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An efficient route to biaryls from aryl halides catalysed by subnanometrical 2,2′-bipyridine liganded Ni–Al clusters

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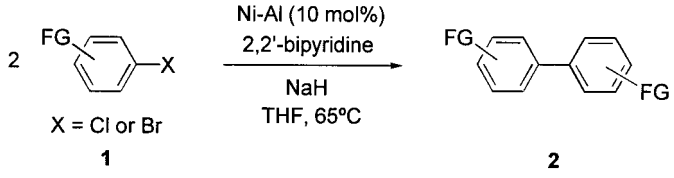
Abstract—It has been shown that the new 2,2′-bipyridine liganded Ni–Al bimetallic clusters are efficient in promoting the catalytic homocoupling of (het)aryl chlorides and bromides. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Biaryls are an important class of organic compounds useful for the synthesis of ligands, non-linear optical materials, polymers or pharmaceuticals.[1] The original route to these compounds is the stoichiometric copper-mediated Ullmann homocoupling of aryl halides.[2] However, the low functional compatibility as well as the harsh reaction conditions generally required for this reaction have motivated the search for milder variants.[3] Then, the efficiency of palladium has been demonstrated in homocoupling reactions of aryl iodides and bromides. These reactions did not use any co-reductants,[4] zinc,[5] hydroquinone,[6] molecular hydrogen[7] or formate salts[8] to regenerate the catalytic active species. However, when using aryl chlorides as starting materials, the reduction often remains a competing process.

In the search for an alternative to palladium catalysts, several nickel-catalysed processes have been reported during the last few years. The primary advantage of these nickel-mediated coupling reaction is the use of the readily available and inexpensive aryl chlorides as chemical feedstock. The use of zerovalent nickel catalysts such as $Ni(CO)_2(PPh_3)_2$[9] or $Ni(cod)_2$[10] has recently been described. In most of these procedures, the active Ni(0) species are generated in situ by reduction of a Ni(II) complex using zinc dust.[11] Finally, Gosmini, Perichon et al. have described the synthesis of symmetrical and unsymmetrical biaryls using the electrochemical reduction of aryl halides in the presence of nickel-2,2′-bipyridine complexes.[12] For years, our laboratory has been reporting homocouplings of aryl and (het)aryl bromides and chlorides in the presence of stoichiometric amounts of liganded Ni(0) generated in situ by activated sodium hydride reduction of $Ni(OAc)_2$.[13] Attempts to catalytically use these reagents failed due to significant reduction of the starting materials. To prevent this drawback, we recently proposed a lithium hydride mediated nickel-catalysed procedure.[14] While this method gave a practical and efficient access to numerous biaryls from aryl halides, the LiH induced Ni(0) regeneration was slow and constituted the rate limiting step of the process. Then, we sought more reactive organometallic reagents. In this context, we found that subnanometrical Ni–Al clusters could easily be prepared by simultaneous reduction of $Ni(OAc)_2$ and $Al(acac)_3$ by activated sodium hydride. Analysis of the organometallic phase by transmission



Scheme 1.

Keywords: catalysis; nickel; aluminium; bimetallic clusters; homocouplings.

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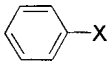
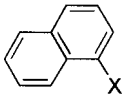
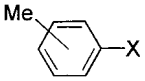
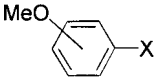
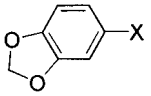
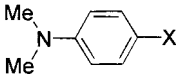
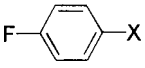
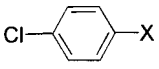
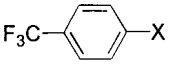
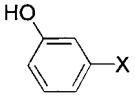
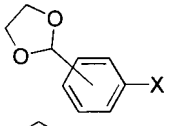
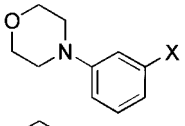
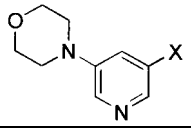
Table 1. Nickel catalysed Ullmann coupling of substituted aryl halides (reactions were performed using 25 mmol aryl halide, 37.5 mmol NaH, 2.5 mmol $Ni(acac)_2$, 2.5 mmol $Al(acac)_3$, 12.5 mmol 2,2′-bipyridine and 1.25 mmol styrene in 40 mL THF)

Entry	Aryl halide		Reaction time (h)	Conversion (%)[a]	Reduction yield (%)[a]	Product	Coupling yield (%)[b]
	ArX	X					
1		Br	1	80	4	**2a**	76
2		Cl	1.5	84	2	**2a**	82
3		Br	1.5	92	–	**2b**	92
4		Cl	2	90	6	**2b**	84
5		*p*-Br	1.5	85	–	**2c**	85
6		*o*-Cl	7	85	3	**2d**	82
7		*m*-Cl	3	96	–	**2e**	96
8		*p*-Cl	3	100	–	**2c**	99
9		*o*-Cl	3.5	97	40	**2f**	57
10		*m*-Cl	1	94	1	**2g**	94
11		*p*-Cl	10.5	59	4	**2h**	55
12		Cl	3	100	–	**2i**	90
13		Br	1.2	50	16	**2j**	34
14		Cl	5	75	5	**2k**	70
15		Br	3	56	–	**2l**	55
16		Cl	1	85	3	**2m**	82
17		Cl	24	99	15	**2n**	84[c]
18		*o*-Cl	24	75	10	**2o**	72
19		*p*-Cl	2	74	–	**2p**	74
20		Cl	6	87	–	**2q**	83
21		Cl	2	53	–	**2r**	53

[a] Determined by GC analysis.
[b] Isolated yields.
[c] 62.5 mmol NaH were used.

electronic microscopy revealed the presence of uniformly sized and very small particles (<0.5 nm) constituted of a homogeneous distribution of nickel and aluminium. The amount of hydrogen evolved indicated that both salts were totally reduced by alkoxide activated NaH. However, energy electron loss spectroscopy showed us that, at the end of the preparation, the in situ formed Al(0) is rapidly oxidised by oxygen contained in the reaction solvent leading to a high dispersion of Ni(0) particles in an aluminium oxide matrix. It is noteworthy that both Ni(0) and aluminium oxide were evidenced by electronic diffraction. The consequence of this dispersion is an enhanced catalytic activity of Ni–Al clusters (compared to classical Ni ones) which has already been evidenced in dehalogenation reactions.[15] Herein, we report detailed studies on the preparation of new 2,2′-bipyridine liganded Ni–Al clusters (Ni–Al-bpy)

and their effectiveness in catalysed homocoupling reactions of (hetero)aromatic halides (Scheme 1).

2. Results and discussion

We first realised an initial optimisation of the catalyst composition using 4-chlorotoluene as the aryl substrate. Some important features emerged. At first and as previously observed in carbon–carbon couplings using stoichiometric amounts of our Ni(0) reagent,[13] 2,2′-bipyridine was found to be the best ligand. The Ni–triphenylphosphine or Ni–phenanthroline complexes did not show any catalytic activity under classical reaction conditions. Moreover, variation of the amount of 2,2′-bipyridine in the catalyst resulted in dramatic changes in the yield of 4,4′-dimethylbiphenyl **2c**. The use of 5 equiv. of 2,2′-bipyridine resulted in optimum homocoupling yield. Higher [bpy/Ni] ratios afforded **2c** in comparative yields while lowering 2,2′-bipyridine amount caused an incomplete conversion of the starting material.

The nature of the precursor salts was also a factor that had obvious effects on the reaction. After a series of experiments, we found that only the combination of $Ni(acac)_2$ and $Al(acac)_3$ gave a Ni–Al catalyst exhibiting high coupling properties. Moreover, this combination was found much more efficient in the absence of activating alkoxide. This result contrasted with those obtained for the Ni–Al dehalogenation catalyst prepared by *t*-BuONa activated sodium hydride reduction of $Ni(OAc)_2$ and $Al(acac)_3$.[15]

In addition, the amount of molecular hydrogen evolved during the preparation of the Ni–Al-bpy coupling catalyst indicated that the initial $Ni(acac)_2$–$Al(acac)_3$ reduction is only effective in the presence of 2,2′-bipyridine. It also appeared that the residual NaH content must be fitted to 1 equiv. relative to the substrate. Indeed, a lower amount gave an incomplete reaction while an excess of hydride increased the reduction of the starting material.

The effect of solvents was finally examined to determine optimum conditions. In toluene, the preparation of the Ni–Al-bpy catalyst was slow (more than 30 h) and reduction of 4-chlorotoluene was the only reaction observed. When the solvent was replaced by 1,2-dimethoxyethane, product **2c** was isolated in 45% yield after 6 h and the amount of dehalogenated product was lowered to 27%. Switching to tetrahydrofuran resulted in a significant increase of homocoupling yield (53%) and this prompted us to chose this solvent for further coupling reactions.

Last but not least, as previously observed in arylaminations catalysed by our Ni(0) reagent,[16] the addition of styrene to the reaction medium is essential to ensure successful reactions. The efficiency of the coupling was significantly increased using only 0.5 equiv. of styrene relative to nickel while the dehalogenation was almost suppressed. The exact role of styrene will be discussed in more details below.

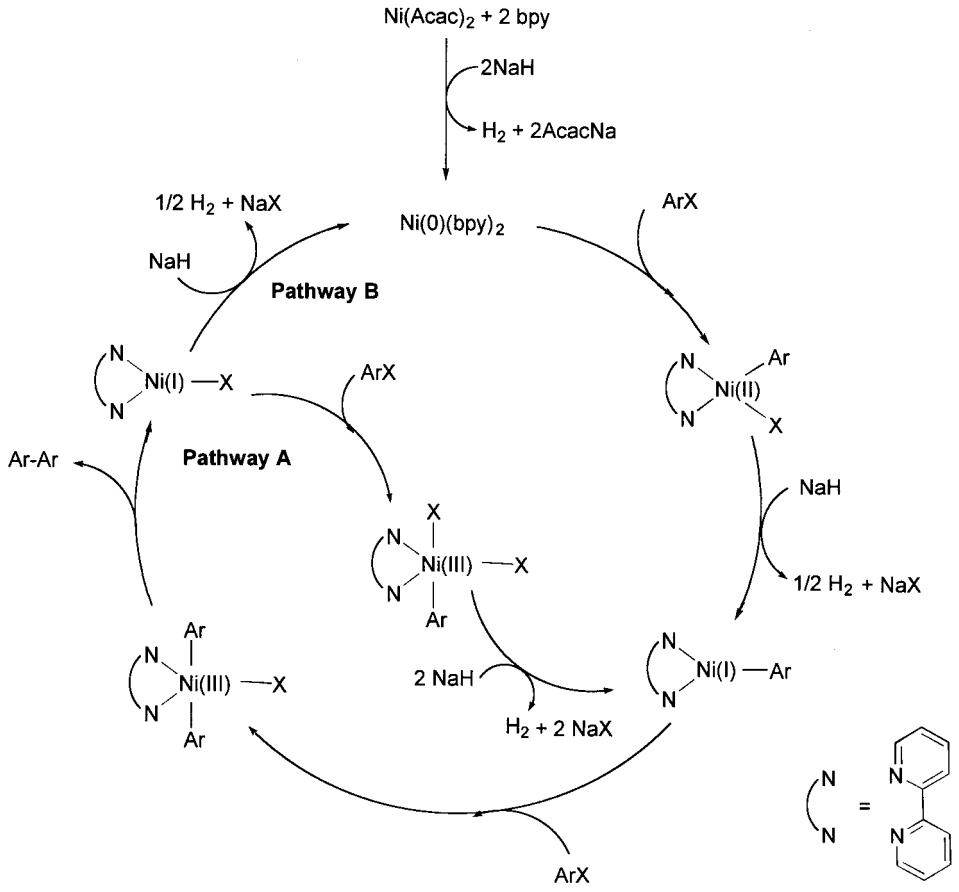
Under the above determined conditions, homocoupling of 4-chlorotoluene using 10 mol% of the 2,2′-bipyridine liganded catalyst gave 99% of 4,4′-dimethylbiphenyl **2c** (Table 1, entry 5).

This Ni–Al-bpy catalysed homocoupling procedure is applicable to a wide range of chloro and bromoarenes (Table 1). Aryl bromides reacted faster than aryl chlorides (compare entries 1 and 2, 3 and 4, 5 and 8). However, all reactions were completed in less than 12 h depending on the steric and electronic properties of the starting aryl halide.

Our reagent is also tolerant to a variety of functional groups on the aryl halide. As expected, the catalyst is very active toward aryl halides substituted by electron-withdrawing groups such as *m*-OCH_3, *m*-OH or *p*-CF_3 (entries 10, 12, 16–21) as a consequence of the favoured nickel insertion into the carbon–chlorine bond. With the less reactive aryl chlorides substituted by electron-donating groups, the homocoupling reaction required longer reaction times and led to lower yields (entries 9, 11 and 13). For example, 4-chloroanisole was only partially consumed (59%) after a 10.5 h reaction time leading to 4,4′-dimethoxybiphenyl **2h** in 55% yield. When *ortho* substituents were present on the aromatic ring, good yields were obtained by extending reaction time (entries 6 and 9), even allowing homocoupling of the sterically hindered *o*-chlorodioxolane in 72% yield (entry 18).

Chemoselective couplings were also performed. A good selectivity was observed when 4-fluorobromobenzene and 4-chlorobromobenzene were used as starting materials. 4,4′-Difluoro- and 4,4′-dichlorobiphenyl were isolated in 70 and 55% yield, respectively (entries 14 and 15) although more complicated by-products were formed, especially with the highly reactive bromochloroderivative. However, the selectivity observed suggests the possibility of iterative coupling reactions. Finally, entry 21 shows that the use of the Ni–Al-bpy catalyst can be extended to chloropyridines.

While the exact mechanism of the couplings remains to be elucidated, it is reasonable to assume that the early stages of the reaction involve oxidative addition of the aryl halide on liganded Ni(0) species[17] followed by sodium hydride reduction of the intermediate Ni(I) complex. A second oxidative addition of ArX results in the formation of a diaryl nickel (III) complex. This step is followed by the reductive elimination of biaryl. Two pathways are available starting from the Ni(I) complex obtained. It may be reduced by sodium hydride to regenerate initial Ni(0) (Pathway B). Alternatively, the Ni(I) complex may undergo oxidative addition of ArX. Subsequent reduction of the Ni(III) complex produced the starting aryl nickel (I) (Pathway A). If pathway B is operative, stoichiometric amounts of styrene relative to the starting aryl halide would be necessary to prevent Ni(0)-catalysed hydrogenolysis of the carbon–halide bond since molecular hydrogen is evolved during regeneration of active nickel species. As we observed, 0.5 equiv. of styrene relative to nickel are sufficient to inhibit this side reaction. Moreover, a great part of styrene (70%, GC monitoring), added simultaneously with the aryl halide, is rapidly transformed into ethylbenzene (<5 min) at the beginning of the reaction and styrene remaining in the reaction medium is not consumed during all the course of the coupling reaction. These results indicate the absence of Ni(0) species during



Scheme 2.

Ni–Al-bpy catalysed homocoupling and that pathway A, depicted in Scheme 2, is the most probable mechanism. Further studies are currently underway to confirm this hypothesis.

3. Conclusion

In summary, we present a new and mild catalyst for Ullmann-type homocoupling reactions. Our methodology is effective for activated and unactivated aryl chorides and bromides by simply employing $Ni(acac)_2$, $Al(acac)_3$ and 2,2′-bipyridine as the catalyst precursors. These results provide the foundation for further investigations into homo and cross-coupling reactions using our highly active Ni–Al-bpy bimetallic catalyst.

4. Experimental

4.1. Materials and instrumentation

Chloro- and bromoarenes were purchased from Aldrich or Lancaster and were freshly distilled prior to use. 2-(2′-Chlorophenyl)-1,3-dioxolane (entry 18) and 2-(4′-chlorophenyl)-1,3-dioxolane (entry 19) were prepared by heating a mixture of 2- or 4-chlorobenzaldehyde (25 mmol), ethylene glycol (75 mmol) and APTS in toluene for 24 h under azeotropic distillation of water. 5-Chloro-3-morpholinopyridine (entry 21) was prepared by nickel-catalysed amination of 3,5-dichloropyridine.[16]

All experiments were performed under nitrogen atmosphere. Tetrahydrofuran was distilled over Na/benzophenone and stored over sodium wires. Sodium hydride (65% in mineral oil, Fluka) was used after two washings with 20 mL THF under nitrogen. Nickel(II) acetylacetonate (Aldrich) and aluminium(III) acetylacetonate (Acros) were used without further purification. 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. Melting points were measured in glass capillaries using a Tottoli instrument. Elemental analyses and HR-EIMS were carried out by the Service de Microanalyses, CNRS, Vernaison, France. The progress of reactions was monitored using a Shimadzu capillary gas chromatograph fitted with a HP1 column (12 m×0.32 mm ID×0.25 μ). Flash chromatography was carried out using silica gel 60 (0.063–0.2 mm) (Merck). All quantifications of reaction constituents were achieved on GC using a known quantity of dodecane as reference standard. All products were isolated and identified by NMR and by comparison with authentic samples. The purity of each final compound was checked by NMR and GC analysis and was found to be >95% in each case.

Except for 3-chlorophenol, all haloarenes were homocoupled

using the standard procedure described below for the synthesis of 4,4′-dimethylbiphenyl.

4.2. General procedure for homocouplings catalysed by Ni–Al-bpy reagents

4.2.1. 4,4′-Dimethylbiphenyl (2c). In an oven dried round-bottomed flask equipped with a magnetic stirrer, a reflux condenser and a dropping funnel, nickel(II) acetylacetonate (2.5 mmol), aluminium(III) acetylacetonate (2.5 mmol) and 2,2′-bipyridine (12.5 mmol) were added to a degreased suspension of sodium hydride (37.5 mmol) in 30 mL THF and the mixture was stirred at 65°C for 8 h. 4-Chlorotoluene (25 mmol) and styrene (1.25 mmol) in 10 mL THF were then added to the black suspension and the mixture was further stirred at reflux for 3 h. After cooling to room-temperature, water (1 mL) and dichloromethane (50 mL) were added and the reaction mixture was filtered. After drying over anhydrous $MgSO_4$ and concentration in vacuo, the crude product was purified by column chromatography on silica gel using hexanes as eluant and **2c** was isolated as a white solid, mp 119°C (lit.,[18] 120.7–121.5°C), in 99% yield.

4.3. Homocoupling of 3-chlorophenol

4.3.1. 3,3′-Dihydroxybiphenyl (2n). 3-Chlorophenol (25 mmol) and styrene (1.25 mmol) in 10 mL THF were added dropwise at room temperature to a degreased suspension of sodium hydride (62.5 mmol) in 30 mL THF. Nickel(II) acetylacetonate (2.5 mmol), aluminium(III) acetylacetonate (2.5 mmol) and 2,2′-bipyridine (12.5 mmol) were then added and the mixture was heated at 65°C for 24 h. After cooling to room temperature, the reaction mixture was acidified with HCl 1N, extracted with dichloromethane (3×40 mL), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (AcOEt/Hexane=10/90) to give 3,3′-dihydroxybiphenyl **2n** as a white solid, mp 124°C (lit.,[19] 123–125°C), in 84% yield.

4.4. Data for new compounds

4.4.1. 3,3′-Bis(morpholino)biphenyl (2q). Obtained as a colorless oil after column chromatography on silica gel (Hexane/AcOEt=50/50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, $^3J=^3J'=8.2$ Hz, 2H), 7.09 (d, $^4J=1.2$ Hz, 2H), 7.08 (d, $^3J=8.0$ Hz, 2H), 6.90 (dd, $^3J=8.0$ Hz, $^4J=2.4$ Hz, 2H), 3.90–3.84 (m, 8H); 3.25–3.18 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.54, 142.83, 129.37, 119.20, 114.88, 114.67, 66.86, 49.39. HR-EIMS calcd for $C_{20}H_{24}N_2O_2$ 324.1837. Found 324.1830.

4.4.2. 5,5′-Bis(morpholino)-3,3′-bipyridine (2l). Obtained as a white solid after column chromatography on silica gel (MeOH/AcOEt=10/90), mp 194°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, $^4J=2.4$ Hz, 2H), 8.31 (d, $^4J=1.2$ Hz, 2H), 7.29 (brdd, 2H), 3.93–3.84 (m, 8H), 3.30–3.24 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.73, 139.25, 137.42, 133.89, 120.23, 66;42, 48.28. HR-EIMS calcd for $C_{18}H_{22}N_4O_2$ 326.1742. Found 326.1710.

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17. Althought the exact nature of the Ni(0) species was not determined, it is reasonable to assume that the formation of the soluble Ni complex $Ni(bpy)_2$ must be taken into account. See for example: Fox, M. A.; Merkert, J. W.; Caubere, P. *New J. Chem.* **1994**, *18*, 447.
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