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Nickel(0)/Imidazolium Chloride Catalyzed Reduction of Aryl Halides

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Dehalogenation of aryl halides was efficiently performed in refluxing THF using a catalytic combination composed of Ni(0)/*N*-heterocyclic carbene (NHC)/*β*-hydrogen-containing alkoxide. IMes·HCl (1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride) and $Ni(acac)_2$ used respectively as carbene and Ni(0) precursors associated to in situ generated *i*-PrONa were found to be the most effective for the dehalogenation of functionalized aryl chlorides, bromides, iodides, and polyhalogenated hydrocarbons.

Introduction

The transformation of aryl halides and especially chlorinated arenes into arenes represents an important chemical transformation in organic synthesis as well as in industrial applications.[1] Due to chloroarenes' deleterious environmental and health impact, researchers were driven to develop practical and effective processes for the reduction of highly toxic chloroarenes into arenes.[2]

A large number of dehalogenating systems using either stoichiometric or catalytic reagents have been developed for this purpose over the years. A clean aryl carbon−halogen to carbon−hydrogen conversion could readily be achieved by transition metal catalyzed hydrogenation (e.g., using palladium[3] or Pd/Fe-carbon composite[4] and nickel[5] catalysts) or by metal-catalyzed reductions mediated by hydrides,[6] Grignard reagents,[7] or alcohols.[8] The $NiCl_2 \cdot H_2O$/Li/4,4′-di-*tert*-butylbiphenyl,[9] Raney Ni−Al alloy in alkaline solution,[10] or SmI_2/THF/HMPT[11] combinations have also been used for the same purpose. Among all these methods, liquid-phase catalytic dehalogenation is of increasing interest because of its simplicity, its effectiveness at low temperature, and the exclusion of more toxic compounds such as dioxins.[2b,d]

Recently, we explored the reactivity of bimetallic Ni−Al catalysts associated to sodium hydride for the dechlorination of alkyl and aryl (poly)chlorides.[12,13] These studies revealed that the rates of reduction of these compounds were by far faster than those realized by our earlier described monometallic nickel catalyst.[14] Moreover, the reactions proceeded with production of the corresponding hydrocarbons in essentially quantitative yields, free from significant side-products. The efficiency of these reagents was presumed to be due to the high dispersion of subnanometrical nickel particles

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formed both during the preparation of the catalyst and in the course of the reduction step.

However, the use of sodium hydride as co-reagent leads to low selectivity since this reagent, associated to Ni(0), is capable of reducing other functional groups such as ketones or nitriles. It was therefore desirable to develop a new reduction process that is more broadly applicable for aromatic dehalogenation than our previous methods and that does not require the use of sodium hydride.

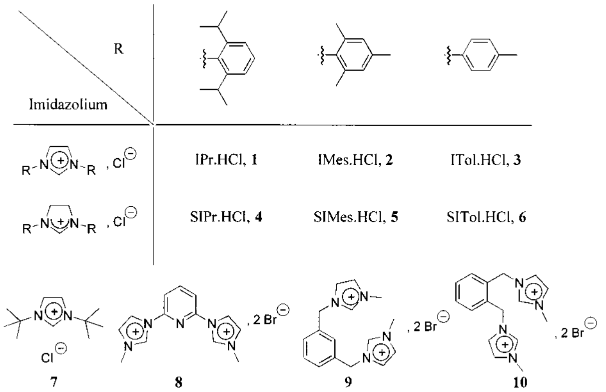
In the course of our work on carbon–nitrogen couplings between aryl chlorides and amines mediated by nickel/*N*-heterocyclic carbene (NHC) catalysts,[15] significant amounts of chloroarene dehalogenation byproducts were observed when arylaminations were conducted in the presence of alkoxides possessing one β-hydrogen and using NaH as co-reagent. Removal of the amine and sodium hydride from the reaction medium and using stoichiometric amounts of in situ generated alkoxide afforded a high yield of the dehalogenated arene. On the basis of these initial results, we were interested in examining the behavior of Ni(0)/NHC catalysts in the dehalogenation of aryl halides.

Concurrent with this work, Nolan has very recently demonstrated that Pd(0) associated to 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene and MeOK was effective for the dehalogenation of aryl chlorides and bromides in refluxing dioxane.[8f] Surprisingly, Ni(II) salts (Ni(OAc)$_2$ and NiCl$_2$) tested in this study as alternatives to palladium did not show any catalytic activity. In view of these results, a study aimed at determining the optimum Ni(0)/NHC system for the catalytic dehalogenation of aryl halides was undertaken.

Results and Discussion

In recent years, it has become clear that NHCs can offer an interesting alternative class of ligands to the ubiquitous phosphines for catalytic applications.[16] Various reactions involving imidazolium salts as precursors to NHCs have recently been reported. These include copolymerization of ethylene and CO,[17] hydrogenation,[18] alkene metathesis,[19] and hydrosilylation.[20] Palladium-catalyzed protocols using NHCs have also been shown to offer a significant advantage for a range of synthetically valuable coupling processes such as carbon–carbon[21] or carbon–nitrogen[22] bond forming reactions. These reports have all demonstrated that such thermally stable and strong electron-donating ligands can be incorporated into these catalysts and that an excess of ligand is not required to prevent aggregation of the metal.

Chart 1. Imidazolium Salts



Alternatively, nickel-catalyzed couplings involving NHCs as ligands have received less attention. Recently, we[15] and others[23] have found that the combination of Ni(0) with electron-rich and sterically demanding SIPr·HCl **4** (SIPr = 1,3-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene) or IMes·HCl **2** (IMes = 1,3-bis(2,4,6-trimethylphenylphenyl)imidazol-2-ylidene) mediates the coupling of aryl halides with amines or organomagnesium reagents.

The results obtained by Nolan[8f] prompted us to examine the effect of the substitution pattern of the carbene ligand as well as the influence of the Ni(0) source during the catalytic dehalogenation process.

Influence of the Carbene Ligand. A survey of catalytic efficiency of various imidazolium salts (Chart 1) was first undertaken on a model reaction involving chlorobenzene and *i*-PrONa, and the results are presented in Table 1.

We have first determined that a 2/1 ratio of monodentate carbene to Ni gave the best combination. Lowering (1/1) or increasing (3/1 or 4/1) this ratio resulted in a decrease of the reaction rate, and poorer yields of the dehalogenated product were obtained. Alternatively, with bis-carbene ligands **9** and **10** or tridentate ligand **8**, experiments were conducted using a Ni/ligand ratio of 1/1.

As expected, dehalogenations run without ligand resulted in no detectable reaction product (entry 1). Contrary to reductions performed under palladium catalysis,[8f] the imidazolium chloride IMes·HCl **2** was

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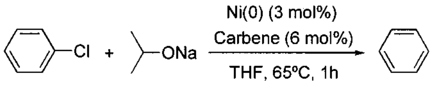
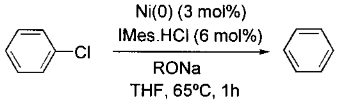
Table 1. Dehalogenation of Chlorobenzene Using Various Carbene Precursors[a,b]

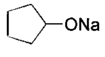
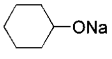
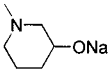
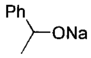


entry	ligand	yield (%)
1		0
2	IPr·HCl, **1**	59
3	IMes·HCl, **2**	96
4	ITolHCl, **3**	32
5	SIPr·HCl, **4**	58
6	SIMes·HCl, **5**	55
7	SITol·HCl, **6**	28
8	**7**	28
9	**8**	51
10	**9**	0
11	**10**	0

[a] Reaction conditions: 10 mmol of chlorobenzene, 0.3 mmol of Ni(0), 0.6 mmol of imidazolium chloride, 30 mmol of *i*-PrONa, 12 mL of THF, 65 °C. [b] Yields were determined by GC and are the average of two runs.

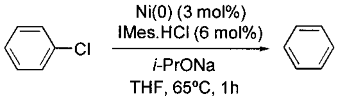
Table 2. Dehalogenation of Chlorobenzene Using Various Alkoxides[a,b]



Entry	Alkoxide	Yield (%)
1	CH_3ONa	0
2	$CH_3OCH_2CH_2ONa$	12
3	$PhOCH_2CH_2ONa$	0
4		79
5		80
6		16
7		33
8	***i*-PrONa**	**96**
9	*t*-BuONa	0
10	C_6H_5ONa	22

[a] Reaction conditions: 10 mmol of chlorobenzene, 0.3 mmol of Ni(0), 0.6 mmol of IMes.HCl, 30 mmol of RONa, 12 mL of THF, 65 °C. [b] Yields were determined by GC and are the average of two runs.

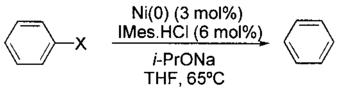
Table 3. Dehalogenation of Chlorobenzene Using Various Nickel(II) Salts[a,b]

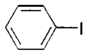
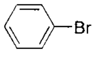
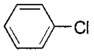
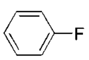


entry	Ni(0) source	yield (%)
1	$Ni(acac)_2$	96
2	$Ni(OAc)_2$	56
3	$NiCl_2$	13
4	$Ni(NO_3)_2$	11
5	$NiSO_4$	11
6	$Ni(C_2O_4)$	12

[a] Reactions conditions: 10 mmol of chlorobenzene, 0.3 mmol of Ni(II), 0.6 mmol of IMes·HCl, 30 mmol of *i*-PrONa, 0.6 mmol of NaH, 12 mL of THF, 65 °C. [b] Yields were determined by GC.

Table 4. Dehalogenation of Aryl Halides[a,b]



entry	aryl halide	reaction time (h)	yield (%)
1		0.25 0.5	95 100
2		0.5 1	93 100
3		0.5 1	88 96
4		1 2	45 45

[a] Reactions conditions: 10 mmol of halogenoarene, 0.3 mmol of Ni(0), 0.6 mmol of IMes.HCl, 30 mmol of *i*-PrONa, 12 mL THF, 65 °C. [b] Yields were determined by GC.

found to be the most effective NHC precursor, leading to the dehalogenated product in 96% yield (entry 3). As summarized in Table 1, the 1,3-diaryl imidazolium chlorides IPr·HCl **1**, ITol·HCl **3**, SIPr·HCl **4**, SIMes·HCl **5**, SITol·HCl **6**, and the 1,3-bis(di-*tert*-butyl)imidazolium chloride **7** allowed lower conversions of the starting material and were found to be less efficient than **2** (entries 2, 4, 5, 6, 7, and 8). Tridentate CNC bis-carbene precursor **8** and bis-imidazolium bromides **9** and **10** led respectively to the formation of a moderately active catalyst (entry 9) or to reagents showing no catalytic activity (entries 10 and 11).

Dihydroimidazolium carbenes are described to be more σ-donating than unsaturated imidazolium-based carbenes and should therefore increase the activity of the catalysts.[24] This increased electron-donating ability of saturated NHC **4**, **5**, and **6** compared to their unsaturated analogues **1**, **2**, and **3** affects active nickel species during the dehalogenation catalytic cycle and seems to render either oxidative addition, β-hydride transfer, or reductive elimination difficult.

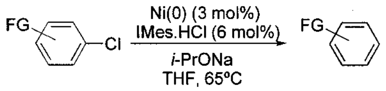
Poor yields observed with bis-carbenes **9** and **10** or tridentate ligand **8** are presumed to be due to a similar increased stability of the metal center which is protected and therefore catalytically inactive.

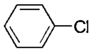
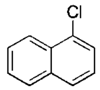
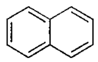
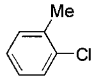
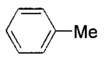
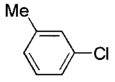
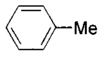
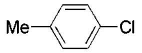
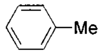
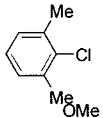
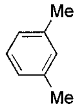
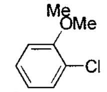
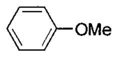
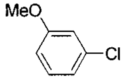
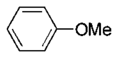
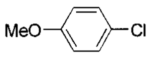
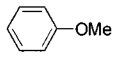
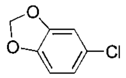
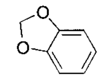
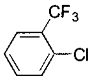
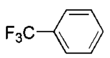
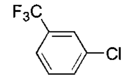
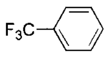
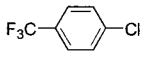
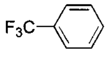
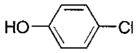
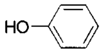
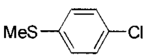
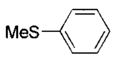
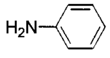
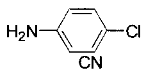
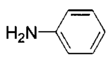
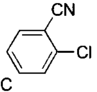
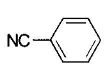
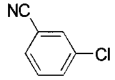
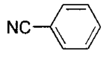
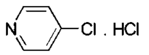
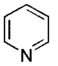
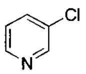
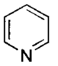
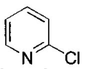
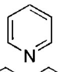
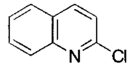
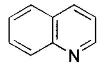
The counterion associated to 1,3-bis(2,4,6-trimethylphenyl)imidazolium was also found to have a profound effect on the outcome of the reaction. The use of the noncoordinating tetrafluoroborate salt of the protonated carbene resulted in a decrease of the dehalogenation yield (56% after 1 h reaction time) compared to **2**, which has a chloride counterion.

Influence of the Alkoxide's Nature and Structure. Several alkoxides were examined under the catalytic reaction conditions for reduction of chlorobenzene (Table 2).

The role of the in situ generated alkoxide is threefold: (1) it initially activates sodium hydride used to reduce $Ni(acac)_2$ into Ni(0) and ensures the repeatability of this reaction, (2) it deprotonates the imidazolium chloride **2** to form the carbene ligand which coordinates to the metal, and (3) it acts as a hydrogen donor since it possesses a β-hydrogen.

Table 5. Dehalogenation of Aryl Chlorides[a,b]



entry	aryl halide	product	reaction time (h)	yield (%)
1			1	96
2			1 1.5	93 100
3			1 2	82 91
4			1 2	96 99
5			1 1.5	97 100
6			1 2	60 70
7			1 1.5	81 89
8			1	100
9			1 1.5	87 95
10			1 2	76 86
11			1	96
12			0.25 0.5	96 100
13			1 2	84 97
14			1 2	80[c] 91[c]
15			1 2	74 74
16			1 2	96[c] 96[c]
17			1 2	84[c] 90[c]
18			1 2	86 90
19			1 2	87 90
20			0.5	97[c]
21			0.5	99
22			0.5	43
23			0.5	51

[a] Reaction conditions: 10 mmol of aryl chloride, 0.3 mmol of Ni(0), 0.6 mmol of IMes·HCl, 30 mmol of *i*-PrONa, 12 mL of THF, 65 °C. [b] Yields were determined by GC and are the average of two runs. [c] Same as in a run with 40 mmol *i*-PrONa.

The use of nonactivated sodium hydride as reductant and hydride source was not effective in these reactions and resulted in slow catalyst formation associated with poor yields of reduction products.

Among alkoxides examined, *i*-PrONa was found to be the most satisfactory (entry 8). The reaction was complete in 1 h in refluxing THF to give benzene in 96% yield.

The use of other alkoxides derived from secondary alcohols such as cyclopentanol (entry 4), cyclohexanol (entry 5), and 1-phenylethanol (entry 7) was found to be less efficient, while 1-methyl-3-piperidinol (entry 6), recently used by our group in desulfurization reactions mediated by Ni(0) catalysts,[25] afforded only 16% of the dehalogenated product.

A tertiary alkoxide like *t*-BuONa was ineffective in this reaction. This indicates that the reduction requires a β-hydrogen on the alkoxide in order to transfer the hydrogen to the aromatic ring. Contrary to palladium-catalyzed dehalogenations,[8a,f] primary sodium alkoxides such as sodium methoxide (entry 1), sodium 2-methoxyethoxide (entry 2), and sodium 2-phenoxyethoxide (entry 3) were found to be inefficient in these reactions. The lack of reactivity observed may be associated with the poor solubility of these alkoxides in THF and with their weak basicity, which does not allow the deprotonation of the imidazolium chloride into the desired carbene ligand even after prolonged reaction times.

Finally, it is noteworthy that sodium alkoxides were by far the most efficient bases in the present study. The use of lithium or potassium isopropoxide resulted in a decrease of chlorobenzene reduction yields (respectively 36 and 70% after 1 h).

Influence of the Ni(0) Precursor. A number of Ni(0) precursors were also tested in optimization experiments (Table 3).

Ni(acac)$_2$ was found to be the best Ni(0) precursor (entry 1). Ni(OAc)$_2$ can also be used (56% yield after 1 h reaction time, entry 2), while dehalogenations of chlorobenzene performed with NiCl$_2$, Ni(NO$_3$)$_2$, NiSO$_4$

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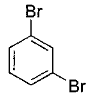
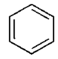
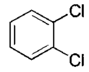
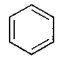
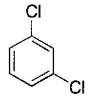
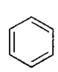
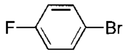
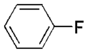
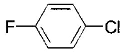
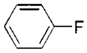
(24) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−955.

(25) Kuehm-Caubere, C.; Guilmart, A.; Adach-Becker, S.; Fort, Y.; Caubere, P. *Tetrahedron Lett.* **1998**, *39*, 8987−8990.

Table 6. Reduction of Polyhalogenated Arenes[a,b]

entry	aryl halide	product	reaction time (h)	yield (%)
1			0.5	100
2			3.0	91
3			2.5	95
4			0.25	72
5			0.25	73

[a] Reaction conditions: 10 mmol of aryl halide, 0.6 mmol of Ni(0), 1.2 mmol of IMes·HCl, 60 mmol of *i*-PrONa, 12 mL of THF, 65 °C. [b] Yields were determined by GC and are the average of two runs.

or $Ni(C_2O_4)$ resulted in poor yields (entries 3−6). The differences in activity displayed by these Ni(0) precursors are directly related to the effectiveness of *i*-PrONa-activated sodium hydride, used to generate Ni(0) and initiate the catalytic cycle, in the reduction of the Ni(II) salt into Ni(0).[26]

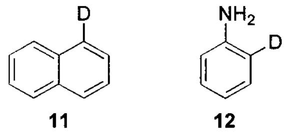
Reduction of Aryl Halides. Although our primary interest was in the reduction of aryl chlorides, Table 4 demonstrates that the scope of the reaction extends beyond aryl iodides and bromides (entries 1 and 2).

Iodo- and bromobenzene reacted quickly (respectively in 0.5 and 1 h) and were quantitatively transformed into benzene. The reactivity of halogens was found to follow the general order of I > Br > Cl, as observed in numerous reduction reactions.[2]

While it may not be surprising that the reduction of these compounds takes place under our reaction conditions, it was unexpected that the Ni(0)/IMes·HCl/*i*-PrONa catalyst was efficient with fluorinated materials. Indeed, the carbon−fluorine bond, which is the strongest bond that carbon can form, is reluctant to coordinate to metal centers and is extremely resistant to reduction.[27] Using 3 mol % Ni(0), 6 mol % IMes·HCl, and 3 equiv of *i*-PrONa relative to fluorobenzene, benzene was obtained in 45% yield after 1 h reaction time and 45% of the starting compound remained. Increasing catalyst loading to 6 mol % or using 6 equiv of *i*-PrONa did not significantly improve this situation. Future work will include efforts to circumvent this limitation and will be reported in due course.

Reduction of Aryl Chlorides. Using the optimal conditions previously determined, it was of interest to investigate the scope and limitations of the dehalogenation protocol. Table 5 illustrates a broad sampling of aryl chlorides that were reduced using the Ni(0)/IMes·HCl/*i*-PrONa catalyst.

Chart 2



11 12

Both electron-poor and electron-rich aryl chlorides were cleanly dehalogenated in good to excellent yields. These Ni(0)/NHC-catalyzed reductions were only slightly sensitive to the steric hindrance of the starting material. Activated (entries 11 and 18) or deactivated (entries 3, 7, and 16) *ortho*-substituted compounds were efficiently reduced, and even 2-chloromesitylene (entry 6) could be transformed into mesitylene in 70% yield after 2 h.

Using 4 equiv of *i*-PrONa relative to the aryl chloride allowed the reduction of substrates bearing an acidic hydrogen such as 4-chlorophenol (entry 14) and 2- or 4-chloroaniline (entries 15 and 16). Noteworthy is the clean reduction of 2- and 4-chlorobenzonitrile (entries 18 and 19), further attesting to the functional group compatibility offered by our reagent. Both compounds were reduced in 90% yield after 2 h, and contrary to other Ni(0) catalysts,[28] no cleavage of the carbon−carbon bond in benzonitrile was observed.

Heteroaromatics such as 4- or 3-chloropyridine behaved similarly (entries 20 and 21). However, strongly activated 2-chloropyridine (entry 22) and 2-chloroquinoline (entry 23) afforded only modest dehalogenation yields due to the formation of 2-isopropoxypyridine and 2-isopropoxyquinoline, in respectively 49 and 46% yield, by a classical S_NAr reaction.

The use of the Ni(0)/IMes·HCl/*i*-PrONa catalyst is also limited to non-ketone educts. For example, 4-chlorobenzophenone leads to 25% diphenylcarbinol and 31% 4-isopropoxybenzophenone as byproducts. Decreasing the reaction temperature or lowering the amount of *i*-PrONa did not significantly improve this situation.

Application of the Ni(0)/IMes·HCl/*i*-PrONa combination to reduction of polyhalogenated aromatics is also possible (Table 6).

Using 3 mol % of the catalyst per carbon-halide functionality, 1,3-dibromobenzene was quantitatively converted into benzene in 0.5 h (entry a). Double dechlorination of 1,2- and 1,3-dichlorobenzene afforded benzene in respectively 91 and 95% (entries 2 and 3). The rate of these reductions was however slower than those noted with monochloroarenes. Chemioselective reductions of 4-bromo- and 4-chlorofluorobenzene into fluorobenzene could also be achieved (entries 4 and 5). However, partial defluorination (near 25%) was observed even after short reaction times.

Deuterium Incorporation and Mechanistic Considerations. Dehalogenations of 1-chloronaphthalene and 2-chloroaniline were carried out using deuterium-labeled sodium isopropoxide $(CD_3)_2CDONa$ as base. It was expected that deuterated naphthalene and aniline would be produced if hydrogen-transfer from isopropoxide to aryl halides took place during the reduction. Taking account of ^1H NMR and GC−MS analysis, the

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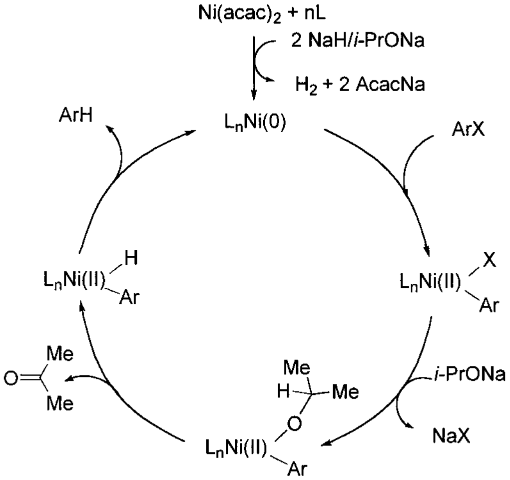
Scheme 1. Proposed Mechanism for the Reduction of Aryl Halides



actual content of D atoms in naphthalene and aniline could be estimated to be superior to 95% of the theorical content, and the clean formation of 1-deuterated naphthalene **11** and 2-deuterated aniline **12** was observed (Chart 2). These deuterium incorporation experiments confirmed that sodium isopropoxide is the main hydrogen donor in the reductions catalyzed by the Ni(0)/IMes·HCl/*i*-PrONa combination.

On the basis of these observations, a likely pathway for reductions mediated by the Ni(0)/IMes·HCl/*i*-PrONa catalyst is outlined in Scheme 1.

The first step involves formation of Ni(0) by reduction of $Ni(acac)_2$ with *i*-PrONa-activated sodium hydride followed by coordination of the carbene ligand to the metal center. Oxidative addition of the aryl halide to the Ni(0) complex is followed by isopropoxide anion attack at nickel and displacement of the halogen atom. Finally, reductive elimination of the arene from an intermediate nickel-hydride complex obtained by β-elimination regenerates the Ni(0) catalyst.

Conclusion

In summary, in this paper, we report a new nickel catalyst for the reduction of halogenated arenes. The Ni(0)/IMes·HCl/*i*-PrONa combination proved to be efficient for the dehalogenation of aryl chlorides, bromides, and iodides in short reaction times and under mild conditions. This catalyst can also induce carbon−fluorine bond reduction, but complete conversions could not be attained. Deuterium incorporation experiments confirmed that the hydrogen atom is introduced from sodium isopropoxide. Our procedure is characterized by the ease and quickness of the reaction, simplicity to manipulate (only nitrogen is needed in these reactions), mildness of the reaction conditions, and the low cost of the reagents. Further applications of this nickel/NHC-catalyzed chemistry directed to the transformation of fluoroarenes will be reported shortly.

Experimental Section

General Procedures. All manipulations were carried out using standard Schlenk techniques under an atmosphere of nitrogen. Gas chromatographic analyses were performed on a Shimadzu GC-17 capillary gas chromatograph fitted with an “Optima 5” column (22 m × 0.25 mm, i.d. × 0.25 μm). All quantifications of reaction constituents were achieved by gas chromatography using a known quantity of dodecane as reference standard. The ^1H and ^{13}C NMR spectra were recorded on a Brucker AM 400 spectrometer, respectively at 400.13 and 100.40 MHz using $CDCl_3$ as solvent.

Materials. Aryl halides, arenes, and nickel(II) acetylacetonate were purchased from Acros and used as received. Sodium hydride (65% in mineral oil) was purchased from Fluka and used after two washings with THF under nitrogen. Tetrahydrofuran was distilled over sodium/benzophenone and stored over sodium wires. Isopropanol was purchased from Acros and distilled over sodium before use. All imidazolium salts were synthesized according to the literature procedures.[21g,29]

General Protocol for Catalytic Reduction of Aryl Halides. A 50 mL Schlenk tube was loaded with degreased NaH (30.6 mmol), $Ni(acac)_2$ (0.3 mmol), IMes·HCl (0.6 mmol), and 6 mL of THF, and the mixture was heated at 65 °C. A solution of *i*-PrOH (30 mmol) in THF was then added dropwise, and the mixture was further heated for 1 h. A solution of aryl halide (10 mmol) in THF (3 mL) was then added, and the reaction was monitored by GC.

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