

Utility of Neodymium Diiodide as a Reductant in Ketone Coupling Reactions

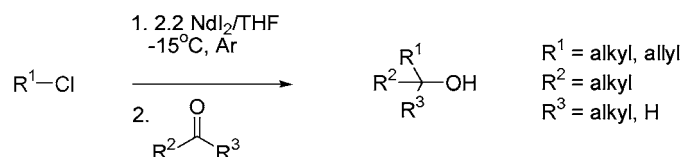
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ABSTRACT



The viability of NdI₂ as a one-electron reducing agent in organic synthesis has been examined by studying coupling reactions between alkyl chlorides and ketones and aldehydes.

For many years, samarium diiodide has been a standard one-electron reductant in organic synthesis.^{1–4} It is broadly useful, and its reduction potential can be enhanced by addition of hexamethylphosphoramide (HMPA).⁵ Recently, there have been rapid advances in the availability of more powerful divalent lanthanide reducing agents useful for organic synthesis. The 1997 discovery of the first molecular complex of Tm(II)⁶ prompted the development of TmI₂ as an alternative for the commonly used SmI₂(THF)_x/HMPA combination.⁵ This Tm(II) reagent can effect more difficult reductions than Sm(II)/HMPA and avoids the carcinogenicity of HMPA. For example, it allows ketone–alkyl halide couplings to be accomplished with chlorides even at low temperatures.⁷

The isolation of the first molecular complex of Dy(II)⁸ provided an even more powerful reductant⁹ that can also

accomplish useful organic transformations.⁸ Hence, even though it initially appeared that Tm(II) and Dy(II) were too strongly reducing to exhibit useful synthetic reductive chemistry in solution, these systems have proven to be viable.^{7,8}

The existence of Nd(II), an even more reducing divalent lanthanide, as a soluble molecular species was recently established by Bochkarev et al.¹⁰ It was uncertain if Nd(II), which has a Ln(III)/Ln(II) reduction potential vs NHE of –2.6 V compared to Sm (–1.55 V), Tm (–2.3 V), and Dy (–2.5 V),⁹ would be viable as a synthetic reagent. We report here that NdI₂ can be used as a lanthanide reducing agent in organic synthesis. In addition to being more reducing, NdI₂ may offer some special advantages over the other divalent lanthanide halide reagents. It is cheaper and has a larger radial size, which can be important in optimizing lanthanide reaction chemistry.

NdI₂ can be generated in 40 g (100 mmol) quantities by direct reaction of metal and iodine at 600 °C.¹¹ This solid can be stored for months at room temperature in the absence of solvent. Solutions are stable under an argon atmosphere¹²

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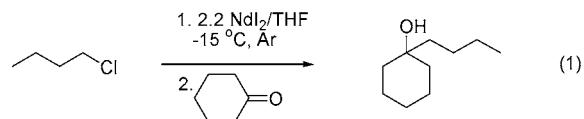
Table 1. Reductive Coupling of Cyclohexanone with Alkyl Chlorides Using NdI₂ in THF

alkyl chloride	% yield (GC, based on unreacted ketone)
<i>n</i> -butyl chloride	97
<i>sec</i> -butyl chloride	99
<i>tert</i> -butyl chloride	0
phenethyl chloride	81

for several hours at $-15\text{ }^{\circ}\text{C}$ but decompose over a period of minutes at room temperature. Hence, NdI₂ must be used quickly once it is put in solution and reactions must be performed at subambient temperatures.

Although NdI₂ is more reactive than the other LnI₂ reagents, its high reactivity actually leads to a simpler experimental protocol. Since the reagent is best stored as a solid and solutions are used immediately, the problem of solutions changing concentration over time is avoided. A standardized solution, typically 0.05 M at $-15\text{ }^{\circ}\text{C}$, can be produced and transferred via a syringe to a flask containing the substrate to be reduced.¹³ The reactions are run at low temperatures and are often complete upon mixing.

The first set of transformations examined with NdI₂(THF)_x were ketone coupling reactions with alkyl halides, since the results could be directly compared with those for SmI₂,^{14,15} TmI₂,⁷ and DyI₂.⁸ Addition of 1-chlorobutane to a solution of NdI₂(THF)_x at $-15\text{ }^{\circ}\text{C}$ immediately dissipated the purple color to form a light green intermediate. After reaction with cyclohexanone, a 97% (GC) yield of the coupled product, 1-butylcyclohexanol, was obtained following aqueous work-up (eq 1). Other chlorides may also be reduced in a similar



manner, as shown in Table 1. It was found that reaction of

(12) We have found that the presence of dinitrogen substantially reduces the stability of solutions, even at $-30\text{ }^{\circ}\text{C}$.

(13) **General Method for Using NdI₂(THF)_x.** A septum-capped flask was charged with black NdI₂ (1.0 g, 2.5 mmol) and a stir bar under argon. The flask was placed in a $-15\text{ }^{\circ}\text{C}$ 2-propanol/ice bath. Precooled THF (45 mL, $-15\text{ }^{\circ}\text{C}$) was added via cannula, immediately producing a purple solution. The solution was stirred for 45 min. An aliquot of the saturated solution was removed and its concentration determined to be 0.05 M by complexometric titration.⁷ An aliquot (24.0 mL, 1.2 mmol) was added via syringe to a septum-covered flask under argon at $-15\text{ }^{\circ}\text{C}$. Subsequently, the organic halide (0.55 mmol) was added via syringe. Once a green solution was formed, the ketone (0.50 mmol) was added via syringe, resulting in a light blue solution. The reaction was then quenched with a saturated solution of NH₄Cl and extracted with ether or pentanes. The organic extract was washed with H₂O ($2 \times 10\text{ mL}$) and dried over MgSO₄. The solvent was removed in vacuo to yield the coupled product.

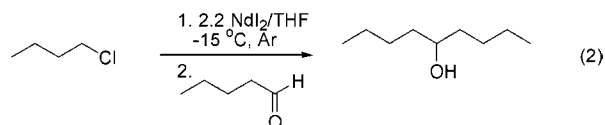
Table 2. Reductive Coupling of 2-Hexanone with Alkyl Chlorides Using NdI₂ in THF

alkyl chloride	% yield (GC, based on unreacted ketone)
<i>n</i> -butyl chloride	100
<i>sec</i> -butyl chloride	77
<i>tert</i> -butyl chloride	0
phenethyl chloride	81
allyl chloride	82

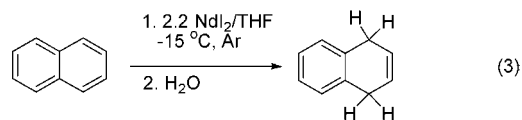
primary and secondary chlorides proceeds in good yield. No reaction occurs, however, when a tertiary chloride is used.

Similar results were obtained using the noncyclic ketone, 2-hexanone, as shown in Table 2.

NdI₂ coupling of an alkyl halide with an aldehyde substrate was also examined. The coupling of 1-chlorobutane with valeraldehyde gave the coupled alcohol, 5-nonanol in 93% yield (eq 2).



NdI₂ in THF has also been found to reduce naphthalene. Reaction of 2.2 equiv of NdI₂ with naphthalene forms an intense blue solution, which after hydrolysis yields dihydronaphthalene (eq 3), i.e., it has Birch reduction-type reactivity.



In conclusion, these preliminary results show that NdI₂ is not too reactive to be useful as a reductant in organic synthesis. Hence, NdI₂ can join TmI₂ and DyI₂ in bridging the gap in available reductants with reduction potentials between those of SmI₂/HMPA and alkali metal/liquid ammonia Birch reductants. It is anticipated that NdI₂ will develop into a broadly useful reagent, just as SmI₂ has developed over the past 20 years.¹⁻⁴

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