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Nickel-Catalyzed Cross-Coupling of Aryl Bromides with Tertiary Grignard Reagents Utilizing Donor-Functionalized N-Heterocyclic Carbenes (NHCs)

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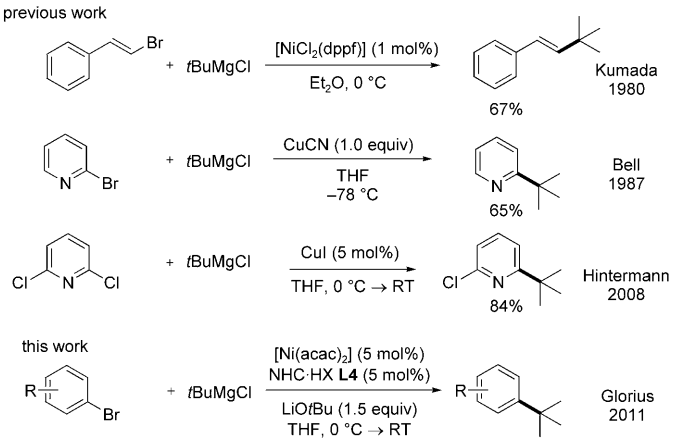
Metal-catalyzed cross-coupling reactions are among the most important transformations in organic synthesis, allowing the efficient construction of complex structures from simpler, readily available building blocks.[1] Many applications in large and small-scale synthesis can be found in different areas such as agrochemicals, pharmaceuticals and supramolecular chemistry. Whereas the coupling of sp^2-hybridized carbon atoms in either reaction partner is well established, the use of C(sp^3)-hybridized substrates presents some challenges.[2] Catalytic cross-coupling of sterically hindered tertiary alkyl substrates is especially difficult, generally resulting in low yields, and thus, only few reports exist.[2–7] A big challenge in this field is not only to get the required level of reactivity, but also to overcome competing pathways like β-hydride elimination, hydrodehalogenation or isomerization.[8]

In an early report, Kumada et al.[4] have shown a nickel-catalyzed cross-coupling of tertiary alkyl Grignard reagents with β-bromostyrene. Cahiez et al.[5] could obtain the same product in similar yield using an Fe catalyst, however, β-hydride elimination became competitive. Furthermore, the group of Bell used a stoichiometric amount of a copper(I) salt to alkylate pyridines and quinolines.[6] Recently, Hintermann et al. reported an impressive selective copper-catalyzed cross-coupling of tertiary Grignard reagents of certain azacyclic electrophiles, but this protocol is limited to chloroazacycles such as pyridines, pyrimidines, quinazolines and quinoxalines (Scheme 1).[7]



Scheme 1. Challenging cross-couplings of tertiary alkyl Grignard reagents.

A general method for the coupling of tertiary alkyl metal reagents with aryl halides would be very desirable. Due to their attractive properties[9] N-heterocyclic carbene (NHC) ligands have found widespread applications in organometallic chemistry and transition-metal catalysis.[10] NHCs have already been successfully applied in Kumada–Corriu–Tamao[11] reactions.[12] Herein we report the Kumada–Corriu–Tamao-type nickel-catalyzed cross-coupling of aryl halides with tertiary Grignard reagents. This practical advance provides selective access to highly substituted tertiary alkyl benzene derivatives, an interesting class of chemical compounds. The coupling of 4-bromobiphenyl with *t*BuMgCl was used as the initial model system. The high reactivity of Grignard reagents is desirable in this coupling, as is their easy accessibility. Functional group compatibility, often a problem in reactions of Grignard reagents, can be expanded, if sufficiently mild reaction conditions can be realized. Using NHC ligands, we tried to prevent the formation of undesired side products. Thus, the sterically demanding easily synthesized ligand precursor **L1**, IAd·HBF_4, was selected for the first screening reactions.

Screening of **L1** together with various commercial Ni, Pd and Cu sources showed [Ni(acac)$_2$] to be a uniquely suited metal precursor, with all other complexes giving lower or no catalytic activity (Table 1, entries 1 and 3). Naturally, no product was obtained in the absence of any metal source (entry 2). In addition, different solvents, bases and reaction temperatures were evaluated.[13] The reaction can be successfully run at 0 °C, and changing the temperature to +40 or −78 °C did lower the yield significantly (entries 4 and 5).[13] The solvent played an important role, non-coordinating solvents only afforded poor or no conversion. On the contrary, ethers, especially THF, were suitable (entries 7, 14, 16). Without an NHC ligand, the desired product could be obtained in decreased yield and selectivity after rather long reaction time (entry 8).[13] For many other substrates this effect was even more pronounced, as became obvious upon studying the substrate scope of this reaction (see below).

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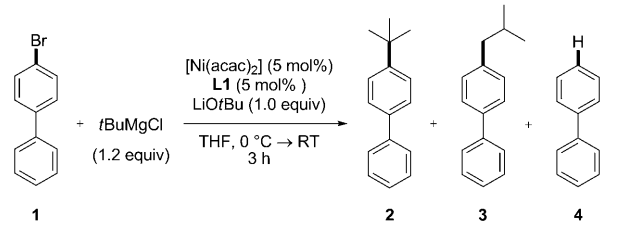
Table 1. Optimization of experimental conditions.



Entry	Variation from the conditions[a]	Yield [%][b]		
		2	**3**	**4**
1	–	65	5	28
2	no $[Ni(acac)_2]$	–	–	–
3[c]	$Ni(OAc)_2$ (instead of $[Ni(acac)_2]$)	20	3	74
4	−78 °C	47	6	47[d]
5	+40 °C	48	13	39[d]
6	KO*t*Bu (instead of LiO*t*Bu)	21	8	71[d]
7	toluene as solvent	–	–	–
8[e]	no ligand	49	3	46
9	**L2**	72	7	21
10	**L3**	66	26	8
11	**L4**	80	18	2
12	**L5**	62	15	23
13[f]	**L4**	**85 (83)**	10	5
14[f]	**L4**, Et_2O as solvent	12	20	68[d]
15[f]	**L4**, DMF as solvent	–	–	–
16[f]	**L4**, dioxane as solvent	27	8	65[d]
17[f]	**L4**, LiCl (instead of LiO*t*Bu)	36	14	50[d]
18[f]	**L4**, added CsOAc (50 mol %)	62	13	25
19[f]	**L4**, added COD (50 mol %)	11	24	65[d]
20[f]	**L4**, $[NiCl_2(glyme)]$ (instead of $[Ni(acac)_2]$)	51	13	36[d]
21[f]	**L4**, no LiO*t*Bu	30	40	30[d]
22[f]	no ligand, no LiO*t*Bu	25	6	69[d]
23[f]	**L4** (10 mol %)	64	17	19

[a] Reactions were carried out on a 0.2–0.4 mmol scale. [b] Determined by ^1H NMR spectroscopy. Isolated yields in parentheses. [c] $Pd(OAc)_2$, $Cu(OAc)_2$, $Ni(COD)_2$, $Fe(acac)_3$ and $Mn(OAc)_2$ showed no conversion. [d] No full conversion, mixture of 4-bromobiphenyl and biphenyl determined by GC-MS analysis. [e] After 12 h reaction time. [f] Reactions were carried out with 1.5 equiv *t*BuMgCl, 1.5 equiv LiO*t*Bu.

This importance of the NHC ligand led us to investigate a series of other NHC ligands (Figure 1).

Hoveyda et al. developed a series of bidentate NHC-based ligands containing a free hydroxyl group, and, more recently Alexakis et al. reported a copper-free asymmetric alkylation with Grignard reagents using alkoxy-substituted NHCs.[14] Inspired by this, we utilized several easily prepara-

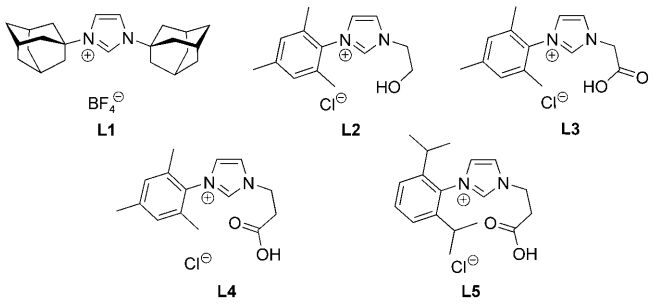


Figure 1. NHCs used in this study.

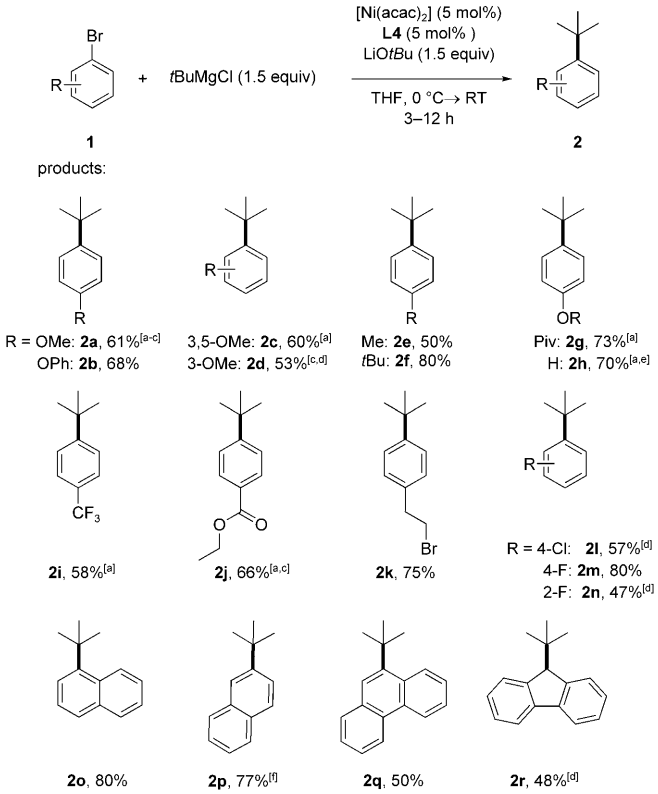
ble ligands (**L1**–**L5**, Figure 1),[15] consisting of a donor function flexibly tethered to one nitrogen and a more rigid substituent such as mesityl or 2,6-diisopropylphenyl on the other nitrogen resulting in a bifunctional NHC (Figure 1). Using the O-donor functionalized ligand **L2**, reactivity and selectivity towards the formation of product **2** of the current transformation could be improved (entry 9). Switching from a hydroxy to a carboxylic acid group led to a decrease in yield whereas elongation of the carboxylic acid alkyl chain again improved the yield (entries 10 and 11). Comparing the selectivity for different substrates we observed a beneficial influence of **L4** on the suppression of the protodebromination and isomerization. Ligand **L5** containing a 2,6-diisopropylphenyl group instead of a mesityl group gave a similar amount of isomerized product **3**, but an increased yield of dehalogenated by-product **4** (entry 12). Neither varying the ligand to metal ratio nor higher catalyst loading increased the yield of the desired product (entry 23). The addition of 50 mol % of benzonitrile to the standard conditions was found to result in nearly complete inhibition of the reaction, indicating that the nitrile group can coordinate to the metal.[13] Obviously, LiO*t*Bu plays an important role, since its replacement by KO*t*Bu or LiCl resulted in lower reactivity (entries 6 and 17). Finally, using 5 mol % of **L4**, 5 mol % of $[Ni(acac)_2]$ and 1.5 equiv of LiO*t*Bu and Grignard we obtained 83 % isolated yield of the desired product after 3 h starting from cheap, commercially available starting materials.

To illustrate the potential of ligand **L4**, we commenced our substrate scope studies with electron-donating groups such as methyl and phenyl ether. A wide range of functional groups is tolerated ranging from electron-donating groups like silyl[16] and alkyl ethers, over electron-neutral to electron-withdrawing substituents like an ester, a halogen or a trifluoromethyl group yielding the corresponding products in moderate to good yields.

Unfortunately, in many cases the isomerization product could not be separated from the main product (due to similar R_F values) and in some other cases the isolated yield was deteriorated by the volatility of the products. Notably, *ortho*-substituted compound **2n** and the polyaromatic compound **2o** were obtained in moderate to good yield (Scheme 2).

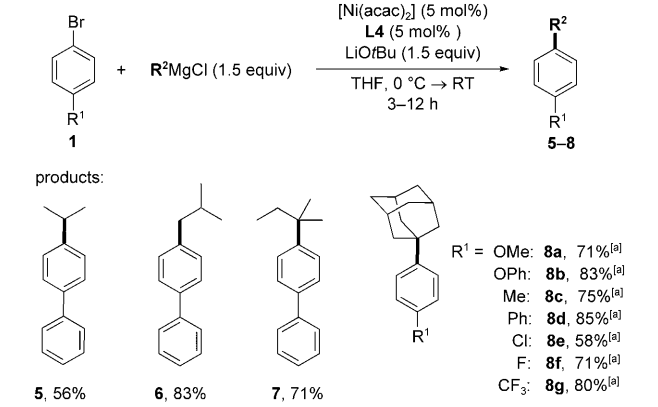
Remarkably, under our optimized conditions aryl chlorides are well tolerated, which facilitates a further functionalization of the product. The marked reactivity difference between sp^2- and sp^3-hybridized organic halides, becomes apparent in the compatibility of alkyl bromides in this reaction, as shown for substrate **2k**. Most remarkable, not only aryl bromides **1** are suitable for this attractive reaction, in some cases readily available triflate **1p** and benzylic bromide **1r** showed proper reactivity. Obvious limitations arise from protic functional groups, for example, alcohols, and groups with high reactivity toward Grignard reagents such as nitriles.

The synthetic flexibility of this new method is supported by the ability to use diverse sterically demanding Grignard

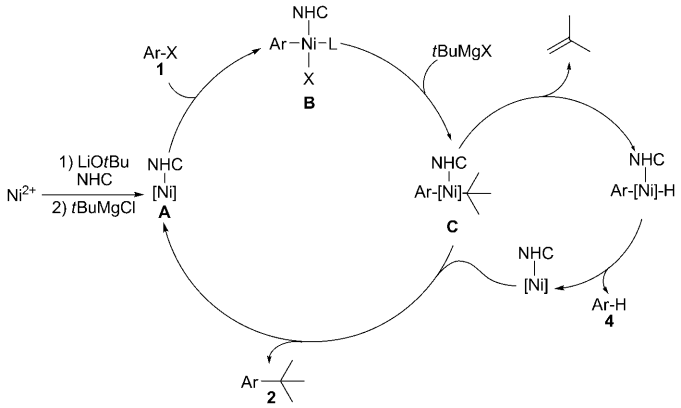


Scheme 2. Substrate scope. Reactions were carried out on a 0.4–1.0 mmol scale. Isolated yields are given. [a] Together with additional 12–15% inseparable *i*Bu isomer. [b] OTf instead of Br: 19% NMR yield. [c] Without NHC: **2a**/**3a**/**4a** 14:8:78; **2d**/**3d**/**4d** 16:0:84; **2j**/**3j**/**4j** 56:16:28; NMR yield. [d] Determined by ^{1}H NMR spectroscopy. [e] Starting material with R = TMS. [f] OTf instead of Br employed.

reagents like *i*PrMgCl, *i*BuMgCl, *t*AmylMgCl and 1-AdMgBr (Scheme 3). 1-AdMgBr is tolerant to a wide range of functional groups and led to very good isolated yields. Further examples are known from Szeimies et al. They reported a nickel-catalyzed cross-coupling of (tricyclo[4.1.0.0^{2,7}]hept-1-yl)-magnesiumbromide with aryl, vinyl and alkynyl halides in moderate yields.[17]



Scheme 3. Catalytic cross-coupling with different Grignard reagents. Reactions were carried out on a 0.4–1.0 mmol scale. Isolated yields are given. [a] 2.0 equiv of 1-AdMgBr.



Scheme 4. Simplified mechanism for the cross-coupling of aryl bromides with *tert*-butyl Grignard reagents and the hydrodehalogenation *via* β-hydride elimination.

The efficiency of the Ni/Mg/NHC system can be explained by the following mechanism (Scheme 4). The imidazolium salt is first deprotonated by the base and leads to the formation of a Ni-NHC complex; reduction of the Ni source by the Grignard reagent leads to **A**. Intermediate **B** is then formed by oxidative addition, followed by transmetalation and reductive elimination. An undesired β-hydride elimination from intermediate **C** would generate a Ni–H species that can undergo a direct reductive elimination to give **4** or a re-addition to the formed isobutene followed by reductive elimination to give **3** (not shown).[18] Our optimization of reaction conditions shows that the β-hydride elimination can be partially avoided by utilizing the donor-functionalized **L4**. It seems that the carboxylate group prevents β-hydride elimination by occupying a free coordination site on the Ni. On the contrary, β-hydride elimination increased in most cases when the reactions were run without NHC (Scheme 2) (entries **2a**, **2d**).

However, it is important to note that the addition of stoichiometric amounts of either TEMPO or galvinoxyl inhibited the reaction, indicating a participation of radicals in this nickel-catalyzed process, which is not accounted for in Scheme 4. Similarly, Knochel[19] and Vicic[20] reported about radical-chain mechanisms in palladium- and nickel-catalyzed cross-coupling reactions of aryl Grignard or alkylzinc reagents.

In conclusion, we have developed a nickel-catalyzed method for the challenging cross-coupling of aryl bromides and triflates with sterically demanding tertiary Grignard reagents. Bifunctional NHC ligands were shown to result in especially selective and efficient transformations. Good yields of the coupled products were obtained and a wide range of functional groups is well tolerated. Further applications of this catalyst system and asymmetric couplings of tertiary alkyl species seem to be within reach.

Experimental Section

General procedure: A flame-dried sealed tube equipped with a stirring bar was heated and cooled under vacuum and back-filled with argon. Ligand **L4** (5.9 mg, 0.02 mmol, 5 mol%), $[Ni(acac)_2]$ (5.1 mg, 0.02 mmol, 5 mol%) and LiO*t*Bu (48 mg, 0.6 mmol, 1.5 equiv) were weighed into the reaction vessel in the glovebox. Anhydrous THF (4.0 mL) was added under a stream of argon and the mixture was stirred for 15 min. A solution of the Grignard reagent (0.6 mmol, 1.7 M in Et_2O) was added slowly, and the reaction mixture stirred for 10 min at 0 °C followed by addition of the aryl halide (0.4 mmol, 1.0 equiv). The solution was stirred slowly warming from 0 °C to room temperature until GC/MS analysis indicated completion of the reaction. Afterwards the mixture was filtered through a small pad of silica and washed with CH_2Cl_2 (2×10 mL). Evaporation of the solvent afforded the crude product, which was purified by column chromatography and pure fractions were checked by GC/MS analysis.

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Keywords: aryl bromides · cross-coupling · Grignard reagents · N-heterocyclic carbenes · nickel

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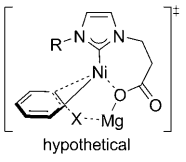

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