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Nickamine: A General Catalyst for Cross Coupling of Alkyl Halides and Direct Alkylation

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Werner Prize winner 2011

Abstract: A nickel pincer complex, Nickamine, is shown to be an active catalyst for a large number of reactions including cross coupling of non-activated alkyl halides and direct C–H alkylation of alkynes and aromatic heterocycles. This work was rewarded by the 2011 Werner Prize from the Swiss Chemical Society.

Keywords: C–H functionalization · Cross coupling · Homogeneous catalysis · Organometallic chemistry · Nickel

Xile Hu was born in 1978 in Putian, China. He received a B.S. degree from Peking University (2000) and a Ph.D. degree from the University of California, San Diego (2004; advisor: Prof. Karsten Meyer). He then carried out a postdoctoral study at the California Institute of Technology (advisor: Prof. Jonas Peters) before joining the faculty of École Polytechnique Fédérale de Lausanne (EPFL) as a tenure-track assistant professor in 2007. His research interests span from organometallic chemistry, synthetic methodology, asymmetric catalysis to bio-mimetic and bio-speculated coordination chemistry to electrocatalysis and artificial photosynthesis.

1. Introduction

I am thrilled to receive, together with Prof. Reto Dorta, the 2011 Werner Prize. This is not only because it is a distinguished honor for young investigators in Switzerland, but also because I teach coordination chemistry at EPFL, and Prof. Alfred Werner was the founding father of this discipline. Coordination chemistry is an integral component of my research program. Together with a group of motivated and talented co-workers, we have embarked on several research projects in homogeneous catalysis,[1,2] bio-mimetic chemistry,[3–8] and energy-related electrocatalysis.[9,10] The starting point of these projects is often the synthesis of new coordination compounds. The Werner Prize recognizes our contributions to the development of synthetic methodologies. Herein I describe some representative examples of our work in this area; these examples all feature the catalytic applications of Nickamine, a new Ni catalyst developed in the group.

2. Motivation

Werner was the first to correctly propose the structure of coordination complexes. He did most of his work using amine and aqua complexes of first-row transition metals. For this reason, these compounds are often called 'Werner complexes'. One of Werner's greatest achievements was the preparation of hexol in 1914, the first non-carbon-containing chiral compound (Fig. 1).[11]

Another major breakthrough in coordination chemistry was the synthesis and structural elucidation of ferrocene in early 1950s (Fig. 1). It marked the birth of modern organometallic chemistry. E.O. Fischer and G. Wilkinson received the Nobel Prize in 1973 for their work on sandwich compounds of this type.[12,13] And another important contribution of Wilkinson is the development of Wilkinson's catalyst, a four-coordinate complex $[Rh(PPh_3)_3Cl]$ (Fig. 1).[14] This compound is a good catalyst for many homogeneous reactions especially

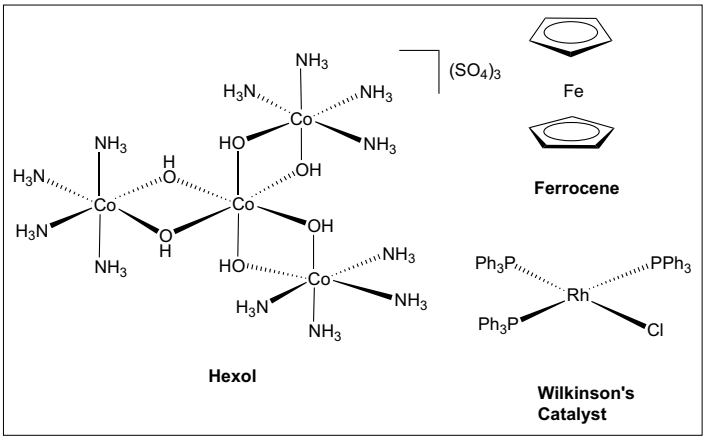

Fig. 1. Legendary coordination compounds.

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hydrogenation. In retrospect, Wilkinson's work revealed a winning recipe for catalyst design: precious metals plus soft ligands. In the last 10 years, three Nobel prizes have been awarded for the advances in homogeneous catalysis, and catalysts based on precious metals and soft ligands show again their superiority: Rh and Ru phosphine complexes for hydrogenation,[15,16] Ru carbene/phosphine complexes for olefin metathesis,[17] and Pd phosphine complexes for cross coupling.[18,19]

Despite tremendous progress, homogeneous catalysis is far from being problem-solved. One major challenge has arisen exactly because many useful catalysts are based on precious and rare metals such as Ru, Pd, Pt, Rh, Au, and Ir. The sustainability of chemical processes based on these catalysts is called in question. Meanwhile, catalysts made of base metals such as Mn, Fe, Co, Ni, and Cu, are not developed to the same degree. This state-of-the-art has largely motivated our work in base metal catalysis. Our starting point happened to be a Werner-type complex – Nickamine (**1**; Fig. 2).

The name 'Nickamine' reflects the composition of this compound – nickel as metal and amine as ligand. The pincer-type bis(amino)amide ligand $^{Me}N_2N$ was chosen because we thought nitrogen donors would match better first-row transition metal ions according to the hard-soft-acid-base principle.[20] The synthesis of the ligand and its coordination chemistry were straightforward.[21–23]

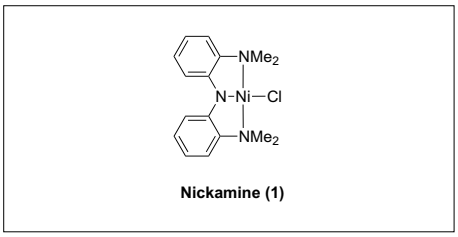


Fig. 2. Structural formula of Nickamine.

3. Cross Coupling of Alkyl Halides Catalyzed by Nickamine

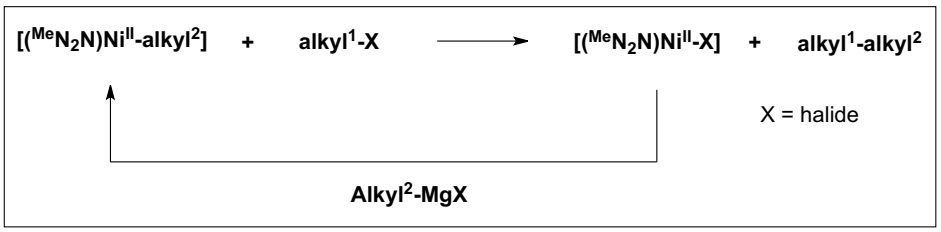
Nickamine was a useful starting material for the synthesis of other Ni complexes bearing the same pincer $^{Me}N_2N$ ligand. For examples, salt metathesis and transmetallation reactions of **1** yielded [($^{Me}N_2N$)Ni-R)], where R is an alkyl, aryl, methoxide, or triflate group.[21,22] It was interesting that [($^{Me}N_2N$)Ni-alkyl)] complexes were stable in solution, even when heated to 80 °C. It turns out that β-H elimination for these complexes is kinetically feasible, but thermodynamically uphill,[24] and that is why these complexes did not decompose *via* β-H elimination.

The reactivity of [($^{Me}N_2N$)Ni-alkyl)] with alkyl halides provides the basis for the applications of Nickamine in cross coupling reactions (Scheme 1).[21] It was found that [($^{Me}N_2N$)Ni-alkyl)] reacted cleanly with alkyl halides to form [($^{Me}N_2N$)Ni-X)] (X = halide) and alkyl-alkyl coupled products. Because [($^{Me}N_2N$)Ni-X)] could react with alkyl Grignard reagents to form back [($^{Me}N_2N$)Ni-alkyl)] (Scheme 1), a catalytic alkyl–alkyl coupling reaction was conceivable using **1** as catalyst. Such a coupling reaction is challenging because metal alkyl intermediates have the tendency to undergo unproductive β-H elimination.[25–27] As a result, new alkyl–alkyl coupling methods are of contemporary interest.

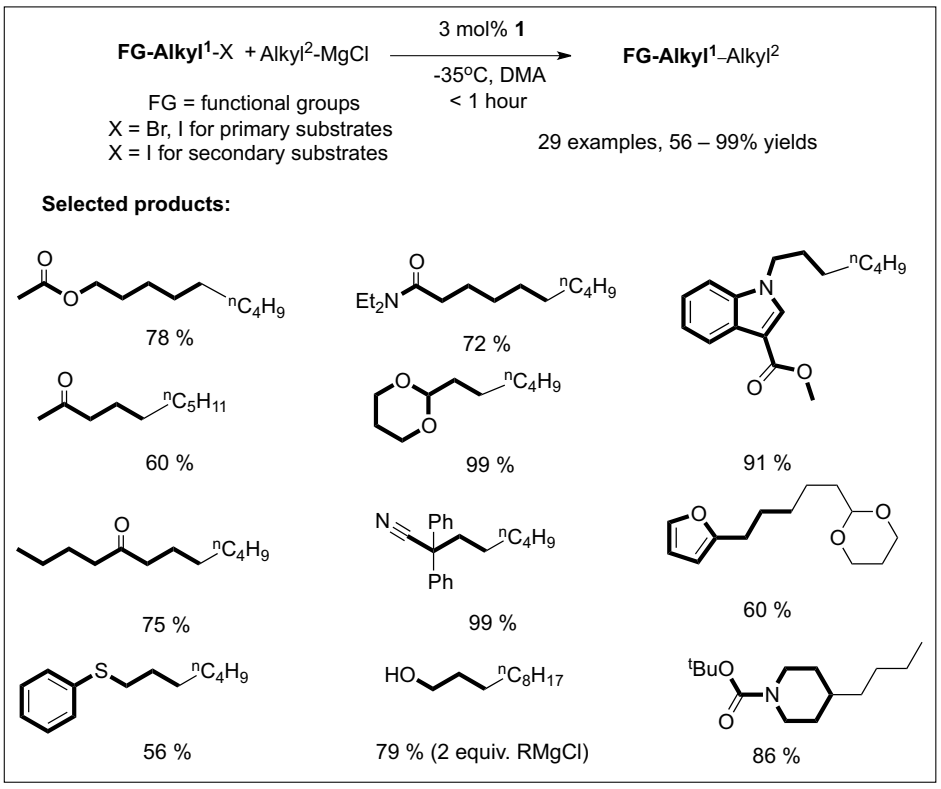
We were delighted to find that complex **1** catalyzed the cross coupling of non-activated alkyl halides with alkyl Grignard regents in high efficiency.[22] The reactions took place at a low temperature (−20 °C). Since Grignard reagents might tolerate various functional groups at this temperature, we thought it might be possible to couple functionalized alkyl halides with alkyl Grignard reagents under similar conditions. In general, this type of alkyl–alkyl coupling necessitates the use of mild organometallic reagents such as zinc, boron, or silicon nucleophiles. Grignard reagents are normally not compatible with functional groups because they are too reactive. Grignard reagents can however be more attractive coupling partners because they are inexpensive, easy to synthesize, and often commercially available.

Indeed, we were able to develop a method to couple functionalized alkyl halides with alkyl Grignard reagents using **1** as catalyst (Scheme 2). The best yields were obtained at −35 °C, just above the melting point of the reaction mixture. Primary alkyl iodides and bromides and secondary alkyl iodides could be coupled. The reactions tolerated a large number of sensitive functional groups such as ester, amide, keto, ether, thioether, acetal, nitrile, and heterocycles.

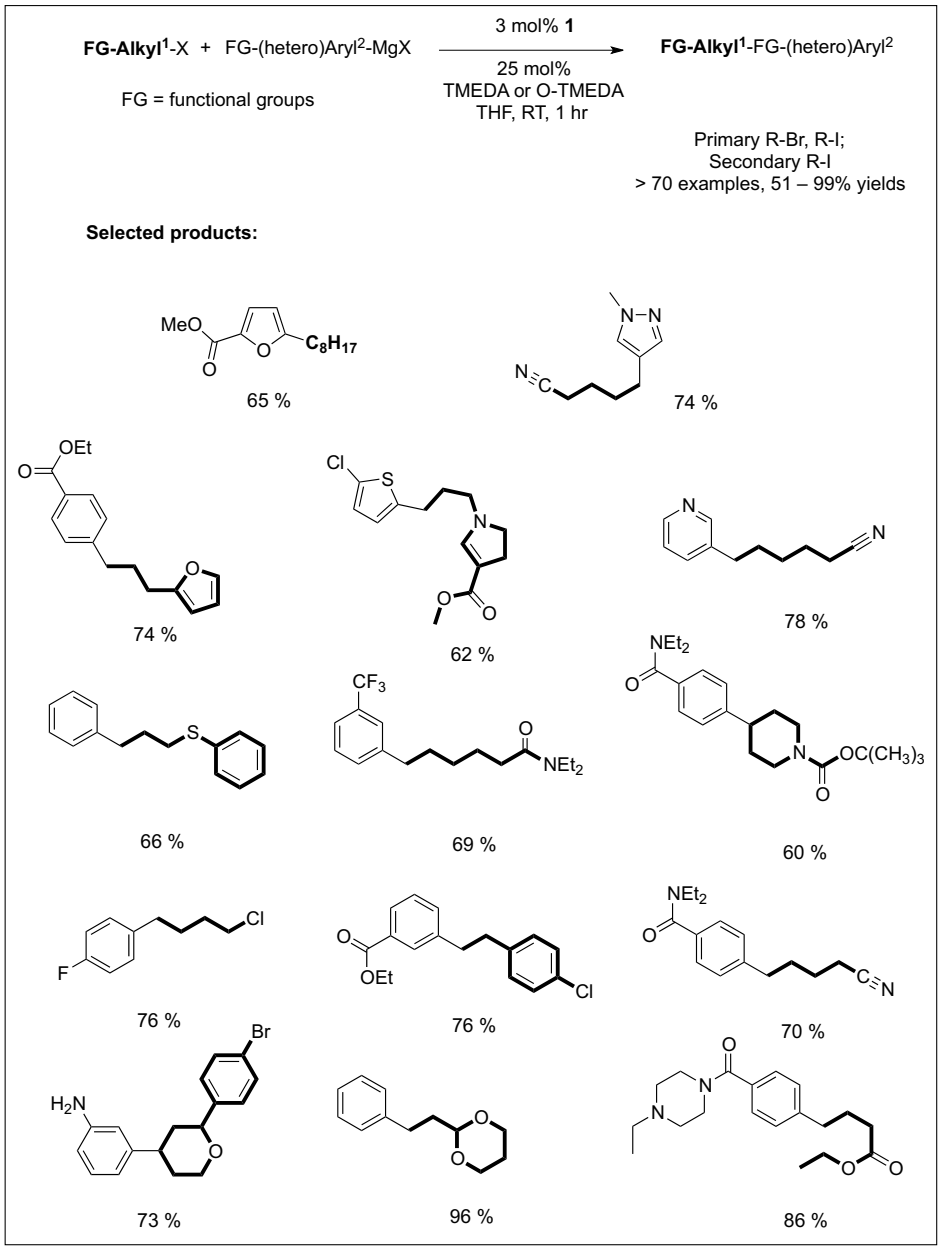
Encouraged by this first success in methodology development, we decided to further explore the Ni-catalysis. An obvious next step was to expand the substrate scope. Thus, we wondered whether we could couple functionalized alkyl halides with aryl and heteroaryl nucleophiles.



Scheme 1. Reactivity and regeneration of [($^{Me}N_2N$)Ni-alkyl)] complexes.



Scheme 2. Alkyl-alkyl Kumada coupling using Nickamine as catalyst.



Scheme 3. Alkyl-(hetero)aryl Kumada coupling using Nickamine as catalyst.

These aromatic groups are ubiquitous in natural products, pharmaceuticals, and organic materials. Again we chose Grignard reagents for the above-mentioned reasons. The alkyl–alkyl coupling protocol was not efficient. However, O. Vechorkin, an outstanding Ph.D. student, was able to develop a new procedure for the alkyl-(hetero) aryl coupling.[28] It turned out a catalytic amount of amine additive such as TMEDA (tetramethylenediamine) or O-TMEDA {bis[2-(N,N-dimethylaminoethyl)]ether} was a key ingredient to ensure a high coupling yield. The additive most likely interacted with Grignard reagent to facilitate the transmetallation to the catalyst while suppressing side reactions such as homocoupling. This coupling method had an impressive substrate scope and group tolerance (Scheme 3). Alkyl halides containing ester, amide, ether, thioether, alcohol, pyrrole, indole, furan, nitrile, conjugated enone, and aryl-halide moieties were readily coupled. Even aryl Grignard reagents containing electron-deficient and/or sensitive ester, nitrile, amide, CF_3 substituents, and heteroaryl Grignard reagents based on pyridine, thiophene, pyrazole, and furan backbones could be used as the nucleophilic coupling partners.

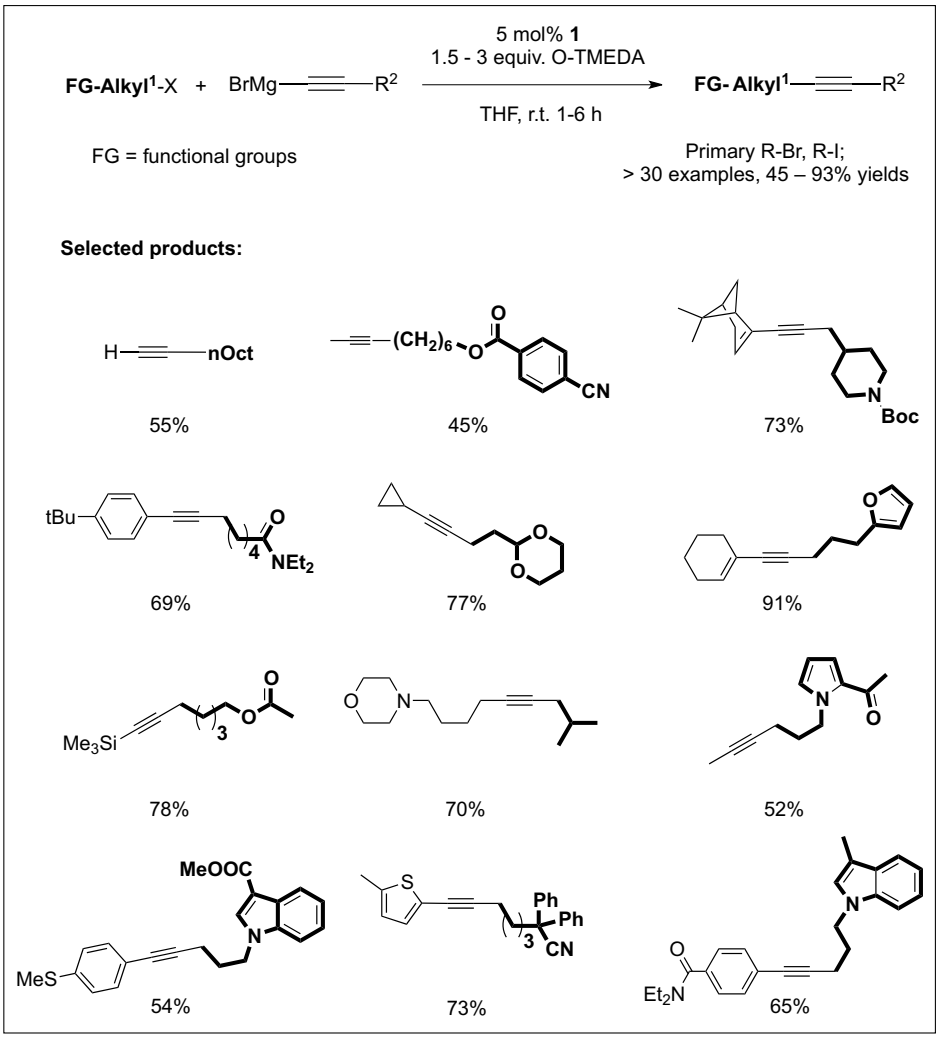
Another interesting reaction is the coupling of non-activated alkyl halides with alkynyl Grignard reagents. This is a simple method to prepare alkynes containing alkyl groups. Such molecules are frequently used as synthetic intermediates to biologically active compounds and organic materials. Currently these molecules are often prepared by reactions of alkali metal acetylides with alkyl halides in liquid ammonia or with HMPA (hexamethylphosphoramide) as solvent or cosolvent at a low temperature (*e.g.* −78 °C). The reaction conditions are complicated and inconvenient, and the carcinogenic effect of HMPA is a source of concern. At room temperature, alkali metal acetylides are quite reactive and may lead to a low functional group tolerance. We found that using **1** as catalyst and O-TMEDA as additive, general and efficient cross coupling of non-activated alkyl halides with alkynyl Grignard reagents could be achieved (Scheme 4).[29] The catalysis again had a wide scope and high group tolerance. The method allowed the streamlined synthesis of alkynes containing non-activated alkyl groups at room temperature.

4. Direct Alkylation Catalyzed by Nickamine

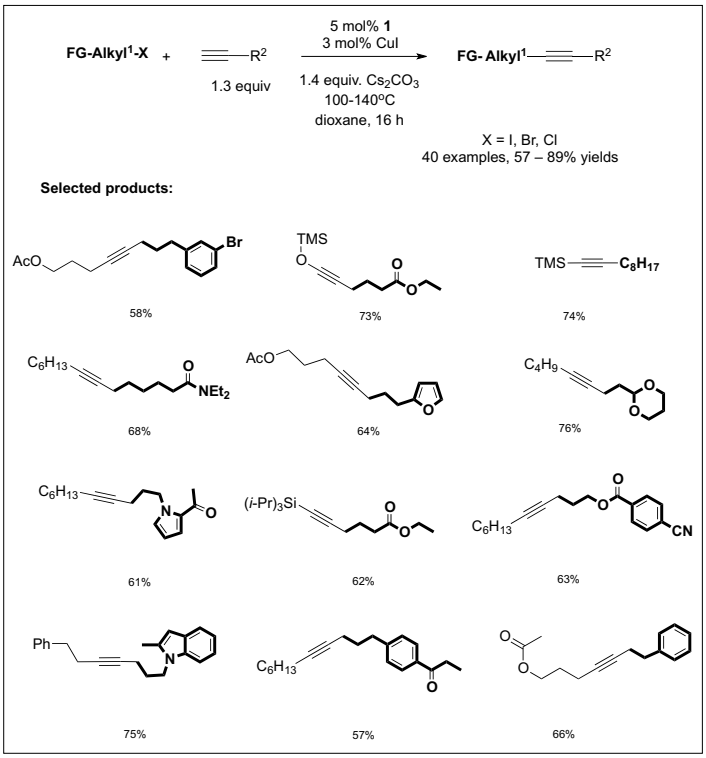
According to preliminary mechanistic studies, reaction of an organometallic species [($^{Me}N_2$N)Ni-R)] with an alkyl halide is the C–C bond forming step in the aforementioned cross coupling reactions. As [($^{Me}N_2$N)Ni-R)] is generated by transmetallation of [($^{Me}N_2$N)Ni-X)] with an organometallic reagent, here Grignard reagent, the coupling requires at least a stoichiometric amount of such reagent. If the same [($^{Me}N_2$N)Ni-R)] intermediate could be generated without a preformed organometallic reagent, more benign and step-economical coupling reactions might be developed. Along this line, we became interested in direct alkylation of weakly acidic C–H bonds. The idea was that these C–H bonds might be deprotonated by a weak base to give a small percentage or even a trace amount of carbon anions, which could then be transmetallated to Ni to form [($^{Me}N_2$N)Ni-R)] and trigger the alkylation.

The first test for this design was Sonogashira coupling of non-activated alkyl halides with alkynes, since the alkynyl C–H bonds in alkynes are slightly acidic. Sonogashira reaction is well developed for aryl and vinyl halides, but prior to our work, there were merely two examples of successful Sonogashira coupling of non-activated alkyl halides.[30,31] The problem is again the problematic β-H elimination. So we were excited to see that **1** could be used as catalyst for Sonogashira coupling of alkyl iodides, bromides, and chlorides with terminal alkynes (Scheme 5). The catalysis tolerated a wide range of functional groups in both coupling partners, and offered a useful alternative to the synthesis of alkyl-substituted internal alkynes.

The second target was direct alkylation of aromatic heterocycles. These molecules are important due to their interesting biological or materials properties. The C(2)–H bonds of heterocycles have pKa values



Scheme 4. Alkyl-alkynyl Kumada coupling using Nickamine as catalyst.



Scheme 5. Sonogashira coupling of non-activated alkyl halides with terminal alkynes using Nickamine as catalyst.

similar to terminal alkynes, and are thus slightly acidic. O. Vechorkin found that a modification of the Sonogashira protocol could lead to direct alkylation of oxazoles, thiazoles, and thiophenes (Scheme 6).[32] Nickamine (**1**) was the best precatalyst. A large number of alkyl halides including chlorides could be used as the alkylating reagents. Both electron-poor and electron-rich heterocycles could be alkylated, which is hard to achieve using alternative methods such as Friedel-Crafts or radical alkylation.

5. Summary and Outlook

In conclusion, the nickel pincer complex Nickamine (**1**) has been shown to be an excellent catalyst for cross coupling of alkyl halides and direct C–H alkylation. The scope encompasses alkyl–alky, alkyl–aryl, alkyl–heteroaryl, and alkyl–alkynyl coupling reactions and direct alkylation of alkynes and heterocycles. It is not an exaggeration to call Nickamine a general catalyst.[33]

We have carried out preliminary mechanistic studies and proposed tentative catalytic cycles for Ni-catalysis.[2] The mechanistic considerations have contributed greatly to the development of catalytic reactions. We plan to further investigate the mechanistic details of these reactions to reach a better understanding of these systems.

The story of Nickamine is not over, as we continue to find interesting applications of this catalyst. At the same time, we are also developing new generations of catalysts that might overcome some of the limitations of Nickamine. For example, we recently reported that Ni-Pengamine complexes were superior catalysts for alkyl–alkyl Kumada coupling of secondary alkyl halides.[34]

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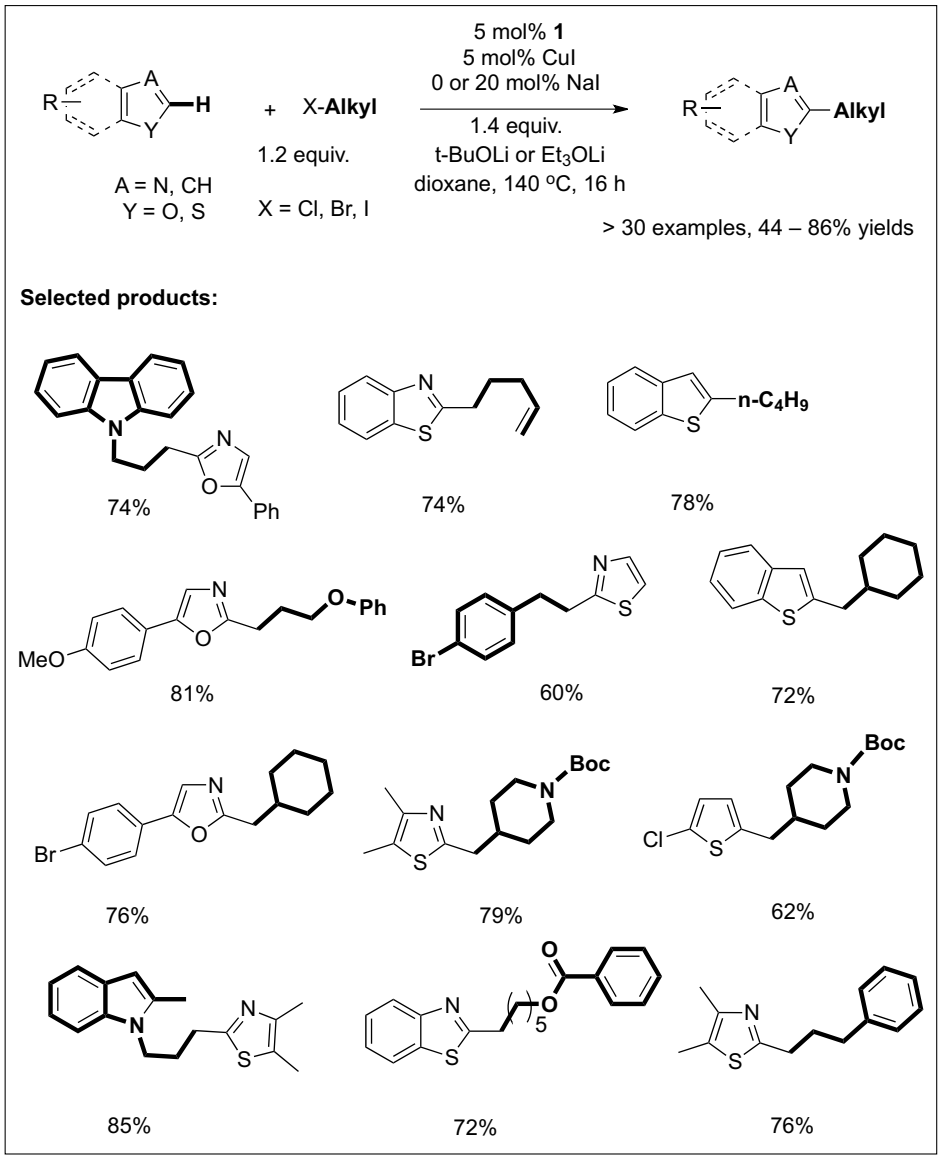

Scheme 6. Direct alkylation of aromatic heterocycles using Nickamine as precatalyst.

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