doi:10.2533/chimia.2014.235
Chimia 68 (2014) 235–238 © Schweizerische Chemische Gesellschaft

Mechanistic Insights into Nickamine-catalyzed Alkyl-Alkyl Cross-coupling Reactions

Jan Breitenfeld§ and Xile Hu*

§SCS-Metrohm Foundation Award for best oral presentation

Abstract: Within the last decades the transition metal-catalyzed cross-coupling of non-activated alkyl halides has significantly progressed. Within the context of alkyl-alkyl cross-coupling, first row transition metals spanning from iron, over cobalt, nickel, to copper have been successfully applied to catalyze this difficult reaction. The mechanistic understanding of these reactions is still in its infancy. Herein we outline our latest mechanistic studies that explain the efficiency of nickel, in particular nickamine-catalyzed alkyl-alkyl cross-coupling reactions.

Keywords: Bimetallic oxidative addition · Cross-coupling · β-Hydride elimination · Mechanistic studies · Nickel

1. Introduction

Our group developed a square planar bis(amino)amido nickel pincer complex – nickamine (**1**, Fig. 1).[1] This complex showed an excellent activity for the cross-coupling of non-activated alkyl halides with aryl,[2] alkynyl,[3] and alkyl Grignard reagents.[1,4,5] Very recently we also demonstrated the Suzuki-Miyaura cross-coupling of alkyl halides with nickamine as catalyst.[6] These results prompted us to study the mechanism in detail and to discover the key features in this system.

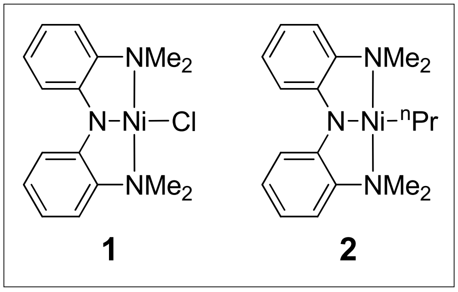


Fig. 1. Structural formula of nickamine [($^{Me}NN_2$)Ni-Cl] (**1**) and [($^{Me}NN_2$)Ni-^{n}Pr] (**2**).

2. Stability of Nickel-Alkyl Intermediates

The nickamine system not only exhibited outstanding catalytic activity, but also showed remarkable stability with respect to alkyl ligands bearing β-hydrogen atoms.[1] Nickel alkyl complexes, for example, Ni-^{n}Pr (**2**, Fig. 1), could be isolated and identified as intermediate species in catalysis as well as in single-turnover reactions. The reluctance of these nickel alkyl complexes towards β-hydride elimination is counted as one of the main reasons for successful alkyl-alkyl cross-coupling. It originates from the fact that β-hydride elimination is kinetically viable but thermodynamically unfavorable.[7] Results obtained from the coupling of secondary alkyl Grignard reagents and olefin-exchange experiments confirmed the kinetic accessibility of a nickel hydride intermediate by β-hydride elimination. The isolation of the nickel hydride complex confirmed its existence.[8]

3. Oxidative Addition

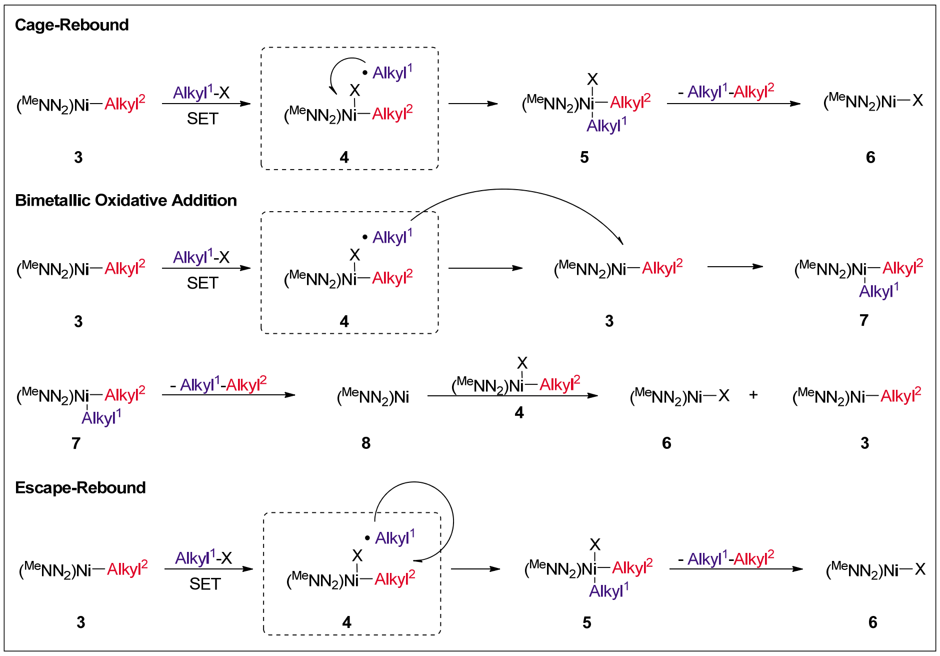
The activation of alkyl halides has been demonstrated to be a radical process for the nickamine system.[5] However, the product formation from the alkyl radical intermediate was unexplained for this type of catalytic reactions. Mechanistically several pathways might be possible. Scheme 1 displays the hypothetical reaction sequences accounting for the reaction outcome. All three pathways assume the activation of the alkyl halide by a nickel-alkyl (**3**) species *via* single electron transfer (SET), leading to a one-electron oxidized nickel(III) alkyl halide intermediate (**4**) with an alkyl radical in close proximity. The alkyl radical might further react in three different possibilities. In the first scenario, *i.e.* the cage-rebound mechanism, the nickel species and the alkyl radical in the solvent cage recombine to form a nickel(IV) bisalkyl halide complex (**5**). Reductive elimination leads to the formation of the coupling product and a nickel(II) halide complex (**6**). In the second scenario, *i.e.* the bimetallic oxidative addition, the alkyl radical leaves the solvent cage and recombines with a nickel(II) alkyl complex (**3**). In this case a nickel(III) bis(alkyl) complex (**7**) is generated. The reductive elimination yields the coupling product and a nickel(I) intermediate (**8**). Comproportionation of the latter with the initially formed nickel(III) alkyl halide species (**4**) would regenerate two nickel(II) complexes. A third scenario is the escape-rebound mechanism. The alkyl radical escapes the solvent cage at first, then recombines with the Ni(III) intermediate (**4**) to form a nickel(IV) bis(alkyl) halide complex (**5**). Reductive elimination of the latter gives the coupling product and a nickel(II) halide complex (**6**).

3.1 *Radical Clock Experiment*

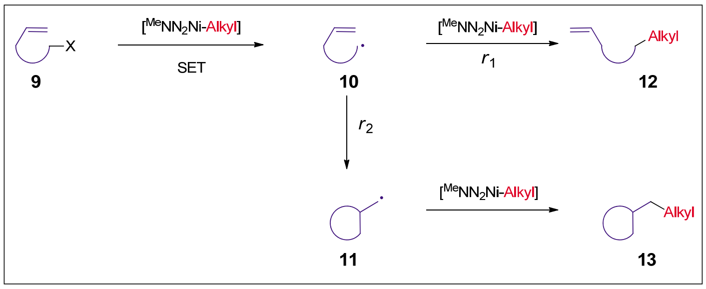
In order to distinguish these mechanisms a radical probe with the ability to perform an irreversible skeletal rearrangement can be used. The theoretical considerations are summarized in Scheme 2. The requirements the radical trap (**9**) has to meet are that both radicals, unarranged (**10**) and rearranged (**11**), can form a cross-coupling product. The ratio of the unarranged (**12**) and rearranged (**13**) coupling products is a function of r_1/r_2 and may or may not be

---

Correspondence: Prof. X. L. Hu
Ecole Polytechnique Fédérale de Lausanne
Institute of Chemical Sciences and Engineering
EPFL-ISIC-LSCI
CH-1015 Lausanne
Tel.: +41 21 693 9781
E-mail: xile.hu@epfl.ch



Scheme 1. Possible pathways for the formation of the coupling product *via* a radical mechanism.



Scheme 2. Outcome of cross-coupling reaction with a radical probe.

dependent on the catalyst loading. This can be used to distinguish the cage-rebound from the bimetallic-oxidative addition and the escape-rebound mechanism.

The cage-rebound reaction should be independent from the catalyst loading, as it can be considered an intramolecular reaction within the solvent cage. The fact that the alkyl radical is leaving the solvent cage results in a dependence on the catalyst loading for the bimetallic oxidative addition pathway as well as the escape-rebound mechanism. A linear dependence for the ratio of (**14**) and (**15**) was observed for the cross-coupling of 3-(2-bromoethoxy)prop-1-ene (**16**) with ^{n}BuMgCl for the nickamine system (Fig. 2), therefore ruling out the cage-rebound mechanism.[9]

In order to assure that the cyclic product was formed by a radical cyclization and not by a concerted mechanism, we performed the reaction with a terminal deuterium labeled radical probe (**16-D**). In a radical pathway two pairs of diastereomers are expected, while the concerted mechanism should only furnish one pair of diastereomers (Scheme 3). Indeed, for the coupling of **16-D** with phenylethyl Grignard we observed two pairs of diastereomers supporting the fact that the cyclic product **15** stemmed from a radical ring-closing reaction.[9]

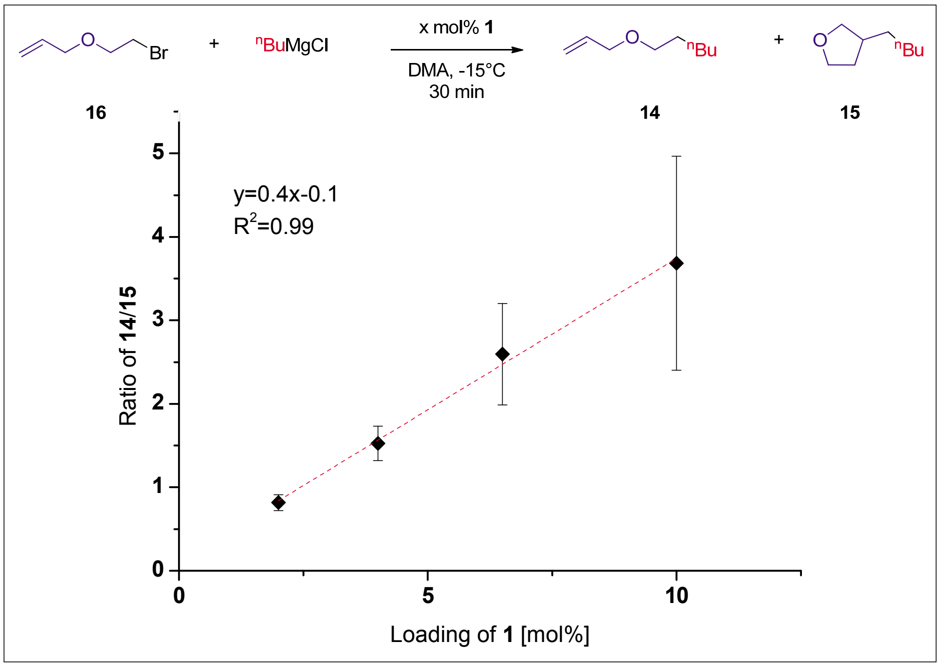


Fig. 2. Dependence of ratio **14** to **15** on the catalyst loading (**1**) for the coupling of **16** and ^{n}BuMgCl.

3.2 *Bimetallic Oxidative Addition*

After excluding the cage-rebound mechanism we were facing the challenge to differentiate between the bimetallic oxidative addition and the escape-rebound mechanism. The two pathways cannot be distinguished by the radical clock experiment. However, they differ in the nature of the nickel species that is formed by recombination with the alkyl radical. In the bimetallic oxidative addition a Ni(II) alkyl recombines with the alkyl radical to form a Ni(III) bisalkyl intermediate, while a Ni(IV) bisalkyl halide species is formed for the escape-rebound mechanism. As synthetic approaches to either Ni(III) or Ni(IV) species were unsuccessful we tried to mimic the bimetallic oxidative addition pathway by the reaction of isolated Ni(II) alkyl complex with an *in situ* generated alkyl radical. Therefore, we irradiated tert-butyl-4-phenylbutaneperoxoate (**17**) in the presence of Ni-^{n}Pr (**2**, Scheme 4). Under these conditions we observed the formation of 13% hexylbenzene (**22**), indicating the feasibility of a reductive elimination from a Ni(III) bisalkyl intermediate.[9]

As no other experimental data were available, we focused on density functional theory (DFT) computations at the M0664,65/def2-TZVP66 level to compare reaction free energies and transition state barrier heights for the reactions of a ethyl radical with **2** or a Ni(III)-^{n}Pr(I) (**18**) to form respective Ni(III)-^{n}Pr(Et) (**19**) or Ni(IV)-^{n}Pr(Et)(I) (**20**, Fig. 3). These results enabled us to exclude the escape-rebound mechanism and identify the bimetallic oxidative addition pathway as the likely operating mechanism.[9]

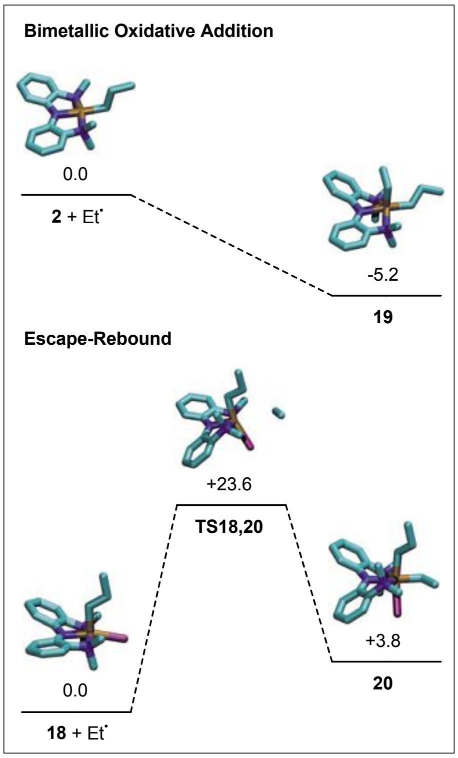
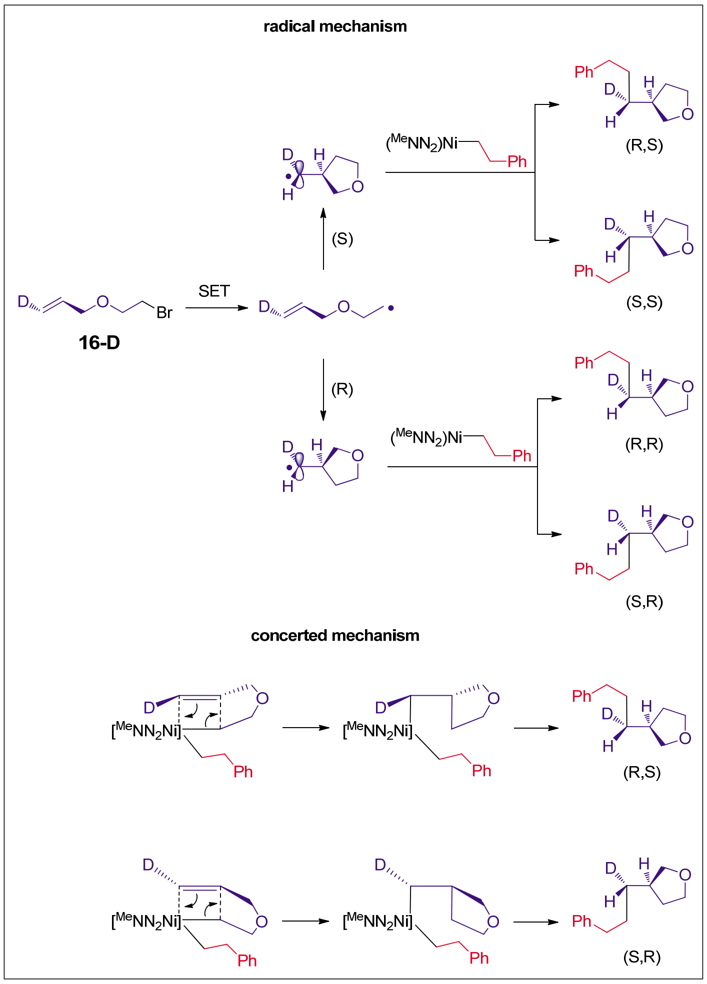
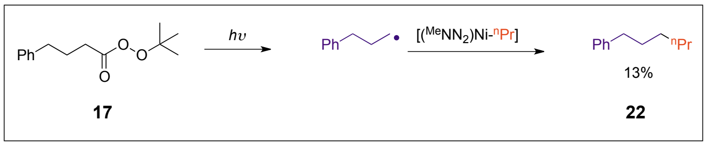


Fig. 3. Structures and reaction free energies computed for the bimetallic oxidative addition and the escape-rebound mechanism (M0664,65/def2-TZVP66 level, values in kcal/mol).



Scheme 3. Stereochemical outcomes of a radical or concerted mechanism.



Scheme 4. Reaction of *in situ* generated radical with complex **2**.

4. Discovering the Key Species

Next we turned our focus on the single-turnover reaction of isolated Ni-^{n}Pr with butyl iodide under catalytically relevant conditions. We determined the half-life of this reaction to be approximately 6 h.[9] This is significantly longer than the actual catalysis, which gives a high yield of coupling product in less than 30 min. Repetition of the experiment in the presence of additional amount of Grignard reproduced a reaction rate similar to that of catalysis.[9] Thus, in the presence of Grignard reagent a catalytically active nickel species is formed. We examined the reaction of **2** with ^{n}PrMgCl or MeMgCl under coupling conditions. In both cases no reaction was observed on the NMR timescale. This indicates that the Grignard reagent does not form a nickelate complex with enhanced nucleophilicity but more likely is only weakly coordinated. In order to support this hypothesis, we conducted a cross-over experiment of **2** and octyl iodide in the presence of variable amount of ^{n}BuMgCl and monitored the ratio of the coupling products undecane and dodecane. The ratio revealed a preference of the coupling of the nickel bound ^{n}Pr over the Mg bound ^{n}Bu fragment. These results suggest that the two alkyl ligands of the key alkyl species [(^{Me}NN$_2$)Ni-alkyl^2](alkyl^2-MgCl) (**21**) are differently coordinated to nickel and not exchangeable.[9]

5. Kinetics of Catalysis

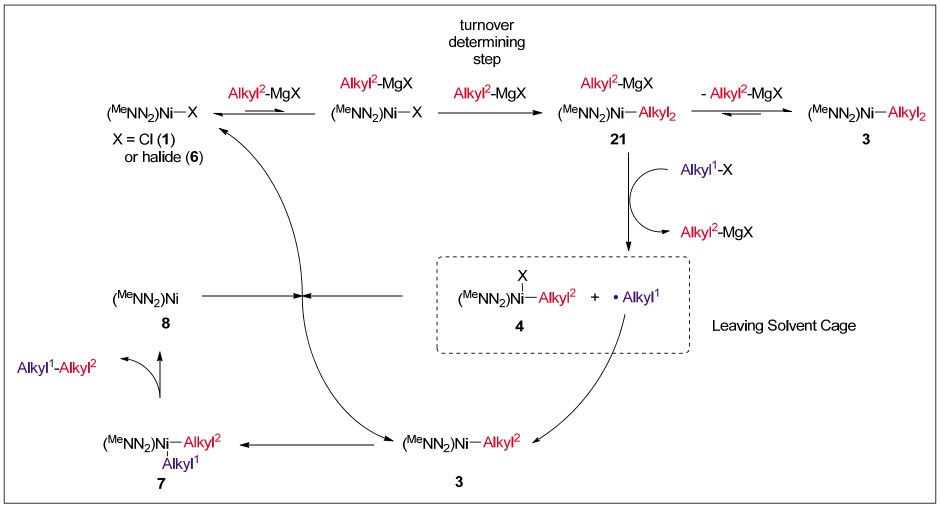
The information of the nature of the active species prompted us to study the kinetics of the catalysis. As model we chose the reaction of 2-phenylethylbromide with ^{n}BuMgCl. An approximately 1st order dependence on the catalyst loading and a 0th order dependence on the alkyl halide were observed. The dependence on ^{n}BuMgCl reagent was found to be 2nd order. The same dependence was found for the transmetalation of nickamine with Grignard in the absence of substrate.[9]

6. Detailed Mechanistic Proposal

Combination of the above-mentioned data led to the catalytic cycle depicted in Scheme 5. In a fast pre-equilibrium the first equivalent of a Grignard reagent coordinates to nickamine (**1**) followed by a turnover-determining, irreversible transmetalation, giving the key intermediate **21**. This explains the 2nd order dependence on Grignard reagent. The catalytically active species is in equilibrium with the four-coordinate Ni(II)-alkyl complex **3**, favoring the latter. Subsequent activation of the alkyl halide *via* bimetallic oxidative addition mechanism leads to the formation of a Ni(III) alkyl halide species (**4**) and a Ni(III) bis(alkyl) intermediate (**7**). The latter reductively eliminates the cross-coupling product and yields an unstable Ni(I) species (**8**) which recombines with the initially formed Ni(III) alkyl halide species (**4**) to produce Ni(II) halide (**6**) and Ni(II) alkyl complexes (**3**). Both **6** and **3** can re-enter the catalytic cycle.

7. Conclusion

In conclusion we revealed important features for the alkyl-alkyl cross-coupling reactions catalyzed by the nickamine catalyst. The overcoming of the problematic β-hydride elimination is attributed to



Scheme 5. Proposed catalytic cycle of nickamine-catalyzed alkyl-alkyl cross-coupling.

thermodynamic factors. The activation of the alkyl halide proceeds *via* a bimetallic oxidative addition mechanism, which circumvents nickel in a +4 formal oxidation state. We discovered that the coordination of a second equivalent of Grignard reagent to the Ni(II) alkyl complex created the key intermediate responsible for the activation of the alkyl halide. Overall, our studies unveiled new mechanistic peculiarities of first row transition metals that may explain their superior activity in alkyl-alkyl cross-coupling with respect to their commonly used higher homologous.

Acknowledgements

This work is supported by the EPFL and the Swiss National Science Foundation (no. 200020_144393/1). We thank Jesus Ruiz for experimental assistance and Dr. Matthew D. Wodrich for DFT calculations and for Fig. 3.

Received: January 16, 2014

---

[1] Z. Csok, O. Vechorkin, S. B. Harkins, R. Scopelliti, X. Hu, *J. Am. Chem. Soc.* **2008**, *130*, 8156.
[2] O. Vechorkin, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 9756.
[3] O. Vechorkin, A. Godinat, R. Scopelliti, X. Hu, *Angew. Chem. Int. Ed.* **2011**, *50*, 11777.
[4] O. Vechorkin, X. Hu, *Angew. Chem. Int. Ed.* **2009**, *48*, 2937.
[5] O. Vechorkin, Z. Csok, R. Scopelliti, X. Hu, *Chem.-Eur. J.* **2009**, *15*, 3889.
[6] T. Di Franco, N. Boutin, X. Hu, *Synthesis* **2013**, *45*, 2949.
[7] J. Breitenfeld, O. Vechorkin, C. Corminboeuf, R. Scopelliti, X. Hu, *Organometallics* **2010**, *29*, 3686.
[8] J. Breitenfeld, R. Scopelliti, X. Hu, *Organometallics* **2012**, *31*, 2128.
[9] J. Breitenfeld, J. Ruiz, M. D. Wodrich, X. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 12004.