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Notes

Accessing Lanthanide Diiodide Reactivity for Coupling Alkyl Chlorides to Carbonyl Compounds via the NdI_3/Alkali Metal Reduction System

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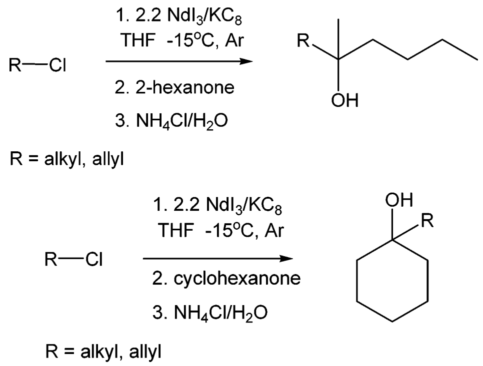
Summary: The combination of NdI_3 and a reducing agent such as KC_8, K, Na, or Ca can mimic the reductive chemistry of NdI_2 in coupling of alkyl and allyl chlorides with carbonyl compounds.

Since Kagan introduced SmI_2 as a one-electron reductant for organic transformations,[1] this compound has become a common reagent in organic synthesis.[2−8] In recent years, the discovery of structurally characterizable molecular diiodide complexes of divalent thulium,[9] dysprosium,[10] and neodymium[11] provided LnI_2 species that were substantially more powerful reductants than SmI_2. TmI_2,[12,13] DyI_2,[10] and NdI_2[14] have all been shown to be viable one-electron reductants like SmI_2 in organic reactions. These divalent lanthanide diiodides have the advantage over SmI_2/HMPA in that HMPA is not needed. The more reducing nature of Tm(II), Dy(II), and Nd(II) [calculated Ln(III)/Ln(II) reduction potentials vs NHE: Sm, −1.5 V; Tm, −2.3 V; Dy, −2.5 V; Nd, −2.6 V][15] allows these diiodides to fill the gap in available one-electron reductants that exists between SmI_2/HMPA and the alkali metals (Na, −2.7 V; K, −2.9 V vs NHE).

Of these new diiodides, NdI_2 is particularly attractive since it is the most reducing and the cheapest. Associated with this high reactivity, however, is the fact that NdI_2 has not been synthesized in solution. Instead, high-temperature solid state methods are required.[16−18] Once NdI_2 is dissolved in THF, the reagent must be kept at low temperature and used immediately to avoid decomposition.

Scheme 1



Recent advances in lanthanide dinitrogen reduction chemistry using the LnZ_3/alkali metal system (Z = monoanion) as a synthetic equivalent of “LnZ_2”[19] prompted us to evaluate the possibility of accomplishing the one-electron reductions possible with NdI_2 using a NdI_3/alkali metal combination. If successful, this method would provide a much easier way to use divalent neodymium as a replacement for SmI_2/HMPA in organic synthesis. It would avoid the high-temperature solid state synthesis of NdI_2 and allow reduction with easily prepared and commercially available NdI_3. Calibration of the amount of active Nd in solution is also simplified since it would be based on NdI_3 rather than the reactive NdI_2/THF solution.

NdI_3 reacts with KC_8 in cold (−15 °C) THF under argon to produce a solution with the same deep purple color as a NdI_2/THF solution.[14] This combination proved to be effective in alkyl chloride/ketone coupling reactions (Scheme 1). The NdI_3/KC_8 reactivity is compared with

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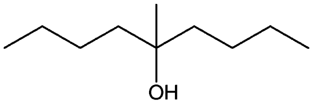
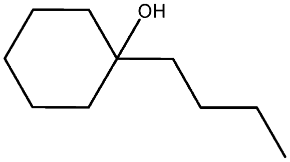
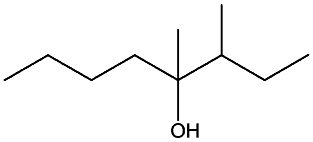
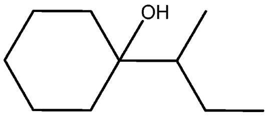
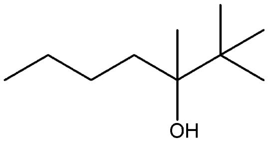
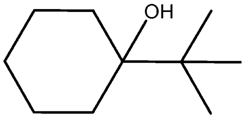
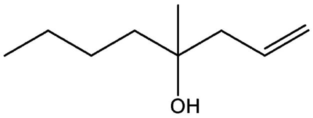
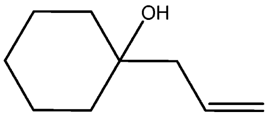
Table 1. Alkyl Chloride Coupling Reactions with 2-Hexanone and Cyclohexanone; NdI_2 vs NdI_3/KC_8

Alkyl Chloride	Ketone	Product	Yield[a] w/ NdI_3/KC_8	Yield[a] w/ NdI_2[14]
n-butyl chloride	2-hexanone		100%	100%
n-butyl chloride	cyclohexanone		100%	97%
s-butyl chloride	2-hexanone		95%	77%
s-butyl chloride	cyclohexanone		91%	99%
t-butyl chloride	2-hexanone		6%	0%
t-butyl chloride	cyclohexanone		0%	0%
allyl chloride	2-hexanone		96%	82%
allyl chloride	cyclohexanone		71%	26%

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[a] GC yield. Based on unreacted ketone.

Scheme 2

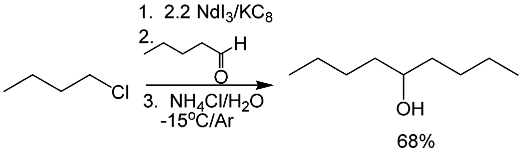

Table 2. Coupling of Alkyl Chlorides and Carbonyl Compounds Using NdI_3 and Various Metal Reductants

	reductant			
substrate	NdI_3/K	NdI_3/Na	NdI_3/Ca	NdI_3/KC_8
n-butyl chloride 2-hexanone	84%	84%	52%	100%
s-butyl chloride 2-hexanone	17%	51%	84%	95%
tert-butyl chloride 2-hexanone	0%	0%	9%	6%
allyl chloride 2-hexanone	74%	64%	55%	96%
n-butyl chloride valeraldehyde	0%	0%	0%	68%

that reported for NdI_2/THF in Table 1. The NdI_3/KC_8 system not only mimicked the NdI_2 coupling chemistry observed with these ketones, but it also typically gave superior yields. NdI_3/KC_8 was also effective in coupling an aldehyde (Scheme 2). However, in this case, the *n*-butyl chloride/valeraldehyde coupled product was obtained in only 68% yield compared to 93% with NdI_2/THF.[14]

To determine if other reductants could be used in place of KC_8 in this NdI_3/reductant method, the coupling of alkyl chlorides with 2-hexanone was examined with NdI_3/K, NdI_3/Na, and NdI_3/Ca. As shown in Table 2, all of these systems led to coupled products according to Scheme 1, although the yields were generally lower than those achieved with KC_8. Interestingly, calcium (chosen because it is one of the cheapest reductants) gives substantially lower yields for reactions with primary alkyl or allyl halides, but provides slightly higher yields when the alkyl halide is tertiary. Another difference in reductant reactivity is that the reaction between *s*-butyl chloride and 2-hexanone using potassium results in lower yields than the analogous reaction with the less reducing sodium. Surprisingly, unlike the reactions using NdI_3 with KC_8, none of these other reductants were successful in performing the coupling reaction with valeraldehyde.

In all cases, except for the coupling reaction with *tert*-butyl chloride and 2-hexanone, yields using NdI_3/KC_8 are significantly higher than those obtained with NdI_3 and the other reductants examined. Blank reactions of *n*-butyl chloride with 2-hexanone under identical conditions using KC_8, Na, K, or Ca in THF at −15 °C in the absence of NdI_3 did not result in any coupling products.

In summary, the NdI_2 reductive coupling of alkyl chlorides with ketones and aldehydes can be mimicked by the NdI_3/(alkali or alkaline earth metal) system. The variation in yields as a function of the reductant observed in this study indicates that there are subtleties to this approach to "LnI_2" reduction chemistry that are not yet obvious. This would not be expected if these reactions simply involved formation of NdI_2 in solution. These variations suggest that this system may be tuned by use of the specific reductant, and future studies will be oriented to optimizing the reductant/substrate combination.

Experimental Section

Synthesis of NdI_3. Neodymium triiodide can be purchased from Strem or Alfa Aesar as an anhydrous powder, or it can be synthesized by direct reaction of neodymium with 1.5 equiv of I_2 according to the Bochkarev method.[17] In this study, this was done in a quartz reactor previously described in the literature[18] by the following method. A small quantity of neodymium metal was added to a quartz crucible. The reactor was heated to 600 °C, and iodine was added. Small amounts of metal and iodine were added alternately. Each addition of iodine resulted in an orange glow in the reaction mixture. After addition was complete, the apparatus was cooled, and the quartz crucible containing the NdI_3 was transferred to an Ar-filled glovebox. The NdI_3 was ground with a mortar and pestle into a green powder. The metal content was analyzed by complexometric titration.[20] Calculated: 27.5% Nd. Found: 29.5% Nd.

Synthesis of Potassium Graphite. Potassium graphite (KC_8) can be prepared on a Schlenk line by the method of Rabinovitz[21] or by the following procedure if a glovebox is available. In a glovebox, K metal (0.541 g, 0.0138 mol) was added to a scintillation vial. Graphite (1.242 g, 0.0129 mol) was added to the vial containing a Teflon stirbar, and the mixture was heated and stirred until a bronze-colored powder resulted.

General Method for Using NdI_3/KC_8. A septum-capped 25 mL Schlenk flask containing a Teflon stirbar was charged with NdI_3 and KC_8 under argon. Precooled (−15 °C) THF was added to the mixture via cannula to produce a purple solution, which was stirred at −15 °C for 40 min. Alkyl halide was added via syringe and stirred for approximately 1 min. A gray-colored mixture resulted. The ketone or aldehyde was added, and the reaction mixture was allowed to stir for 1 h. The reaction was quenched using a saturated NH_4Cl solution and extracted with hexanes.

The reactions using potassium, sodium, and calcium were conducted in a similar manner. In these cases, the colors of the solutions after the halide addition were light green. Subsequent ketone addition gave a light blue solution.

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