118** Feringa type; **119** N-arylphosphoramidite (or You) type; **120** (π-allyl)-Ir complex with You type ligand.



In the course of our studies in iridium-catalyzed allylic alkylation, we were able to recrystallize  $\beta$ -Ketoester **112f** from *i*-PrOH/hexanes such that crystals suitable for X-ray analysis were obtained. Via single crystal X-ray diffraction studies, we were able to unambiguously assign the absolute stereochemistry of the products generated in studies presented in Chapter 4 (see Appendix 5 *vide infra* for detail). With this data in hand, and with knowledge of the spatial orientation of ( $\pi$ -allyl)-Ir complex **120**, we are able to begin speculation as to the origin of stereoselectivity in our allylic alkylation reaction.

What we believe to be the two most likely approaches of linear enolate nucleophiles prior to the bond-forming event are depicted in Figure A5.2.2 (**121** and **122**). In this depiction, the diene ligand, BINOL backbone of the ligand and protruding tetrahydroquinoline methyl create a steric environment around the metal center in which approach of the nucleophile is necessarily via the bottom-right quadrant. Our finding that aliphatic ketone substrates fare poorly with respect to diastereoselectivity leads us to hypothesize a potential  $\pi$ - $\pi$  stacking interaction between the tetrahydroquinoline and ketone aryl group may be important in orienting the nucleophile. Our finding that lithium is a crucial component of the reaction mixture leads us to suppose that rigidly enforced enolate geometry is also essential with respect to diastereomeric outcome. Given these data, we believe that the approach shown to the left (**121**) is most plausible, in that both a  $\pi$ -stacking interaction is possible and enolate geometry is enforced.

**Figure A5.2.2.** Approach of the enolate nucleophile in the Ir-catalyzed allylic alkylation.



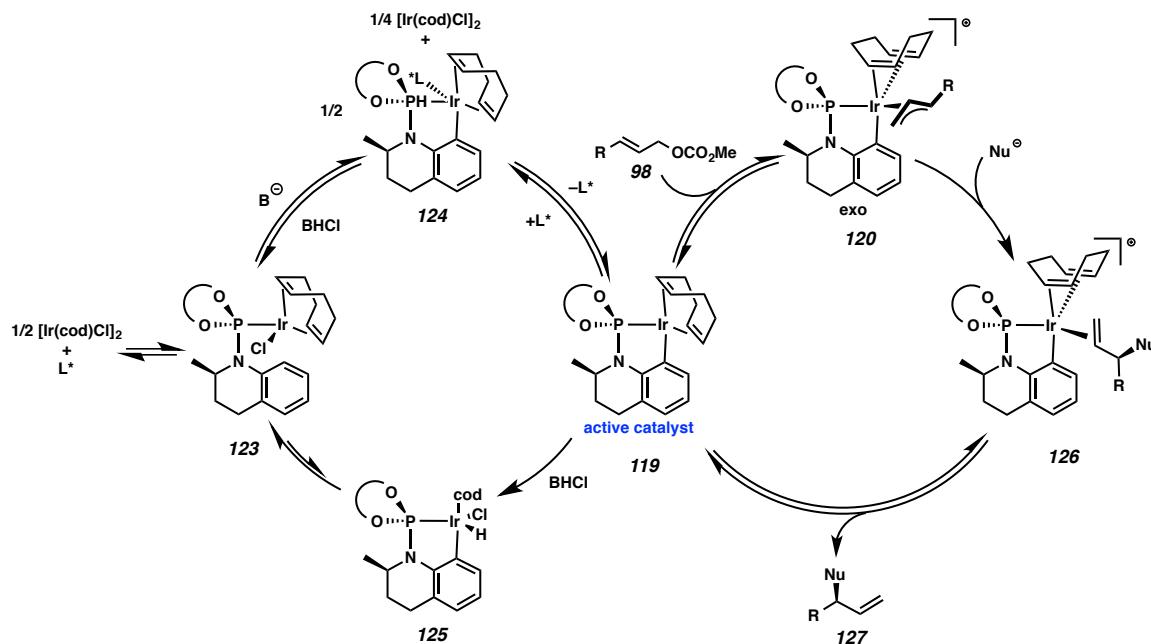
The catalytic cycle we propose to be operative is depicted below in Figure A5.2.3.

Beginning with dissociation of the precatalyst dimer, and association of an equivalent of iridium with ligand, we arrive at species **123**. Base promoted C–H insertion followed by loss of an associated ligand delivers the active catalyst species (**119**).<sup>105</sup> This complex may then undergo oxidative addition into cinnamyl carbonate **98** to deliver *exo* ( $\pi$ -allyl)-iridium complex **120**, which may then be attacked by an enolate nucleophile to give olefin-bound iridium complex **126**. Finally, dissociation of the olefin gives the allylated product and regenerates the active catalyst species.

While the cycle presented below is plausible, and is in line with what is known in the literature<sup>79</sup> it is also conjecture. More evidence is needed to confirm or support a variety of discreet steps; for example the reversibility of C–H insertion (i.e., **125**  $\rightarrow$  **123**, **124**  $\rightarrow$  **123**). Moreover, the discreet steps in such a cycle may change depending on the particular precatalyst, base and ligand that are employed.<sup>76d</sup> As such, further investigations to elucidate the mechanism of this iridium-catalyzed allylic alkylation are

warranted, and should serve to inform the development of new modes of reactivity for these iridium complexes.

**Figure A5.2.3.** Proposed catalytic cycle for iridium-*N*-arylphosphoramidite complex-catalyzed allylic alkylation



### A5.3 REFERENCES AND NOTES

(104) The *exo* complex is defined as having the C2–H bond of the allylic moiety pointing toward diene, whereas the *endo* isomer places the C2–H bond of the allylic moiety pointing toward the amine part of the ligand.

(105) While this has been shown to be the case for Feringa type ligands, unpublished work by the You group indicate that in the case of N-aryl phosphoramidite ligands, the iridacycle does not coordinate a second equivalent of ligand.