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CHALLENGES AND OPPORTUNITIES OF TRANSITION METAL CATALYZED REACTIONS

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ABSTRACT

For the production of organic compounds, Transition metal catalyzed processes are essential. Homogeneous catalysis provides a rapid route to novel organic compounds, which are then examined for their desired qualities, assisting in the resolution of existing health, environmental, energy storage, and other issues. The development of new transition metal complexes for catalysis of fundamental organic reactions, the use of metal catalysts in the synthesis of unique organic compounds, and the creation of synthetic metallo-enzyme-like molecules are all topics that we hope to cover in this Special Issue. The asymmetric forms of C—H borylation have only lately become widely accepted as an effective method for synthesizing organoboron molecules. These findings highlighted the need of creating new chiral ligands for asymmetric C—H borylation. A quick summary of current developments, difficulties, and possibilities is provided below.

Keywords: Transition metal, Catalyzed, Molecules, Borylation, enantioselectivity

I. INTRODUCTION

Due to their partially full d-orbitals, which enable them to readily give and take electrons from other molecules, transition metals make good catalysts. There are still certain processes that are triggered by early transition metals. The development of novel transition metal catalysts and improving the efficiency of catalytic processes are currently active areas of study despite their lengthy history in catalysis. They have also become a valuable tool for a variety of synthetic and non-synthetic transformations thanks to the advancement of supporting ligands. Stille,

Buchwald-Hartwig, Negishi, Heck, Miyaura-Suzuki, and Sonogashira reactions are a few examples of transformations that employ transition metal catalysts.

For decades, scientists have struggled to perform selective chemical changes on biomolecules in their natural state. High chemo selectivity in the presence of a complex pool of functionalities is required, together with the restrictions of converting high-yielding reactions carried out in organic solvents at high temperatures to aqueous media and luke warmness. By creating water-compatible reactions involving reactant pairs with high reciprocal reactivity, the subject of bio orthogonal chemistry emerged in answer to this problem. In vitro, in cells, and in live creatures, this has dramatically widened the study area for chemists and biologists, allowing them to explore and utilize chemical changes that were previously impossible. The requirements and interests of researchers from all fields continue to shape this synthetic paradigm.

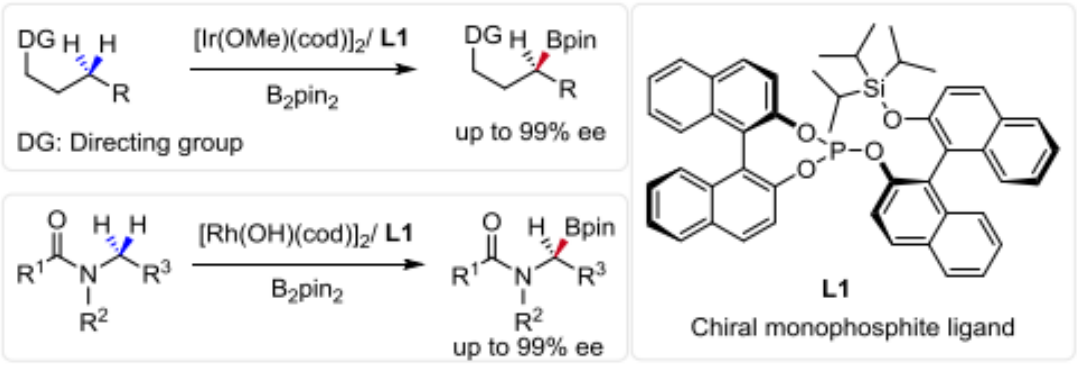
The combination of concepts and technologies from the domains of transition metal catalysis, medicinal chemistry, and cell transport under the bio orthogonal banner is one of the most intriguing new developments in the field that has been seen by a number of laboratories. The intracellular breaking of allylcarbamate bonds using Ru or Pd catalysis was the focus of early investigations into the use of organometallic catalysts in live cells to carry out certain xenobiotic changes rather than to directly elicit a pharmacological effect.

The productions of a mitochondria-targeted fluorophore inside cells showed that these cell-penetrating Pd-functionalized nano-devices also exhibited the ability to mediate SuzukieMiyaura cross couplings. The possibility of employing transition metal catalysts (TMCs) as bio orthogonal tools to reveal structures capable of influencing biological activity was first kindled by these early investigations.

II. RECENT ADVANCES

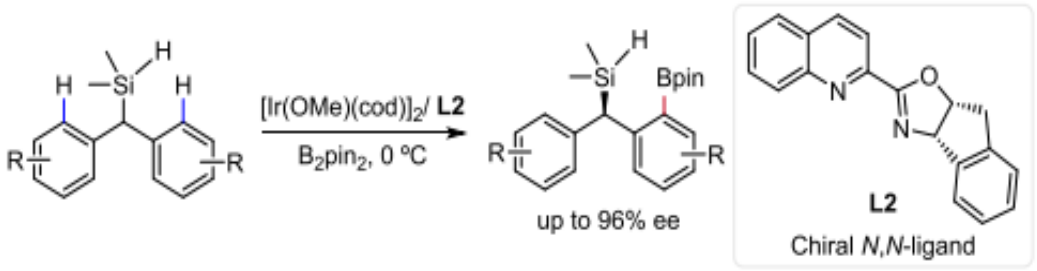
Organic synthesis has long struggled with the asymmetric selectivity of inactivated enantiotropy methylene C—H bonds. The Sawamura group discovered in 2017 that chiral mono phosphoramidite ligands might facilitate the borylation of methylene C(sp^3)—H bonds with considerable enantioselectivities. Using the 1,1'-Bi-2-naphthol (BINOL)-based chiral monophosphite ligand L1, they reported an iridium-catalyzed asymmetric borylation of unactivated methylene C(sp^3)—H bonds in 2-alkylpyridines and 2-alkylazole derivatives

(Scheme 1). High site- and enantio selectivity were used to borolate the C(sp^3)—H bond at the -position of the heteroatom in the directing group. The formation of a monophosphite-Ir-tris(boryl) complex, which provided a tight chiral reaction pocket to distinguish the enantiotopic methylene C—H bonds, was crucial to this asymmetric catalysis. Sawamura recently disclosed a Rh-catalyzed enantioselective borylation of N-adjacent C(sp^3)—H bonds that enables the production of chiral α-aminoboronates utilising the same chiral ligand L1. It is noteworthy that this borylation process was successfully used to synthesize the anticancer medicine bortezomib by site- and stereoselective C(sp^3)—H borylation of an unprotected dipeptidic chemical.



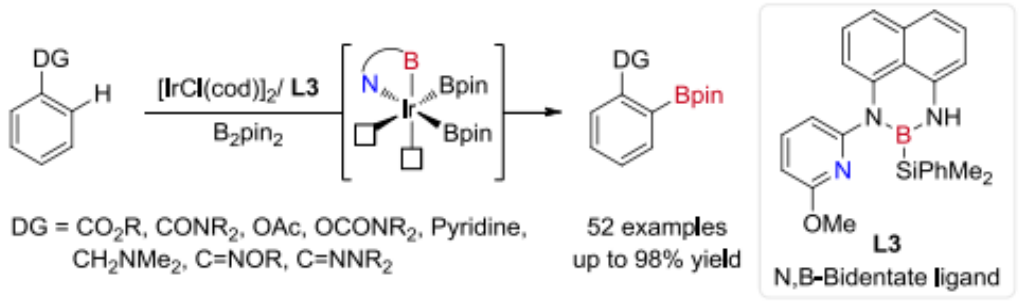
Scheme 1: Iridium-catalyzed enantioselective borylation of methylene C(sp3)—H bonds using chiral monophosphite ligand

Asymmetric C—H activation frequently involves the desymmetrization of symmetrical molecules by the differentiation of enantiotopic carbons. Under moderate circumstances, Shi and Hartwig created a silyl-directed, iridium-catalyzed asymmetric borylation of aromatic C—H bonds with good to exceptional enantioselectivity. A number of recently identified chiral quinolyl oxazoline ligands are essential to the success of this asymmetric process (Scheme 2). Lower enantioselectivity was observed for substrates having an ortho-substituent, such as methyl and fluoro. The silyl directing group can be added, deleted, or converted to other functional groups such the silyl ether, silanol, and hydroxyl group.



Scheme 2: Silyl-directed iridium-catalyzed asymmetric borylation of aromatic C—H bonds

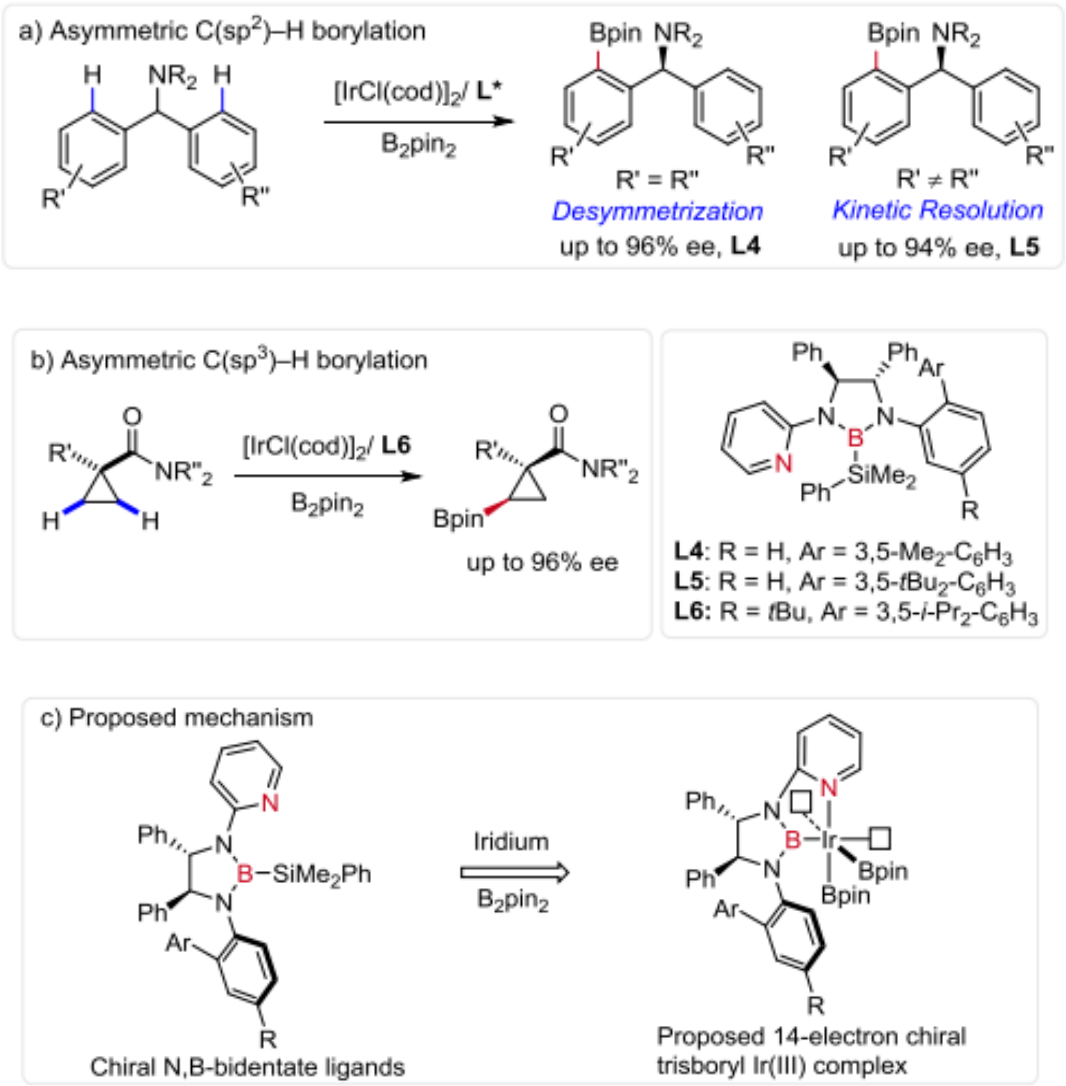
The Li group created a series of silylborane precursors in 2017 for oxidatively adding N,B-bidentate boryl ligands to iridium (Scheme 3). These preligands served as the foundation for the development of an effective catalytic system for the targeted borylation of C(sp^2)-H and C(sp^3)-H bonds. To produce the borylated products in good to exceptional yields, a wide variety of directing groups, including ester, oxime ether, hydrazine, amide, carbamate, and pyridine, may be compatible in this reaction. These borylation processes were carried out with broad substrate coverage and good regioselectivity.



Scheme 3: N,B-bidentate ligand for directed ortho borylation

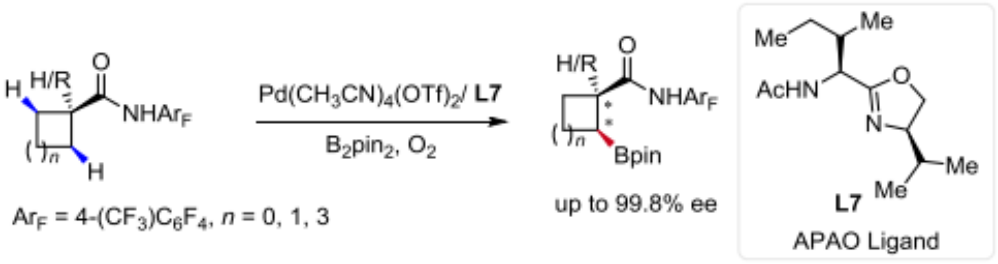
The Xu group has recently created a variety of chiral bidentate silylborane ligand precursors for the asymmetric C(sp^2)—H borylation of diarylmethylamines, which was inspired by Li's work (Scheme 4a). The kinetic resolution of racemic diarylmethylamines might also be accomplished using the catalytic method. A variety of chiral borylated diarylmethylamines with good to exceptional enantioselectivity were produced. Products made from substrates with electron-withdrawing groups often have higher ee values than those made from substrates with electron-donating groups. The active catalysts (Scheme 4c), which can be docked by a directing group and a prochiral C(sp^2)—H bond, are 14-electron chiral trisboryl Ir(III) complexes with two

accessible coordination sites. The Xu group later produced an amide-directed iridium-catalyzed asymmetric C(sp^3)-H borylation of cyclopropanes by further modification of the chiral N,B-bidentate ligands (Scheme 4b). A number of cyclopropylboronates with good to exceptional enantioselectivities were produced from a range of substrates having α-aryl and α-alkyl substituents. The medicine Levomilnacipran, which has received FDA approval, was also created using this process.



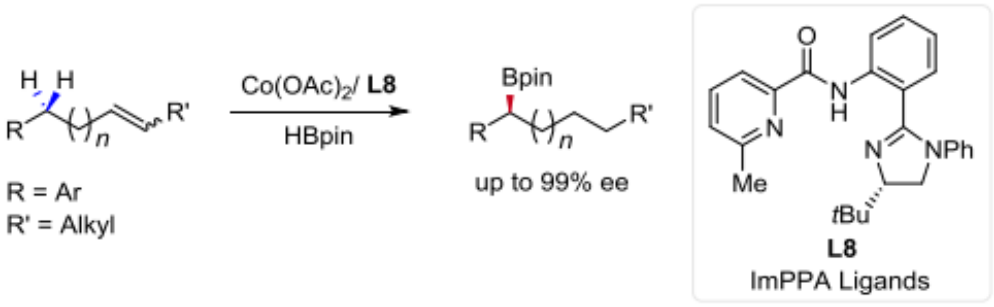
Scheme 4: Chiral N,B-bidentate ligand enabled iridium-catalyzed asymmetric C(sp2)—H and C(sp3)—H borylation

Yu and associates created a Pd(II)-catalyzed enantioselective C(sp^3)-H borylation of weakly coordinating carboxylic amides, in contrast to the iridium catalysts previously discussed. The key to realising this reaction was the use of chiral bidentate acetyl-protected aminomethyl oxazoline (APAO) ligands (Scheme 5). Substrates with α-tertiary and α-quaternary carbon centres were tolerated well. Cyclic amides, particularly the cyclobutanes, may be effectively borylated with high yields and enantioselectivities. Low yields or diastereoselectivities plagued the borylation of cyclopropanes and cyclohexanes.



Scheme 5: Palladium-catalyzed enantioselective C(sp3)—H borylation using APAO ligand

Cobalt-catalyzed asymmetric distant C-H borylation of internalalkenes through successive alkene isomerization/hydroboration has been reported by Lu and coworkers, in contrast to the C-H borylation mediated by a coordinative directing group shown above (Scheme 6). This reaction makes use of the chiral imidazoline phenyl picoliamide (ImPPA) ligand. The chiral secondary organoboronates with excellent regio- and enantioselectivity might be prepared using a variety of internal alkenes or a combination of internal alkenes.



Scheme 6: Cobalt-catalyzed enantioselective remote C—H borylation of internal alkenes via alkene isomerization

III. OPPORTUNITIES AND CHALLENGES

In recent years, there has been a lot of interest in the asymmetric borylation of $C(sp^2)$—H and $C(sp^3)$—H bonds. The discovery of new chiral ligands greatly facilitated these reactions. The restrictions and difficulties associated with asymmetric C—H borylation processes, however, remained clear. To begin, these reactions frequently required substrates with activated C—H or unique directing groups. Second, the substrate range of the present asymmetric C—H borylation process was somewhat small. Substrates with a varied electron nature and steric hindrance often affected the enantioselectivities. Last but not least, this field urgently requires more efficient and integrated catalytic systems with strong regio- and stereoselectivity. The simple asymmetric C—H borylation would undoubtedly be extremely useful in chemical synthesis and drug development.

IV. CONCLUSION

Supratherapeutic drug levels that might spread to healthy organs and cause injury could be produced by combining the injection of catalytic devices with high in vivo productivity with a precursor of an ultrapotent cytotoxic agent. Low-productive catalysts should not be used with low-to-moderate activity chemotherapeutics, as this approach is likely to yield local levels of drug below the therapeutic threshold. In the journey from preclinical research to clinical development, all of these factors will need to be addressed. Our ability to devise strategies and procedures that address them will determine if we are successful in translating the usage of TMCs as bioorthogonal medicinal devices. The bar has been raised.

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