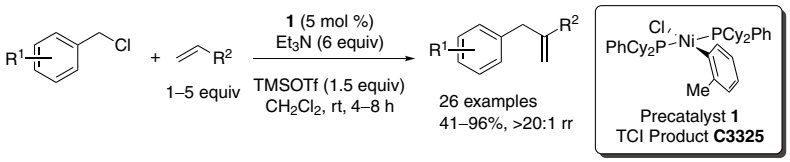
Research Article

Development of an Air-Stable Precatalyst for Use in Homogeneous Nickel Catalysis: A Case Study in the Mizoroki–Heck Reaction of Benzyl Chlorides and Simple Alkenes

Eric A. Standley, Timothy F. Jamison

Abstract: The Mizoroki–Heck-type reaction of benzyl chlorides and simple, electronically unbiased alkenes was developed as a new method for carbon-carbon bond construction. This transformation represents a novel addition to the existing methods for alkenylation reactions, and like numerous other nickel-catalyzed reactions, relies on bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$) as catalyst. Through fundamental understanding of the role the 1,5-cyclooctadiene ligands play in the reaction, a new, air-stable precatalyst was successfully developed for the transformation. This precatalyst enables the reaction to be performed without caution to exclude oxygen from the reaction, significantly increasing the convenience and usability of the reaction. The knowledge gained from this research led to the development of a library of structurally-related, air-stable nickel complexes suitable for use as precatalysts in a wide array of reactions.



- Highly regioselective Mizoroki–Heck reaction of unbiased, terminal alkenes
- Air-stable and highly active precatalyst to replace $Ni(cod)_2$
- All reagents can be used without purification and degassing

Keywords: nickel catalysis, air-stable precatalyst, Mizoroki–Heck reaction

1. Introduction

Homogeneous catalysis plays a central role in numerous fields, such as the materials, pharmaceuticals, agrochemicals, as well as bulk and commodity chemicals industries. In particular, palladium and copper have been used in these fields for many years, and especially in the last 20 years, palladium catalysis has been extensively developed and ubiquitously adopted in many settings.[1] While palladium and copper are normally the metals of first choice for a diverse set of reactions, most notably cross-coupling and amination reactions, nickel has been the subject of continued investigation as an alternative to these metals. However, the last 10 to 15 years have seen numerous exciting discoveries and developments in nickel catalysis that have demonstrated nickel's value for much more than its ability to catalyze the most traditional sp^2-sp^2 cross-coupling reactions.[2]

In 2010, I came to the Massachusetts Institute of Technology to begin my PhD. A major reason I chose to go to MIT was to work with Prof. Timothy Jamison, whose research program had produced seminal contributions in, among other areas, nickel-catalyzed reductive coupling.[3] Many of the diverse coupling partners used in these reductive coupling reactions were subsequently incorporated as key steps in the total syntheses of natural products such as (–)-terpestacin[4] and amphidinolides T1 and T4.[5] Even before joining his research group, we had many discussions about possible directions for my future research to take. A common theme to these discussions, whether in the context of nickel-catalyzed reductive couplings, carbonyl-pi couplings, or Mizoroki–Heck couplings, was the pivotal role that the starting nickel source plays in the outcome of the reaction. Throughout the many different transformations developed by the Jamison group, bis(1,5-cyclooctadiene)nickel(0), or $Ni(cod)_2$, was almost always used as the nickel source of choice. This is a highly versatile metal complex, which is itself an active catalyst in many transformations, and also combines readily with numerous types of ligands to form ligand-supported, zerovalent nickel species. This allows a single precursor to be readily diversified into an

active catalyst species for countless transformations simply by combination with the appropriate ligand. While this versatility is valuable in a research setting, the use of $Ni(cod)_2$ is not without difficulty and liabilities; it is highly sensitive to oxygen, and even under an inert atmosphere, it slowly decomposes to nickel metal unless stored cold.

Even in cases where an air-stable precatalyst can be employed, a hallmark of nickel chemistry is the extreme sensitivity of catalytic species and intermediates to oxygen. Thus all solvents, reagents, and reaction vessels must be thoroughly degassed and kept inert. As a result, many of the transformations that have been developed using $Ni(cod)_2$ as catalyst are not employed to the extent they could be if the experimental challenges associated with their use could be avoided. With this context in mind, I began work on my PhD with an aim to develop new ways to enable the more convenient and expedient use of nickel catalysis, both of new transformations and as applied to existing transformations.

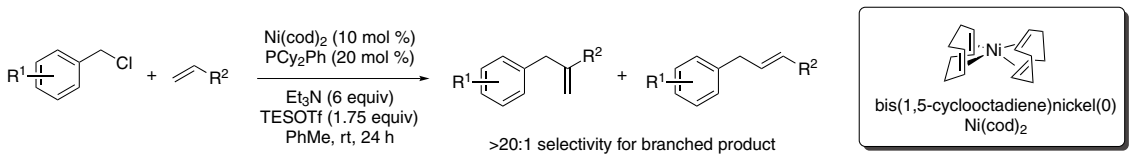
2. Nickel-Catalyzed Mizoroki–Heck Reactions

At the outset of my work in this field, I was working in collaboration with my mentor Dr. Ryosuke Matsubara. At the time, Dr. Matsubara was a visiting scholar in the Jamison group, and is now an associate professor at Kobe University in the group of Prof. Masahiko Hayashi. In his time in the Jamison group, he developed a nickel-catalyzed Mizoroki–Heck-type coupling reaction of simple alkenes and benzyl chlorides, which is highly selective for reaction at the internal position of the alkene (Scheme 1).[6] Traditionally, the Mizoroki–Heck reaction has been most often employed with alkenes possessing an electronic bias to control the regiochemical outcome of the reaction. This work considerably expanded the scope of substrates available for use in the Mizoroki–Heck reaction to include simple, monosubstituted alkenes lacking such bias.

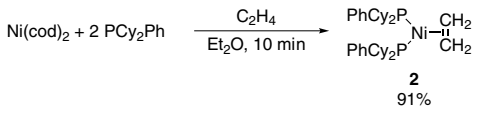
We initially began work by attempting to extend the scope of the reaction to include electronically unbiased, disubstitued alkenes. Early on, we observed the 1,5-cyclooctadiene ligands being functionalized, rather than the target alkene. This observation led to the idea that the 1,5-cyclooctadiene ligands, while generally easily displaced by phosphine ligands, cannot be completely ignored. Ultimately it was this observation that showed the true necessity of a cod-free precatalyst for this transformation, but also illuminated the potentially much wider application of such precatalysts.

To evaluate our hypothesis about the role of the 1,5-cyclooctadiene ligands, we needed to find a reliable way to access a phosphine-supported Ni(0) species that did not contain any 1,5-cyclooctadiene. Initial attempts led to catalyst species that either had poor stability or were significantly impure. The solution to this problem came from a literature search of zerovalent nickel complexes, which led us to $(PPh_3)_2Ni(\eta^2\text{-}C_2H_4)$, **2**.[7] This complex is an air-sensitive, but readily isolable complex that we imagined could be suitable for modification to include different phosphine ligands. When the desired dicyclohexylphenyl phosphine was used in place of triphenylphosphine for its synthesis, the corresponding $(PCy_2Ph)_2Ni(\eta^2\text{-}C_2H_4)$ (**2**) was isolated in good yield (Scheme 2). Use of this complex as a catalyst in the benzylation reaction was successful, and in fact showed improved performance relative to the system of $Ni(cod)_2$ and PCy_2Ph which we had traditionally employed.

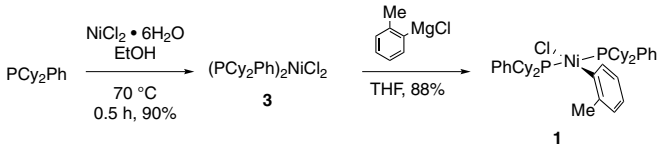
The knowledge gained through the use of this precatalyst in the Mizoroki–Heck reaction of benzyl chlorides was highly informative, but at this stage I had not even begun to address the principal challenge I had originally set out to, namely to improve the usability of this reaction by avoiding the use of any air-sensitive reagents. Additional literature searching and some helpful discussions with Prof. Stephen Buchwald and his graduate students made us aware of some relevant work carried out many decades ago by Chatt and Shaw.[8] These researchers had investigated the synthesis of a series of Ni(II) complexes substituted with phosphine ligands and substituted arenes, many



Scheme 1. Nickel-catalyzed Mizoroki–Heck reaction of benzyl chlorides and simple alkenes



Scheme 2. Synthesis of $(PCy_2Ph)_2Ni(\eta^2\text{-}C_2H_4)$



Scheme 3. Two-step synthesis of $(PCy_2Ph)_2Ni(o\text{-tolyl})Cl$ (**1**)

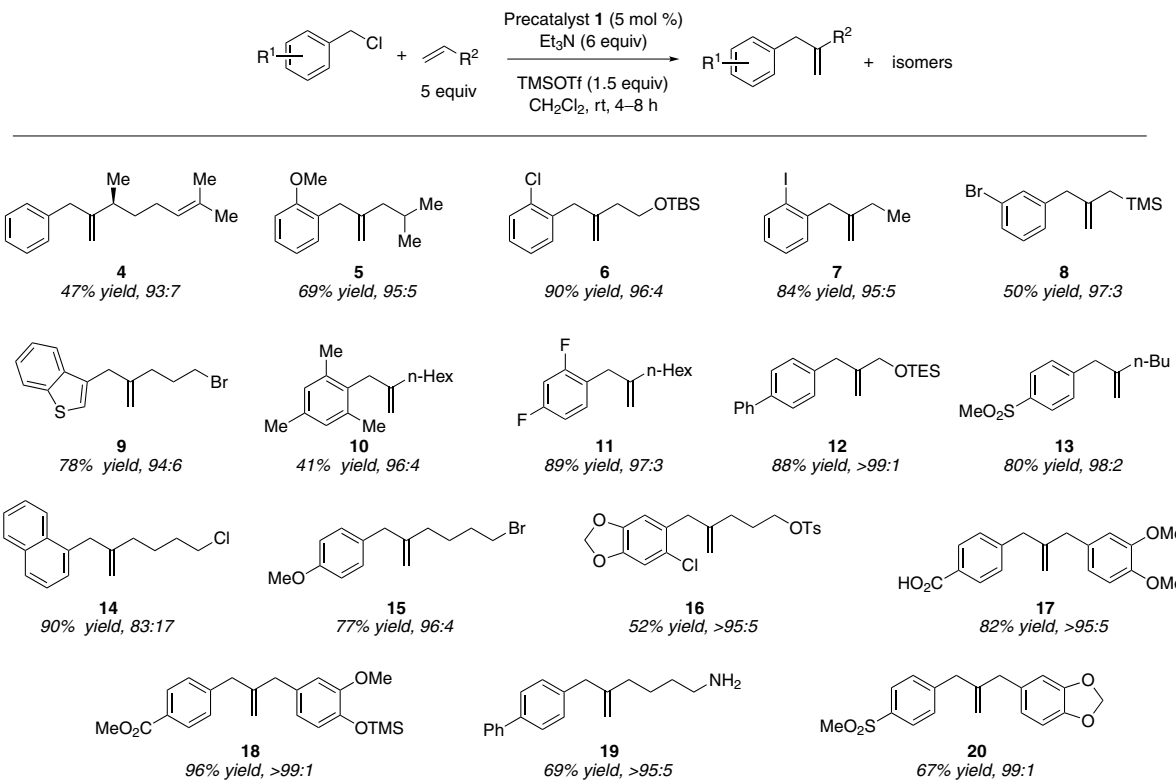
of which possessed at least some stability towards oxygen. After initial lab trials, we quickly arrived at an optimized synthesis of $(PCy_2Ph)_2Ni(o\text{-tolyl})Cl$ (**1**). This complex is an air-stable, diamagnetic solid which can be readily prepared from dicyclohexylphenyl phosphine, nickel chloride hexahydrate, and *o*-tolylmagnesium chloride in a high-yielding, two step sequence (Scheme 3).

The use of **1** as a precatalyst for this transformation enables several changes to the reaction protocol. First, it is no longer necessary to degas or purify the solvents and reagents used for the reaction. Second, due to the absence of the 1,5-cyclooctadiene ligands, the catalytic system is much more active, meaning a lower catalyst loading (5 mol % rather than 10 to 15 mol %) can be employed. Third, because $Ni(cod)_2$ is incompatible with certain solvents, a wider range of solvents can be used. In this case, changing from toluene to dichloromethane provided a further rate enhancement to the reaction, something that would not be possible with $Ni(cod)_2$ as the precatalyst. Overall, these changes add to the convenience and usability of the reaction, but they also enable the reaction to work with substrates that did not work with the original protocol. Specifically, because a Lewis Acid activator, triethylsilyl triflate or trimethylsilyl triflate, is used, acid-sensitive substrates were in some cases beyond the scope of the reaction. By moving to a more active catalyst system, the reaction time could be considerably shortened, allowing the rate of the desired benzylation reaction to be high enough to outcompete the acid-mediated decomposition.[9] Selected examples are illustrated in Scheme 4. In all cases, high regioselectivity for the branched product is observed in preference to the linear products, and the products can be isolated in good to excellent yield after column chromatographic purification on silica gel.

Subsequent to our work on the Mizoroki–Heck reaction, we sought to understand more about the generality of this type of precatalyst. A large assortment of phosphine ligands were successfully incorporated into precatalysts of this architecture, covering a significant portion of the phosphine ligands most commonly used in homogeneous nickel catalysis. Both monodentate and bidentate phosphine ligands with a variety of alkyl and aryl substituents were successfully used to yield nearly 20 different air-stable nickel complexes suitable for use as precatalysts in nickel-catalyzed reactions.[10]

3. Conclusion and Outlook

Looking forward, the use of nickel catalysis continues to increase as new methods are developed, particularly as nickel's propensity for one-electron and redox chemistry is further understood and exploited.[11] As such, new means to access the required active nickel species from readily available and convenient-to-use precursors is an ongoing focus of research and development. As the field of nickel catalysis further matures, it is our hope that researchers will continue to not only develop new transformations, but continue to place emphasis on the usability of the developed reactions. While novel transformations push the boundaries of organic synthesis, the uptake of these reactions by chemists, both in academia and in industry, is often limited by practical considerations.



Yields given are of isolated products after purification by column chromatography. Regioratio is reported as the ratio of the major isomer to the sum of all other isomers observed.

Scheme 4. Selected scope of the Nickel-catalyzed Mizoroki–Heck reaction of benzyl chlorides and terminal alkenes

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Intoduction of the author:

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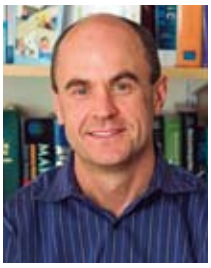
Eric Standley is a research scientist at Gilead Sciences, Inc., based in Foster City, California working in the field of pharmaceutical process development. He completed his undergraduate education in his home town of Boise, ID, USA, during which time he worked with professors Don Warner and Eric Brown carrying out research in the areas of organic synthesis and bioinorganic synthesis, respectively. Subsequently he went on to complete his PhD at the Massachusetts Institute of Technology as a NSF Graduate Research Fellow under the guidance of Prof. Timothy Jamison. His research and thesis focused on the development of new, air-stable precatalysts and on the development of new nickel catalyzed reactions. Later he joined the research laboratory of Prof. Dr. Frank Glorius at the University of Münster, Germany as an Alexander von Humboldt Postdoctoral Fellow. His research there centered on the development and application of new photochemical methods for high-throughput reaction discovery and development. In his free time, Eric enjoys cycling, hiking, and spending time with his wife and dog.



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Tim Jamison was born in San Jose, CA and grew up in neighboring Los Gatos, CA. He received his undergraduate education at the University of California, Berkeley. A six-month research assistantship at ICI Americas in Richmond, CA under the mentorship of Dr. William G. Haag was his first experience in chemistry research. Upon returning to Berkeley, he joined the laboratory of Prof. Henry Rapoport and conducted undergraduate research in his group for nearly three years, the majority of which was under the tutelage of William D. Lubell. A Fulbright Scholarship supported ten months of research in Prof. Steven A. Benner's laboratories at the ETH in Zürich, Switzerland, and thereafter he undertook his PhD studies at Harvard University with Prof. Stuart L. Schreiber. He then moved to the laboratory of Prof. Eric N. Jacobsen at Harvard University as a Damon Runyon-Walter Winchell postdoctoral fellow. In 1999, he began his independent career at MIT, where his research program focuses on the development of new methods of organic synthesis and their implementation in the total synthesis of natural products.
http://web.mit.edu/chemistry/jamison/

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