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# A Perspective in Catalysis: Development of Efficient Methods in the Age of Sustainability

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*Abstract:* Contemporary organic chemists have expended significant efforts in expanding the scope of sustainable methodologies in catalysis and synthesis. Our lab seeks to contribute to this goal by developing new methods that utilize cheap and abundant catalysts to provide solutions to persisting obstacles in the synthetic community, with simultaneous attentiveness to associated basic research. From this viewpoint, we will specifically address our work using nickel to control nucleophile isomerism, a work which led to the discovery of a catalytic Thorpe-Ingold effect, and other areas of interest that are being actively pursued. As observed throughout, these works made maximum effort to include an abundance of heterocycles and complex molecular motifs to further enhance the translational impact of these discoveries.

**Keywords**: Catalysis · Homogenous · Mechanism · Nickel · Sustainable


***Josep Cornella (Pep)*** was born in La Bisbal del Penedès, a small town in south Catalunya. He graduated in chemistry in 2008 from the University of Barcelona and undertook MSc studies in the Department of Organic Chemistry studying the chemistry of allylboron reagents. After completing his masters thesis, he moved to the United Kingdom to pursue doctoral studies in the group of Prof. Igor Larrosa (QMUL). In early 2012, he earned his PhD working on the use of aromatic carboxylic acids as aryl donors in metal-catalyzed decarboxylative reactions. He then moved back to Catalunya, where he joined the group of Prof. Ruben Martin (ICIQ) as a Marie Curie Postdoctoral Fellow. There, he developed novel transformations involving Ni-catalyzed C–O bond activation and carbon dioxide insertion into organic molecules. In 2015, Pep obtained a Beatriu de Pinós Fellowship to carry out further postdoctoral studies in the group of Prof. Phil S. Baran at The Scripps Research Institute, California, USA. During this time at Scripps, he worked on the discovery and implementation of new transformations based on the concept of 'redox-active esters' as practical and readily available partners for Ni- and Fe-catalyzed C–C bond forming reactions. In spring 2017, he was appointed as a Max Planck Group Leader in the Department of Organometallic Chemistry at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany. In summer of the same year, he obtained a Max Planck Research Group Leader (MPRGL) position in the same Institute, to create and lead the *Sustainable Catalysis Laboratory.*

***Matthew O'Neill*** was born in Cleveland, Ohio. In 2017 he graduated from the University of Notre Dame, where he carried out four years of undergraduate research with Paul Helquist and Olaf Wiest. His work primarily focused on utilizing Ni and Pd catalysis to rapidly access molecules of interest as therapeutics for rare neurodegenerative diseases. He spent two periods away from Notre Dame, the first enjoying a research stay at Heidelberg Universität under the direction of Stephen Hashmi. Additionally, he spent a summer in the lab of Phil Baran at The Scripps Research Institute exploring the chemistry of 'redox-active esters'. Beginning in the summer of 2017 he moved to the Max-Planck-Institut für Kohlenforschung as a Fulbright Scholar to join the group of Josep Cornella. He explored a variety of Ni and Pd-catalyzed transformations during his stay. In June of 2018 he matriculated as a NIH Medical Scientist Training Program fellow to Vanderbilt School of Medicine.

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## 1. Introduction

### 1.1 *Catalysis in the 21st Century*

Advances in organic synthesis during the latter half of the previous century forced chemists to reassess the prevailing paradigms of their times.[1] As chemists continuously refined their art with unprecedented degrees of control and fidelity, both internal and external factors converged to reassess the metrics of progress and the role of chemistry itself as a central science.[2] Two notions coincided to shape the emergent views of the contemporary synthetic chemist: the arrival of synthetic methods capable of shaping nearly any conceivable molecule into being, as well as the seminal contributions of catalysis to heightened retrosynthetic analysis. Combining these pivotal developments situated chemists in a position that engendered a shift in focus towards some of the most persistent and salient issues currently pressing the community – specifically, the development of methods that permit expedient access to high-value molecules in an economical, sustainable, and safe manner, while also seeking to discover and refine knowledge of unknown and elusive reactivity. Indeed, the intimate link between basic research and worthwhile application is poised to represent the pinnacle of academic research in the coming years.[3] From this perspective, our group seeks to answer these questions with fundamental work on mechanistic and applied catalysis, with the aim of exploring the characteristics and potential of inexpensive transition metal and main group catalysts, while aspiring to capture the utility of such discoveries through synthesis driven applications.

As frequently acknowledged, the contexts of application play a significant determining role in assessing the potential utility of new methodologies. Accordingly, we have made a substantial effort to accommodate a great variety of heterocycles and complex molecules, both of which maintain a privileged position in the translational domain of chemistry.

### 1.2 *Scope of this Perspective*

In this perspective we seek to provide a concise overview of our research interests, and show how these conform to the goals outlined above. Specifically, we would like to share our efforts towards developing a new system for C–F activation that retains secondary nucleophile fidelity and a closely-related catalytic Thorpe-Ingold effect. Areas of future interest are also examined. We hope to particularly highlight the robustness of these approaches and our purposeful efforts to display wide functional group compatibility. Our research benefits strongly from a fundamental affinity for basic research, though it simultaneously provides an opportunity to empower chemists through translationally oriented projects. We hope to showcase our enthusiasm for these research directions, and encourage complementary investigations in the community.

## 2. C–F Activation and Secondary Nucleophile Additions

### 2.1 *C–F Bonds as Synthetically Viable Electrophiles*

At the present time, the prevailing paradigm regarding C–F bonds is to perceive them as a privileged late-stage installation, primarily to confer favorable pharmacokinetic properties to a potential lead compound, or to impart an electronic perturbation to arrive at a more ideal material.[4] Indeed, the last decade has witnessed many elegant solutions to accomplish these goals, collectively representing enormous advances in the synthetic toolbox. In many cases, these translational advances have been underpinned by improved understandings of the basic underlying chemistry, thereby serving as excellent inspirations to work at this interface.[5] While these results are certainly capable of standing alone, they collectively engender a perspective ascribing the C–F bond to serve solely as an end, and not a means. Accordingly, this view places a natural constriction on the points of molecular divergence in chemical space. With advances in ligand design, long-regarded 'intractable' electrophiles can now be routinely activated. In particular, novel catalytic systems based on nickel have enabled new methods for the robust activation of C–O and C–F bonds despite their very high inherent bond strength (Fig. 1).[6] In addition to more commonly encountered aryl electrophiles, fluorine-containing building blocks are also commercially available and typically of comparable expense to their traditional halide congeners. Interestingly, C–F bonds can additionally serve as orthogonal handles for modular synthesis, a feat not always guaranteed by discrimination among traditional halide electrophiles. Fluorine further possesses a unique ability to serve as a directing group, thus exerting a twofold purpose (*intrinsic* and *extrinsic*). Proceeding from this point, we aimed to help expand upon this trend by developing a mild method to activate C–F bonds for secondary nucleophile installation.

### 2.2 *Secondary Nucleophile Isomerization*

Undertaking the effort to develop methods for C–F bond activation, we hoped to provide a general solution to controlling the regiointegrity of alkyl nucleophiles in cross couplings, a longstanding issue since the first contributions of Kumada in the early 1970s (Scheme 1A).[7] Particularly, secondary alkyl nucleophiles possess an inherent proclivity to undergo β-H elimination and subsequent migratory insertion to arrive at the primary alkyl nucleophile as shown in Scheme 1B.[8] In many contemporary applications, it is of the utmost importance to incorporate secondary and tertiary nucleophiles to create more complex C($sp^2$)–C($sp^3$) bonds. Particularly in drug discovery, the overreliance on 'flat' molecular topologies created by the revered classic cross-coupling reactions has unfortunately provided few candidates capable of ligating complex protein surfaces, while in material science, the need for more diverse chemical space is felt equally acutely.[9]

Original efforts to forge such molecular constructs relied on using a '*reverse polarization*' approach in which the nucleophile is situated on the C($sp^2$) moiety to intercept a C($sp^3$) halide. Powerful protocols were developed that arose from this disconnection and have been reviewed in detail elsewhere.[10] In contrast, the use of alkyl nucleophiles and aryl electrophiles would be a conceptually distinct approach, but general methods to overcome isomerization have proven challenging. Previous synthetic entries into addressing this intricacy have been nicely developed, and comprise an extensive array of different reaction parameters, employing Ni, Pd, Cu, Fe, and a wide assortment of different nucleophile and electrophile combinations.[11] Despite this wealth of reactivity, completely universal protocols remain elusive. Indeed, the practitioner is still required to discriminate among the best combination given other peripheral functionality, commercial availability, and selectivity dictated by the application. We therefore sought to initiate our studies with a specific unmet gap (C–F bond activation with Grignard nucleophiles), and potentially gleam insights that could provide a direction to greater universality for later applications. Lastly, this first investigation would underscore the ability to contribute to synthetic praxis with a novel method, but also provide a chance to illuminate mechanistic details throughout the investigation.

In fulfilment of this goal, we arrived at a set of conditions that enables a variety of secondary Grignard reagents to react in good yields with aryl- and heteroaryl C–F bonds, without experiencing significant loss of isomer fidelity (Scheme 2A).[12] Of critical import to a method's realistic utility is the ability for such catalytic systems to tolerate an extensive array of hetero-

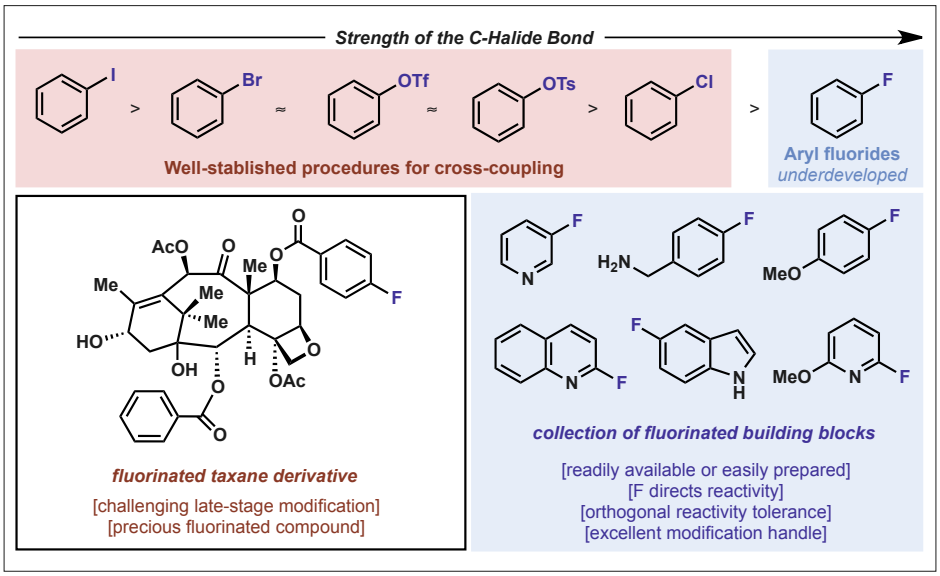
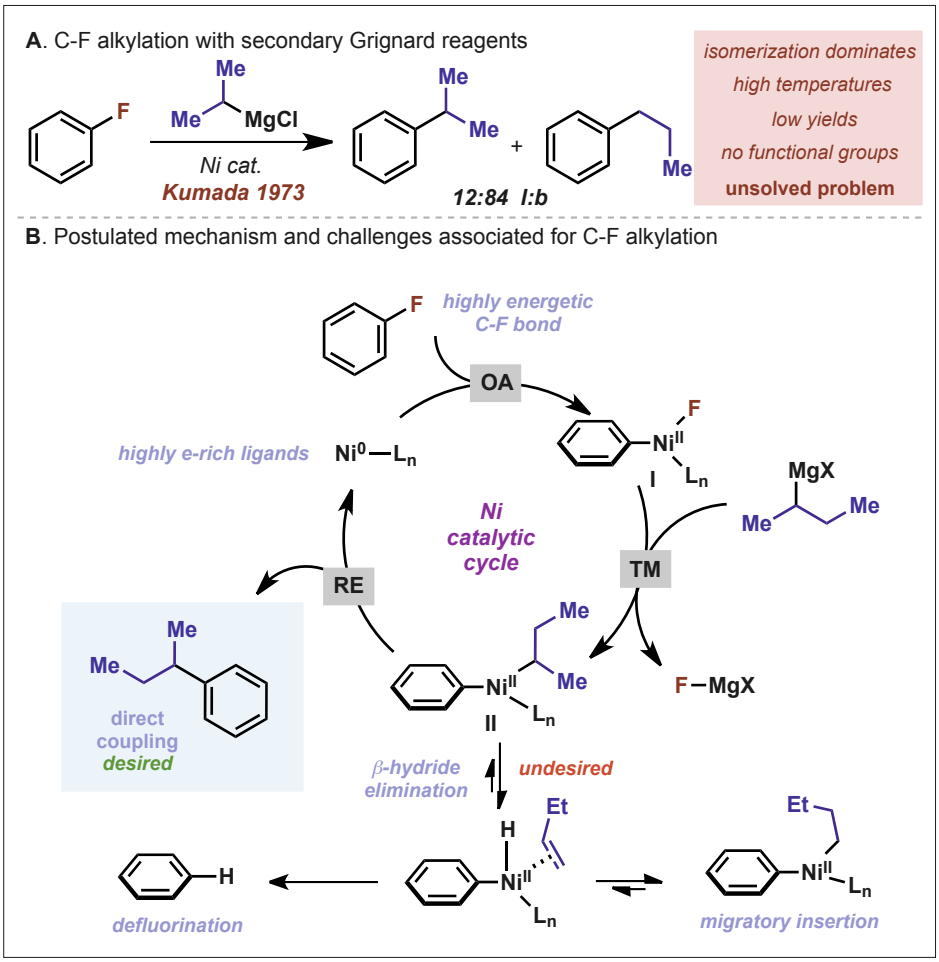



Fig. 1. Aromatic halides as cross-coupling partners.




Scheme 1. A. Kumada's early work. B. Challenges and pitfalls of retention of configuration in secondary nucleophiles.

cycles and sensitive functionalities, which otherwise traditionally relegates such work to the halls of academia. Accordingly, we developed a method that is compatible with not only common arenes bearing an array of functional groups modulating electronics, but also variously substituted pyridines, thiophenes, pyrroles, pyrazoles, pyrimidines, quinolones, and indoles. We further demonstrated how this method could be used to divergently access disubstituted pyridines, a strategy that utilized the directing group ability of fluorine (Scheme 2B). The reaction is simple to setup, and commences from readily-available Grignard nucleophiles, without further requirement of modification prior to nucleophile installation. At the time, it is limited to secondary nucleophiles and attempts to expand the scope to include tertiary Grignards were unsuccessful.[13]

## 3. A Catalytic Thorpe-Ingold Effect

### 3.1 *gem-Dialkyl Substitution in a Bidentate Phosphine Ligand*

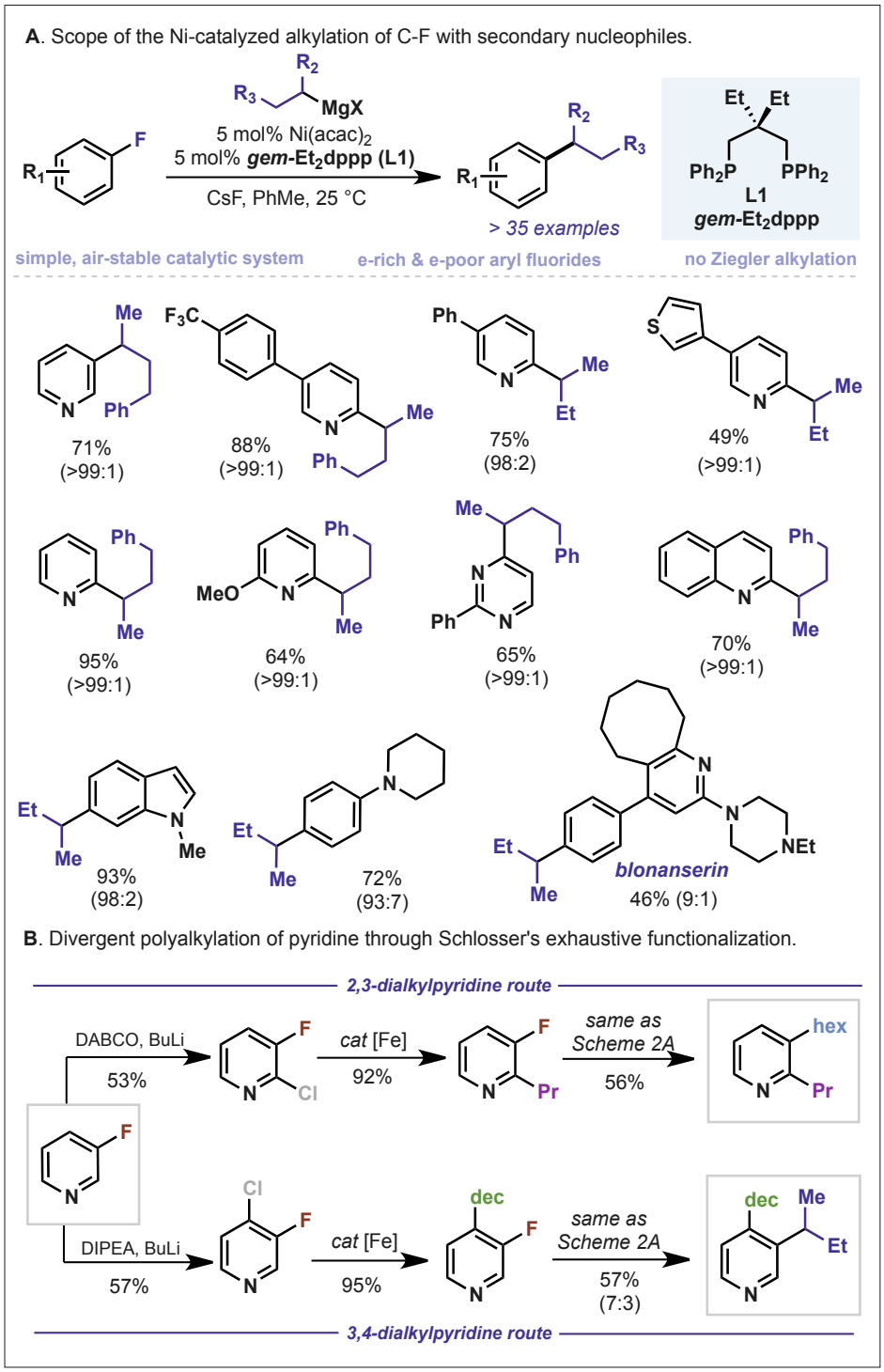
During the course of ligand optimization towards increasing the branched product ratio, an interesting *gem*-dialkyl effect was discovered in the ligand backbone. The Thorpe-Ingold effect is traditionally invoked in the context of kinetics, whereby *gem*-dialkyl substitution induces a conformational constraint which accelerates the reaction by positioning the two interacting hemispheres of the molecule in proximity.[14] In 2009 Bouwman studied the use of *gem*-dialkyl effects to control chemoselectivity in reactions with ruthenium catalysis, being able to dictate between C– and O–allylation products based on substitution patterns.[15] Another elegant demonstration of this effect is the work of Goldberg and Moloy, in which dppp ligands with various backbone substitutions were explored to probe the reductive elimination of methyl groups from an octahedral platinum compound.[16] As is the case with bidentate phosphine ligands, an equilibrium of chelation states exists, with monodissocation proffering a fleeting open coordination site necessary for the reductive elimination event from the octahedral platinum center. Consequently, they found that when ligands bearing substituents that exaggerated the magnitude of the Thopre-Ingold effect, the rate of reductive elimination slowed due to the increased saturation of the metal coordination sites. As our critical intermediate was a square planar compound, we conversely sought to adopt this strategy to diminish the open coordinate site frequency through tighter chelation (Scheme 3A).

By synthesizing variously disubstituted dppp analogues, we were able to empirically assess this hypothesis. During initial screening of conditions, the dppp backbone had been identified as a promising lead in accord with the early efforts of Kumada. After exploring the efficacy of these ligands under the reaction conditions, a correlation between angles induced by substitution and respective selectivites could be validated. A pleasing trend among the angle, yield, and selectivity collectively corroborated the plausibility of the Thorpe-Ingold effect (Scheme 3B). X-ray structures of each ligand with $NiCl_2$ were obtained to confirm the angles and explore the trend. It was also noteworthy that further increases in selectivity could be accomplished with the use of a catalytic quantity of CsF. Previous reports have proposed that the F anion can interact with the metal to help fully saturate the empty coordination sites and assist in favoring reductive elimination over β-H elimination. Indeed, a relatively analogous effect was observed by Cook during an application reacting aryl C–O electrophiles with Grignard reagents by means of Fe catalysis.[17] In this instance, complete reversals of branched to linear ratios were observed when $FeF_3 \cdot H_2O$ was used rather than $FeCl_3$. This dramatic reversal of reactivity was attributed to the β-agostic interactions that underpin this deleterious isomerism.

It has further been observed that the Thorpe-Ingold effect can be operative in cases beyond C–F electrophiles. The corresponding elevated reactivity gives promise to the realization of more general methods to uniformly activate an entire set of aryl halides in excellent yields. In the near future, we hope to further elucidate the cause of this observation, and fully probe it to explore the generality of its nature.

## 4. Further Research Directions

In addition to interests in Ni for $C(sp^2)$–$C(sp^3)$ bond construction and ligand design, a more general interest in the intricacies of organometallic chemistry has manifested itself through explorations of low-valent metal species as catalytically active complexes. Literature reports of negative oxidation-state transition metals have been reported, but their catalytic activities (with the exception of Fe) have generally been poorly explored. Such a situation immediately presents itself as an exciting opportunity to gain new knowledge into basic




Scheme 2. A. Scope of the Ni-catalyzed alkylation of C-F bonds. B. Regiodivergent synthesis of alkylpyridines.

reactivity, and expand beyond the catalytic manifolds traditionally encountered in contemporary literature.

While research focused on transition metal-mediated catalysis has exhibited nearly indescribable utility, expanding the scope of tractable catalysts to main group elements would represent an entirely distinct conceptual entry to sustainable catalysis. Non-toxic main group metals capable of acting as catalysts would avoid both the cost and toxicity associated with a number of transition metals currently in use, thus representing substantial progress in a sustainable direction. Not only would this enable improved applications, but the necessary gains in basic research to bring this aspiration to fruition would be immensely valuable.

We are actively engaged in preliminary efforts towards both of these goals, while also remaining focused on better understanding the nature of the Thorpe-Ingold effect for ligand design. The integration of multiple approaches to catalysis has imbued these efforts with great satisfaction, and we look forward to reporting these findings in due course.

## 5. Conclusion

Realizing the aspirations of synthetic chemistry for recognition as a sustainable and predictable science still necessitates significant advances in our mechanistic understanding of catalytic systems and the complementary implementation of respective synthetic applications. Indeed, the field is uniquely situated as a linchpin among disciplines, being given the unique ability to accelerate the development of various other fields while continuing to refine its own foundation.[18] By intimately combining these two pursuits, we have attempted to put into praxis the thought that mechanism underlies synthesis, which correspondingly empowers translational impact. While limited in our experience so far, we hope to have conveyed an overview of our research interests and the current direction of our research group. We are optimistic that rigorous catalysis research will offer many intellectual treasures over the next several decades, and importantly provide solutions to many of the outstanding problems in pharmaceutical, material science, energy, and agrochemical domains.

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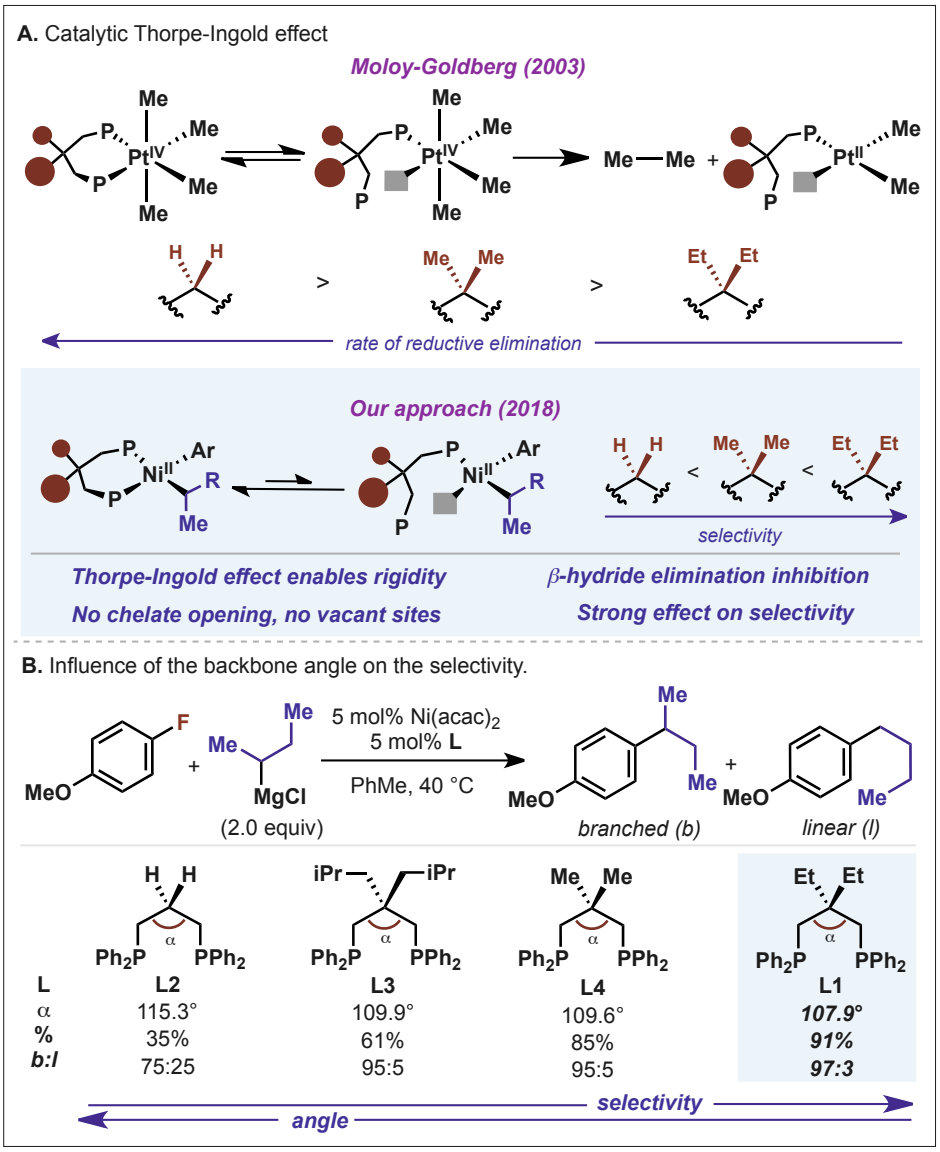


Scheme 3. A. Moloy and Goldberg mechanistic investigations. B. Influence of the Thorpe-Ingold effect in the ligand backbone.


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