**NiCl₂ and NiCl₂ = 6H₂O: A very Useful Mild Lewis Acid in Organic Synthesis**

Compiled by Philippe Labrie

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**Introduction**

Lewis acids are very useful reagents in organic synthesis. The classical Lewis acids currently used include BF₃·OEt₂, ZnCl₂, SnCl₂, TiCl₄ and many others. Nickel chloride can be also added to this list. NiCl₂ is a mild Lewis acid that promotes a wide variety of organic transformations in aqueous medium or organic solvent and may be used either catalytically or stoichiometrically. NiCl₂ was also used in a key step in the synthesis of bi-benzopyran-4-ol, tetrahydrodicanrenone B² and Allo-pumiliotoxins.³ NiCl₂ is a selective reductive agent when used with hydrides such as LiAlH₄ and NaBH₄. In fact, the mixture of NiCl₂ and NaBH₄ is used to prepare nickel boride,⁴ a reducing agent for many functional groups: azide,⁵ nitrile,⁶ NO bond,⁷ alkene⁸ and haloalkane.⁹ NiCl₂ was used in the regioselective rearrangement of dienols,¹⁰ ring-opening of epoxide,¹¹ nickel(II)/chromium(II) chloride-mediated addition to aldehydes or ketones,¹² Suzuki cross-coupling,¹² Biginelli reaction,¹³ reductive Heck-like reactions,¹⁴ nickel-catalyzed cross-coupling reaction of Grignard reagents¹⁵ and homo-coupling reactions.¹⁶

**Abstract**

**(A)** Suzuki cross-coupling with ArBr and ArI can be carried out with PhB(OH)₂ in good yields using NiCl₂·6H₂O as a catalyst precursor.¹²

\[
\text{Ar-X} + \text{PhB(OH)₂} \rightarrow \text{NiCl₂·6H₂O, K₃PO₄} \rightarrow \text{Ar-Ph}
\]
dioxane, 12 h
11 examples (6-87%)

**(B)** NiCl₂-(1,3-butadiene) catalyzes the cross-coupling reaction of alkyl chlorides, bromides, and tosylates with Grignard reagents under mild conditions.¹⁵

\[
\text{R-X} + \text{R'MgX} \rightarrow \text{cat. NiCl₂, 1,3 butadiene} \rightarrow \text{R-R'}
\]
R= alkyl  R’= alkyl, aryl  8 examples (56-100%)
X = Cl, Br, OTs

**(C)** A general and convenient preparation of unsymmetrical N,N’-carbodiimides was achieved by the nickel(II)-catalyzed reaction of isocyanides with primary amines using molecular oxygen as an oxidant.¹⁷

\[
\text{R₁-NH₂} + \text{CNR₂} \rightarrow \text{10 mol% NiCl₂, O₂ or air, benzene, reflux 1-3 h} \rightarrow \text{R’N=C=NR’}
\]
molecular sieves 4 Å or Na₂SO₄
8 examples (48-88%)
(D) Aryl halides are readily homocoupled using a catalytic amount of NiCl₂/CrCl₂ and bipyridyl-type ligand 1 in the presence of manganese at room temperature in good yield.\(^{16a}\)

\[
\begin{align*}
\text{Ar-X} + \text{R-N₂} &\xrightarrow{\text{NiCl₂/CrCl₂, bipyridyl, Mn, THF, rt., 19-24 h}} \text{Ar-Ar} \\
\end{align*}
\]

\(^9\) examples (25-98%)  

(E) Azides are efficiently reduced to the corresponding amines with Sm/NiCl₂·6H₂O in excellent yields under mild conditions.\(^{18}\)

\[
\begin{align*}
\text{R-N₂} &\xrightarrow{\text{Sm/NiCl₂·6H₂O, THF, 40°C, 24 h}} \text{R-NH₂} \\
\end{align*}
\]

14 examples (70-90%)  

(F) Nitriles are rapidly reduced to primary amines with nickel boride at room temperature.\(^{6}\)

\[
\begin{align*}
\text{ArCN} &\xrightarrow{\text{NiCl₂, NaBH₄, Dry EtOH, rt., 5 min}} \text{ArCH₂NH₂} \quad \text{major} \\
&\quad \text{(ArCH₂)NH₂} \quad \text{minor} \\
\end{align*}
\]

19 examples (55-95%)  

(F) A Biginelli reaction was efficiently used for the synthesis of 3,4-dihydropyrimidinones from aldehydes, β-keto esters and urea in ethanol, using NiCl₂·6H₂O.\(^{13}\)

(G) An intramolecular Nozaki–Kishi cyclization was efficiently employed in the cyclization of Z-vinyl bromides to the corresponding cyclopentenols in good yields.\(^2\)

\[
\begin{align*}
\text{Br} &\xrightarrow{\text{NiCl₂, CrCl₃, DMF, rt.}} \text{R} \\
\text{R} &\xrightarrow{\text{NaBH₄/ NiCl₂·6H₂O, moist alumina, hexane}} \text{R} \\
\end{align*}
\]

7 examples (60-83%)  

(H) In the presence of moist alumina, aliphatic and aromatic alkenes were hydrogenated quantitatively to alkenes under mild conditions with NaBH₄/NiCl₂.\(^6\)

\[
\begin{align*}
\text{R²} &\xrightarrow{\text{NaBH₄/ NiCl₂·6H₂O, moist alumina}} \text{R²} \\
\end{align*}
\]

9 examples (91-100%)  

References