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Kumada–Tamao–Corriu Coupling of Heteroaromatic Chlorides and Aryl Ethers Catalyzed by (IPr)Ni(allyl)Cl

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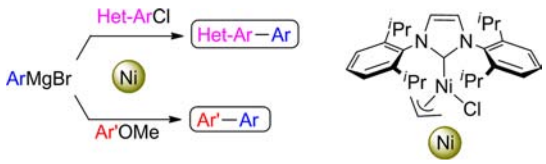
ABSTRACT



The complex (IPr)Ni(allyl)Cl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidene) catalyzes the cross-coupling reactions of heteroaromatic chlorides with aryl Grignard reagents. Catalyst loadings as low as 0.1 mol % have been used to afford the products in excellent yields. This nickel-based catalytic system also promotes the activation of the C_{Ar}–O bond of anisoles in the Kumada–Tamao–Corriu reaction under fairly mild conditions.

Transition-metal-catalyzed cross-coupling reactions constitute one of the preferred synthetic tools for making new carbon–carbon bonds, particularly between aromatic substrates.[1] Among the different cross-coupling methods developed for aromatic C–C bond formations, the coupling of aryl halides with aryl Grignard reagents, the Kumada–Tamao–Corriu (KTC) reaction,[2] represents the most straightforward and atom-economical[3] way to biaryl synthesis since arylboron (Suzuki–Miyaura),[4] zinc (Negishi),[5] tin (Stille–Migita),[6] or silicon (Hiyama)[7] nucleophiles are usually prepared from arylmagnesium reagents. Despite this advantage, the high reactivity of organomagnesium reagents makes them incompatible with certain functional groups and also reduces the selectivity of the coupling process generating variable amounts of homocoupling byproducts. Recently, two remarkable examples from the groups of Buchwald[8] and Nakamura[9] have shown how the appropriate choice of either the ligand or the metal source could overcome the above-mentioned drawbacks.

In the KTC reaction, nickel-based catalysts particularly display good activity toward aryl chlorides,[2c,10] the less

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[§] Universidad de Sevilla.

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(9) (a) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844. (b) Hatakeyama, T.; Hashimoto, S.; Ishikuza, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949.

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reactive yet,[11] at the same time, the cheapest and most widely available among the aryl halides. Nickel complexes bearing either P-[2c,12] or C-based[13] (N-heterocyclic carbenes, NHCs) ligands accomplish such transformations even at room temperature. Moreover, phenol-derived electrophiles represent an attractive low cost alternative to organic halides in cross-coupling processes.[14] However, these substrates are even more challenging to activate since the bond dissociation energy (BDE) of the $C_{Ar}-O$ bond is higher than that of the corresponding $C_{Ar}-Cl$.[14a] Not surprisingly, recent outstanding examples of the activation of $C_{Ar}-O$ in different cross-coupling reactions have been addressed by using nickel-based catalysts stabilized with electron-rich and sterically demanding phosphane or carbene ligands.[15]

Recently, we have described the first examples of room temperature nickel-catalyzed amination of aryl and heteroaryl chlorides.[16] These couplings were performed in the presence of the well-defined complex (IPr)Ni(π-allyl)Cl.[17] As continuation of this work, we report herein that this catalytic system is highly active in KTC couplings with heteroaryl chlorides. Furthermore, this complex also effectively promotes the cross-coupling of aromatic Grignard reagents with anisoles under fairly mild reaction conditions.

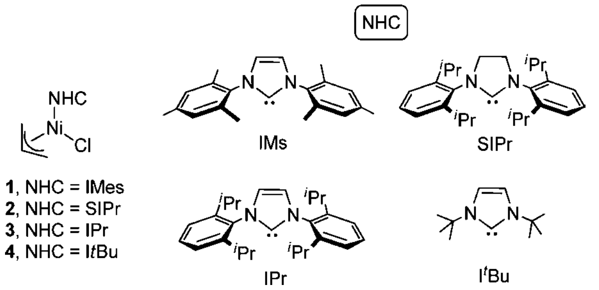
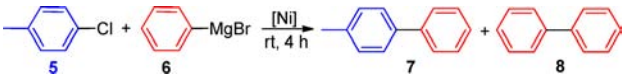


Figure 1. Nickel(II) complexes employed in this work.

We began by evaluating the catalytic activity of a series of (NHC)Ni(allyl)Cl[17] complexes (Figure 1) in the KTC reaction of 4-chlorotoluene with phenylmagnesium bromide, using 5 mol % of the Ni(II) precatalysts at room temperature. The results obtained are summarized in Table 1. We encountered significant differences in the catalytic behavior of these NHC−Ni(II) complexes under the conditions employed. The reactions catalyzed by complexes **1** and **2** afforded moderate yields of the desired product together with considerable amounts of the homocoupling byproduct (entries 1 and 2). Conversely, derivative **3** promoted a highly selective reaction exclusively furnishing 4-methylbiphenyl in 75% yield (entry 3). Finally, the most bulky I*t*Bu[18] also suppressed the byproduct formation, but complex **4** exhibited lower catalytic activity (entry 4) compared with that of the IPr-derivative, **3**.

Table 1. Screening of Nickel Complexes **1**−**4**[a]



entry	catalyst	yield[b] (%) **7**	yield[b] (%) **8**
1	(IMes)Ni(allyl)Cl (**1**)	48	10
2	(SIPr)Ni(allyl)Cl (**2**)	50	19
3	(IPr)Ni(allyl)Cl (**3**)	75	0
4	(I*t*Bu)Ni(allyl)Cl (**4**)	65	0

[a] Reaction conditions: aryl chloride (0.5 mmol), PhMgBr (0.75 mmol), nickel complex (5 mol %), total volume of THF (1 mL). [b] Isolated product yield.

Once complex **3** was identified as the most active catalyst, we tested it in the KTC reaction of heteroaryl chlorides as

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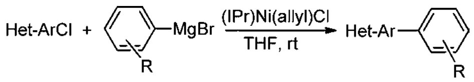
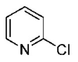
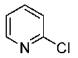
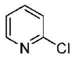
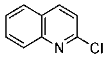
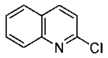
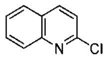
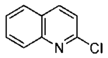
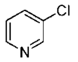
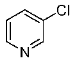
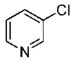
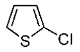
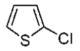
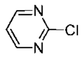
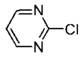
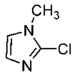
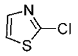
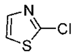
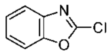
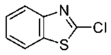
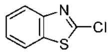
(20) Only examples on the use of heteroarenes in KTC with group 10 metals are quoted here: (a) Bonnet, V.; Mognin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 5717. (b) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem.—Eur. J.* **2007**, *13*, 150. (c) Jothibasu, R.; Huang, K.-W.; Huynh, H. V. *Organometallics* **2010**, *29*, 3746. (d) Ghosh, R.; Sarkar, A. *J. Org. Chem.* **2010**, *75*, 8283. (e) Li, F.; Hu, J. J.; Koh, L. L.; Hor, T. S. A. *Dalton Trans.* **2010**, *39*, 5231. (f) Liu, N.; Wang, Z.-X. *J. Org. Chem.* **2011**, *76*, 10031.

coupling partners. Despite the interesting applications of arylated heterocyclic compounds,[19] heteroaromatic halides have been rarely used as substrates in cross-coupling reactions,[8,13c,f,20] a fact that is related with the coordination ability of the heteroatom to the metal center.

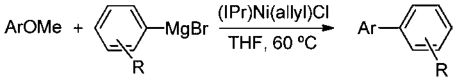
Table 2. Cross-Coupling of Heteroaromatic Chlorides with Ar′MgBr Catalyzed by **3**[a]

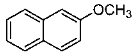
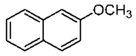
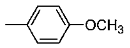
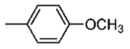
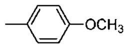
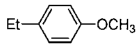
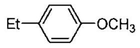
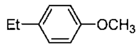
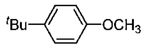
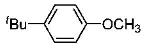
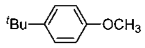
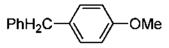
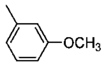
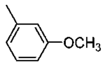
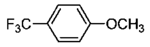
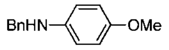
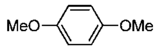
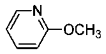
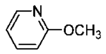


entry	Het-ArCl	R	cat. load	time (h)	yield (%)[b]
1		H	1 0.3 0.1	1 1 1	95 95 86
2		*p*-Me	0.1	1	99
3		2,4,6-Me$_3$	0.1	5	95
4		H	0.1	2	99
5		*p*-Me	0.1	2	94
6		*p*-N(Me)$_2$	0.1	1	95
7		2,4,6-Me$_3$	0.1	2	99
8		H	1	8	89
9		*p*-Me	1	8	93
10		2,4,6-Me$_3$	1	8	29
11		*p*-Me	5	12	98
12		2,4,6-Me$_3$	5	12	99
13		H	5	24	72
14		*p*-Me	5	24	74
15		*p*-Me	5	12	48
16		H	5	12	93
17		*p*-Me	5	12	95
18		2,4,6-Me$_3$	2	24	96[c]
19		H	5	24	74[c]
20		*p*-Me	5	24	88[c]

[a] Reaction conditions: heteroaryl chloride (0.5 mmol), ArMgBr (0.75 mmol), Ni complex (5 mol %), THF (1 mL). [b] Isolated yields, average of two experiments. [c] No reaction was observed in the absence of the Ni catalyst.

Table 3. Cross-Coupling of Aryl Ethers with ArMgBr Catalyzed by (IPr)Ni(allyl)Cl[a]



entry	aryl ether	R	time (h)	yield (%)[b]
1		H	24	82[c]
2		*p*-Me	24	94[c]
3		H	24 12	76[c] 95
4		*p*-Me	12	95
5		*p*-N(Me)$_2$	12	95
6		H	12	88
7		*p*-Me	12	88
8		*p*-N(Me)$_2$	12	80
9		H	12	59[d]
10		*p*-Me	12	67[d]
11		*p*-N(Me)$_2$	12	52[d]
12		*p*-Me	12	85
13		H	12	75
14		*p*-Me	12	81
15		*p*-Me	12	58
16		*p*-Me	12	49
17		H	12	89
18		H	24	71
19		*p*-Me	24	95

[a] Reaction conditions: aryl ether (0.5 mmol), ArMgBr (0.75 mmol), nickel complex (5 mol %), total volume of THF (1 mL). [b] Isolated yields. [c] Reaction performed at room temperature. [d] Reaction performed at 80 °C.

First, we carried out some experiments to optimize the catalyst loading and the reaction time. To our delight, the reaction of 2-chloropyridine and phenylmagnesium bromide was completed in 1 h (89% isolated yield), at room temperature, with only 0.1 mol % of **3** (Table 2, entry 1). Under these conditions 2-chloropyridine and 2-chloroquinoline were coupled effectively with different arylmagnesium bromides within 1−5 h with yields varying from 94 to 99% (entries 1−7). Reactions with the most hindered 2,4,6-Me$_3$C$_6$H$_2$MgBr required longer reaction times to afford quantitative yields of the coupling products (entries 3 and 7). For these reactions, turnover frequency numbers (TOFs) varied from 190 to 990 h^{-1}, the highest values found (to the best of our knowledge) for a KTC reaction with heteroaromatic chlorides catalyzed by nickel.[21] The coupling of 3-chloropyridine, a less reactive substrate, was achieved with 1 mol % of catalyst in 8 h (entries 8−10). 2-Chlorothiophene could also be used as a substrate in this transformation affording very high yields of the coupling products using 5 mol % of the nickel catalyst (entries 11 and 12). The presence of two heteroatoms on the chloride moiety decelerated the reaction, being that it is necessary to increase the catalyst loading to 5 mol % and extend the reaction time to 24 h to complete the coupling processes (entries 13−20). It is interesting to note that couplings of 2-chlorobenzoxazole with both PhMgBr and p-MeC_6H_4MgBr took place in high yield in the absence of the nickel catalyst.

There are only a few reports regarding the use of aryl ethers as electrophiles in nickel-catalyzed KTC reactions.[22] In those examples, nickel phosphine complexes have been the catalysts of choice to carry out the coupling processes. Dankwardt[22c] described a highly active nickel phosphine (PCy_3 or $PPhCy_2$) complex for these transformations, but reactions required a large excesss of Grignard reagents as well as the addition of an excess of phosphine ligand to achieve high conversions. The nickel phosphine catalyst developed by Wang et al.[22e] were very active in the coupling of methoxynaphthalene with aryl Grignards, but the reactions with phenyl methyl ether were performed at high temperatures (120 °C). As far as we are aware, NHC ligands have not been used as ancilliary ligands in this type of reaction. Hence, we sought to apply our IPr−Ni(II) catalytic system to the cross-coupling reactions of anisoles with arylmagnesium reagents. In the presence of 5 mol % of the IPr−Ni(II) precatalyst, 2-methoxynaphthalene reacted with both PhMgBr and p-MeC_6H_4MgBr at room temperature, affording the corresponding products in excellent yields (Table 3, entries 1 and 2). These results prompted us to examine the activation of the C−O bond of less reactive phenyl methyl ethers. Under these conditions, the reaction of p-methyl anisole and PhMgBr produced the expected biaryl in lower yield (76%, entry 3). However, an increase in the reaction temperature to 60 °C resulted in quantitative formation of the coupling product after 12 h (entry 3). This method was successfully applied to different alkyl-substituted anisoles and aryl Grignard reagents furnishing moderate to high yields of biaryls (entries 3−15), although it was ineffective for hindered Grignard reagents such as mesitylmagnesium bromide. A secondary amine functional group on the aromatic ring was also tolerated (entry 16). Under the same reaction conditions, the dual arylation of 1,4-dimethoxybenzene was efficiently achieved (entry 17). In addition, 2-methoxypyridine also combined with both PhMgBr and p-MeC_6H_4MgBr to afford the corresponding coupling products in good yields (entries 18 and 19).

These results suggest that the presence of the IPr ligand facilitates the activation of the C_{Ar}−O bond by the Ni center, allowing the reactions to be carried out without using either a large excess of the Grignard reagent[22c] or high temperatures.[22e]

In conclusion, we have developed a protocol for the KTC reaction of challenging electrophiles such as heteroaryl chlorides and anisoles based on the use of the (IPr)Ni(allyl)Cl complex as the catalyst. Very high TOF values for the coupling of chloropyridines and -quinolines were obtained. In addition, the activation of the C_{Ar}−O bond of substituted phenyl methyl ethers has been successfully achieved under fairly mild reaction conditions.

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Supporting Information Available. Experimental details and spectroscopic data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[21] Nakamura et al. reported a nickel catalytic system with bidentate hydroxy-phoshine ligand which accelerates the KTC reaction by Ni/Mg bimetallic cooperation. A TOF value of 240 h^{-1} was calculated for the reaction of 2-fluoropyridine with PhMgBr (see ref 12a).

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