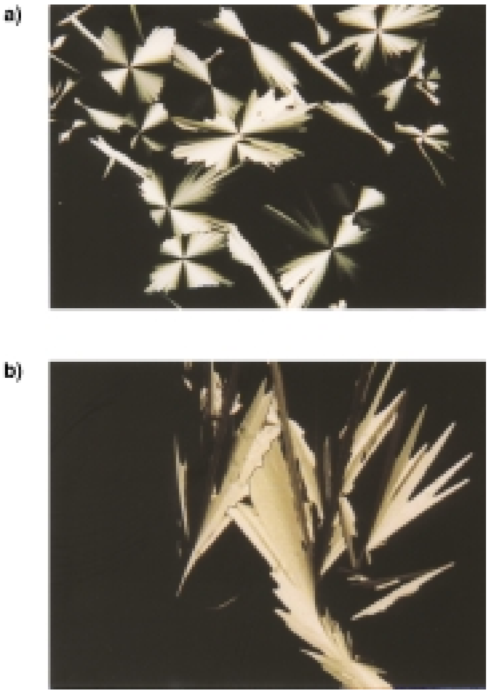

Figure 1. Representative thermal-optical polarized microscopy pictures showing the textures of the hexagonal columnar (Φ_h) mesophases of a) **(*3,4–3,5*)12G2-CH$_2$OH** upon cooling from 76 °C to 54.9 °C at 1 K min^{-1}; and b) **(*3,4*-(*3,5*)^2)12G3-CO$_2$CH$_3$** obtained upon cooling from 50 °C to 45.1 °C at 1 K min^{-1}.

as the disclike molecule **(*3,4*-(*3,5*)^3)12G4-X** can adopt a globular shape in solution. The extent of site isolation will increase from the fourth to the fifth and higher generations.

These results suggest synthetic methods that place X in the center of a single spherical monodendron. Such a molecule would generate an ideal site-isolation mechanism both in the bulk and in solution.

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Nickel-Catalyzed Cross-Coupling of Aryl Chlorides with Aryl Grignard Reagents**

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Christian W. K. Gstöttmayr, and
Wolfgang A. Herrmann*

Dedicated to Professor Wilhelm Keim on the occasion of his 65th birthday

The Grignard cross-coupling mediated by nickel and palladium catalysts[1, 2] represents a useful synthetic approach to biaryls, terphenyls, and oligoaryls which are important

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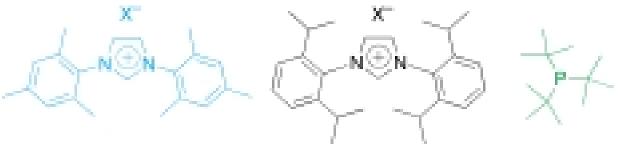
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

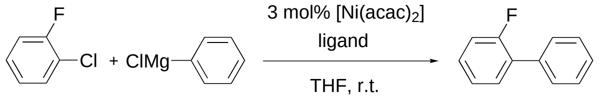
building blocks of natural products, liquid crystals, polymers, and ligands.[3] Although sterically demanding phosphanes and imidazolin-2-ylidenes assist palladium(0) to activate aryl chlorides in catalytic cross-coupling reactions,[4] these systems are less effective in the Grignard cross-coupling of aryl chlorides with arylmagnesium halides. Their drawback is the necessity for elevated reaction temperatures, which can lead to problems with regard to selectivity.[5] The same drawback exists with the use of the heterogeneous catalyst Ni/C.[6]

Herein, we report on a first economical catalyst system based on nickel for the coupling of aryl chlorides with aromatic Grignard reagents in high yields even at ambient temperature. The air-stable, conveniently available imidazolium salts **1** and **2** as well as tris(*tert*-butyl)phosphane **3** were identified as the most efficient ligands for this general methodology with nickel(II) diacetylacetonate.



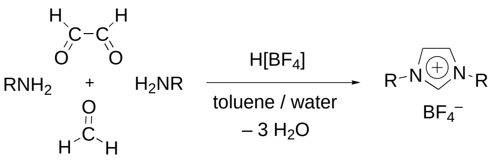
1 X⁻ = [Cl]⁻, [BF$_4$]⁻ **2** **3**

To speed up the optimization process,[7] we employed a ^{19}F NMR spectroscopic screening of a large variety of phosphanes, arsanes, and N-heterocyclic carbenes as ligands in combination with various metal precursors[8] to get a meaningful semiquantitative time/conversion correlation even in the primary screen. ^{19}F{^{1}H} NMR spectroscopy was chosen to analyze the reactions for various reasons[9] including the inertness of C–F bonds under the reaction conditions.[10] Phenylmagnesium chloride and 1-chloro-2-fluorobenzene proved suitable substrates for this assay [Eq. (1)]. As the screening results at this stage did not require exact yield determination, we assumed integration faults due to proton decoupling and deviations due to defluorination to be small.[11]



(1)

Generally, imidazolium salts as precursors to N-heterocyclic carbenes[12] are especially suitable for high-throughput approaches since their synthesis by a multicomponent one-pot reaction under mild conditions in the presence of air and moisture[13] can be parallelized more easily than, for example, that for phosphanes. Appropriate counterions such as [BF$_4$]$^-$ or [PF$_6$]$^-$ allow the isolation of the pure product salt by simple filtration or phase separation [Eq. (2)].[11, 14]

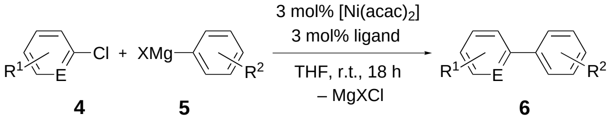


(2)

The primary screen at ambient temperature provided the following findings: 1) [Ni(acac)$_2$] (acac = acetylacetonate) is much more active than [Pd$_2$(dba)$_3$] (dba = dibenzylideneacetonate) or Pd(OAc)$_2$, 2) the imidazolium salts **1** and **2** as well as the phosphane **3** are the best ligands and induce highest selectivity, 3) only an equimolar amount of the activating ligands with regard to the metal is necessary, and 4) the anions of the imidazolium salts do not exhibit activity and selectivity effects.

The most active systems were then subjected to preparative-scale experiments with different aryl chlorides and arylmagnesium compounds (Table 1). The electronic properties of the aryl chlorides display the expected consequences, that is electron-poor arenes are most reactive. Steric congestion is partially tolerated by the system as demonstrated by 2-chlorotoluene, but two *ortho*-substituents as in 2-chloro-*m*-xylene hamper useful conversions. Generally, the catalysts are less sensitive to steric bulk on the organometallic reagent than on the aryl halide (entries 13–19, Table 1).[11]

Table 1. Nickel-catalyzed Grignard cross coupling at ambient temperature.[a]



	4		5		6 [%][b]		
Entry	R^1	E	R^2	X	1	2	3
1	H	N	H	Cl	> 99	> 99	92
2	4-CF$_3$[c]	C	H	Cl	90	96	47
3	4-CH$_3$	C	H	Cl	72	81	89
4	4-OCH$_3$	C	H	Cl	67	71	71
5	2-CH$_3$	C	H	Cl	70	73	72
6	2,6-(CH$_3$)$_2$	C	H	Cl	4	13	12
7	H	N	4-OCH$_3$	Br	> 99	> 99	> 99
8	4-CF$_3$[c]	C	4-OCH$_3$	Br	> 99	> 99	38
9	H	C	4-OCH$_3$	Br	95	93	> 99
10	4-CH$_3$	C	4-OCH$_3$	Br	85	88	87
11	2-CH$_3$	C	4-OCH$_3$	Br	77	77	77
12	2,6-(CH$_3$)$_2$	C	4-OCH$_3$	Br	8	5	28
13	H	N	2,4,6-(CH$_3$)$_3$	Br	> 99	> 99	94
14	4-CF$_3$[c]	C	2,4,6-(CH$_3$)$_3$	Br	78	91	52
15	H	C	2,4,6-(CH$_3$)$_3$	Br	99	> 99	99
16	4-CH$_3$	C	2,4,6-(CH$_3$)$_3$	Br	96	95	> 99
17	4-OCH$_3$	C	2,4,6-(CH$_3$)$_3$	Br	98	98	87
18	2-CH$_3$	C	2,4,6-(CH$_3$)$_3$	Br	78	77	75
19	2,6-(CH$_3$)$_2$	C	2,4,6-(CH$_3$)$_3$	Br	3	2	5

[a] Aryl chloride (1.0 equiv), Grignard reagent (1.5 equiv), [Ni(acac)$_2$] (3 mol%), ligand (3 mol%), THF, room temperature, t = 18 h. [b] GC yield of desired product **6** using diethyleneglycol-di-*n*-butyl ether as internal standard. For full details on product distribution see the Supporting Information. [c] Reagents were used as received.

The time/conversion diagram in Figure 1 for the coupling of 2-chlorotoluene with 4-anisylmagnesium bromide [Eq. (3)] reveals that the catalysts with ligands **1**–**3** differ only in their turnover frequencies (TOF) at the beginning of the reaction, but result in roughly the same turnover numbers (TON). The analogous palladium systems do not catalyze the reaction under these mild conditions efficiently. Neither of the nickel

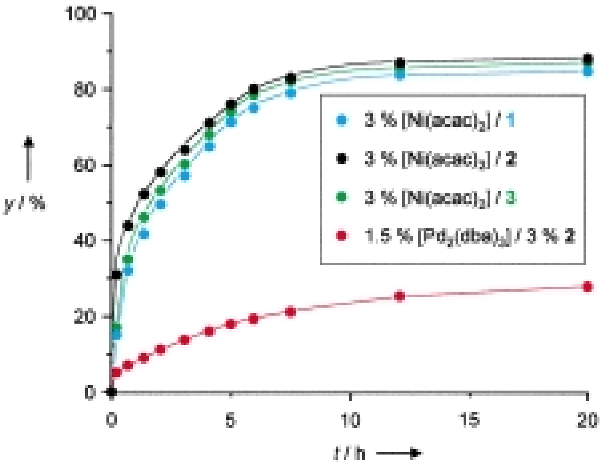


Figure 1. Comparison of the time/conversion characteristics of ligands **1**–**3** in the nickel-catalyzed Grignard cross-coupling reaction. The most active palladium catalyst is included for comparison. (y = yield of 4-methoxy-2′-methylbiphenyl; 2-chlorotoluene (2.00 mmol), 4-anisylmagnesium bromide (3.00 mmol) in THF (3 mL), [Ni(acac)$_2$] (0.06 mmol), ligand (0.06 mmol), diethyleneglycol-di-*n*-butyl ether (50 mg), THF (10 mL)). systems has an induction period. Homocoupling products of the Grignard reagents were observed in all reactions and are formed only at the beginning of the reaction.[11]

In some reactions minor amounts (<1%) of by-products such as terphenyls occur, suggesting radical side reactions as observed in other nickel-catalyzed cross-coupling reactions.[15] Nevertheless, the electronic influence of the aryl chloride on the reaction rate and the product distributions indicate that the bulk of the reaction follows a polar pathway. Further by-products derived from activation of C_{Ar}–OCH_3 or C_{Ar}–F bonds were formed in amounts of 3% and below, and only after the C–Cl bond had been converted completely as no chlorine containing biphenyls were detectable.

Regarding the coordination mode of the ligand derived from **1** and **2** under the reaction conditions, the formation of an imidazolin-2-ylidene complex of nickel(0) was identified by characteristic ^{13}C NMR signals.[16]

In summary, highly active catalysts based on nickel as the catalytically active metal were developed for the Grignard cross-coupling reaction of aryl chlorides at ambient temperature and at low catalyst loading. Furthermore, a modified high-yield, facile work-up procedure for the synthesis of imidazolium salts allows the efficient high-throughput screening of N-heterocyclic carbene ligands.

Experimental Section

A Schlenk tube was charged with [Ni(acac)$_2$] (7.7 mg, 0.03 mmol), ligand **1**, **2**, or **3** (0.03 mmol), and the aryl chloride (1 mmol) under an atmosphere of dry nitrogen. After addition of THF (1 mL) and the internal standard diethyleneglycol-di-*n*-butyl ether (50 mg), the mixture was stirred for 5 min until the catalytic reaction was initiated by dropwise addition of the Grignard reagent (1.5 mmol, ca. 1 M in THF) by syringe at ambient temperature. The reaction was ceased by addition of methanol (1 mL). Yield was determined by GC/MS analysis.

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