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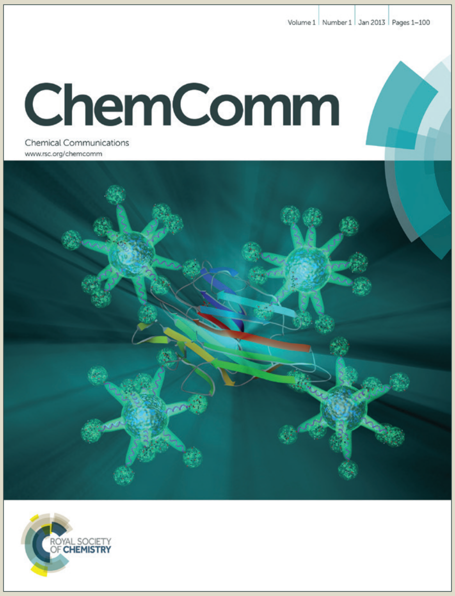

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ARTICLE TYPE

From acetone metalation to the catalytic α-arylation of acyclic ketones with NHC–nickel(II) complexes

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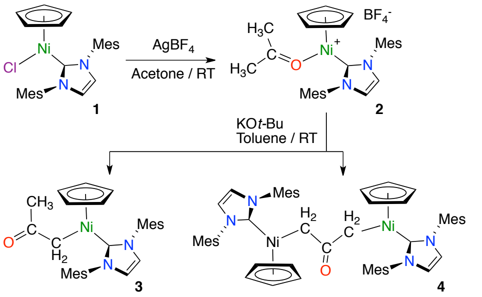
Air-stable N-heterocyclic carbene–nickel(II) complexes at concentrations as low as 1 mol% exhibit high catalytic activity for the α-arylation of acyclic ketones and join a highly restricted list of nickel catalysts for this key reaction. Mechanistic investigations suggest a radical pathway.

The palladium-catalyzed α-arylation of ketones has been the method of choice to access the α-aryl carbonyl motifs found in many organic compounds that possess interesting pharmacological and biological properties.[1] Nevertheless, from the perspective of its use in commercial syntheses, it suffers from the high costs of palladium and of its associated ligands. The search for less expensive catalytic systems, is therefore of interest.[2]

Whilst copper has also received some attention,[1,2] the first-row counterpart of palladium, nickel, is an attractive surrogate to the latter in terms of its abundance and low cost.[3] Moreover, thanks notably to its easy access to multiple oxidation states and to its increased nucleophilic character, it might allow a different and complementary reactivity.[4] Notwithstanding the fact that direct α-arylation of ketone and ester enolates were first reported with this metal in the 1970s,[5,6] nickel systems have, since then, barely been studied. Moreover, almost all of the few reported examples involve the highly air sensitive Ni(COD)$_2$ complex with relatively high loadings – typically ranging from 5 to 10 mol% – and excess ligand.[7] In addition, these systems only achieve the arylation of *cyclic* ketones or esters. Thus, to date, we are aware of only *one example* using a well-defined nickel(II) catalyst precursor (for the arylation of *acyclic* ketones). Nevertheless, here too, relatively demanding conditions (10 mol% catalyst) were required to observe respectable yields.[8]

In this context, we recently reported that cyclopentadienyl (Cp) nickel–N-heterocyclic carbene (NHC) complexes are able to activate C–H bonds of labile acetonitrile[9,10] and acetone[11] ligands in the presence of a strong base. In the latter case, the reaction resulted in the formation of a rare example of nickel-acetonyl complex **3**,[12,13,14] as well as that of a unique example of a dinickel-oxyallyl complex **4** resulting from the double base-promoted nickelation of acetone (Scheme 1).

The isolation of such nickel-C-bound enolate complexes, which are important intermediates in α-arylation reactions of carbonyl derivatives,[1] coupled with the fact they could be protonated back from **4** to **3**,[11] and from **3** to **1**,[15] suggested that this family of CpNi(II)-NHC complexes might be used as catalyst precursors in such C(sp^2)–C(sp^3) coupling through C–H bond cleavage.



Scheme 1 Base-promoted acetone metalation to give the nickel C-bound enolate complexes **3** and **4**

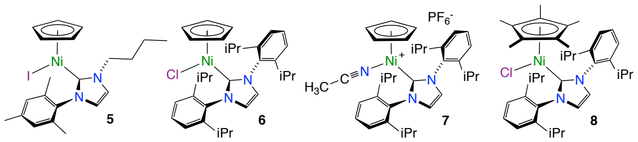
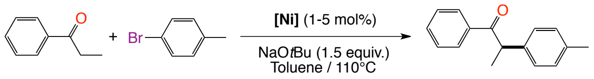


Fig. 1 Selected half-sandwich NHC-nickel complexes

Initial studies focused on the coupling of propiophenone with 4-bromotoluene in toluene at 110 °C in the presence of 1.5 equiv. of NaO*t*Bu as a base and of 5 mol% of complexes **1**, **5**, **6**, **7** or **8** as possible catalytic precursors (Fig. 1). Under these conditions,

Table 1 α-Arylation of propiophenone with 4-bromotoluene catalyzed by complexes **1**, **5-8**[a] and [Ni{(iPr$_2$Ph)$_2$NHC}(PPh$_3$)Cl$_2$].[8]



Entry	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	**1** (5)	24	25
2	**5** (5)	24	0
3	**6** (5)	24	65
4	**7** (5)	24	60
5	**8** (5)	24	61
6	**6** (3)	24	78
7	**6** (1)	24	60
8	**6** (1)	48	> 97
9	[Ni{(*i*Pr$_2$Ph)$_2$NHC}(PPh$_3$)Cl$_2$] (10)	24	65

[a] Reaction conditions: propiophenone (1.2 mmol), 4-bromotoluene (1 mmol), NaO*t*Bu (1.5 mmol), **1**, **5-8** (1-5 mol%) in toluene (3 mL) at 110 °C. [b] Yields determined by GC; average value of two runs.

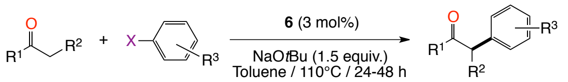
the iodide complex **5**, which we have shown to be highly active in Suzuki coupling,[16] proved to be totally inert (Table 1, entry 2). In contrast, complex **1**,[17] which bears the more bulky 1,3-dimesitylimidazol-2-ylidene (Mes_2NHC), together with a chloride instead of an iodide ligand, gave an encouraging 25% GC yield after 24 h of reaction (entry 1). Switching to the even more bulky 1,3-*bis*-(2,6-diisopropylphenyl)imidazol-2-ylidene containing [($iPr_2Ph)_2NHC$] complex **6**[18] allowed a further yield enhancement to 65% (entry 3). However, using the cationic (ESI†) and Cp*[19] derivatives of **6** yielded no further improvement (entries 4 and 5).

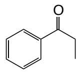
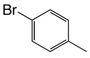
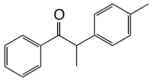
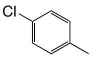
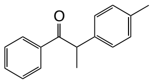
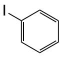
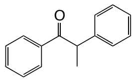
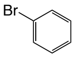
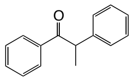
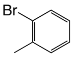
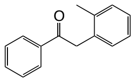
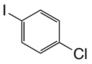
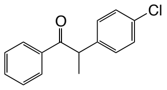
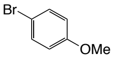
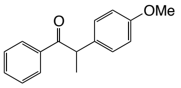
This was encouraging, as this catalytic activity superseded the results reported with the only other known well-defined Ni(II) catalyst precursor for this reaction, the related *trans*-[Ni{$(iPr_2Ph)_2NHC$}$(PPh_3)Cl_2$] (entry 9).[8] Nevertheless, since **6** is known to catalyze aryl halide dehalogenation under similar conditions,[18] and this process may compete with α-arylation, we subsequently decided to test whether the reaction could be further optimized by decreasing the catalyst loading. Satisfyingly, lowering the catalyst loading to 3 mol% allowed a significant yield improvement to 78% (entry 6), and reducing this even further to 1 mol% allowed us to observe full conversion after 48 h of reaction (entry 8). The latter observation also clearly demonstrated that the active catalytic species is long-lived. These results make the **6**/NaO*t*Bu mixture in toluene[20] the most efficient nickel-based system reported to date for the α-arylation of ketone enolates in terms of pre-catalyst loading.[6-8]

With these optimized conditions in hand, we then examined the scope of the α-arylation ketone reaction (Table 2), by on one hand, reacting propiophenone with a series of haloarenes (entries 1-12), and on the other, by reacting 4-bromotoluene with various ketones (entries 13-23). Propiophenone was arylated in good to excellent yields with iodo- and bromo-substituted benzene or *p*-toluene (entries 1, 3, 4). However, it does not react with chloro derivatives (entry 2). This allowed us to obtain 2-(*p*-chlorophenyl)propiophenone selectively in 89% yield from 4-iodo-chlorobenzene (entry 7). The presence of electron-withdrawing or -donating groups on the aryl halide seems to have little influence, and moderate yields were obtained with both electron-rich and electron-poor derivatives after 24 h of reaction (entries 8, 10, 12). Running the reactions for 48 h, nevertheless, allowed us to obtain excellent yields with *p*-methoxy and *p*-*tert*-butyl bromobenzene (entries 9, 11). Finally, the sterically encumbered 2-bromotoluene gave poor yields, even after 48 h of reaction (entries 5, 6).

On the other hand, 4-bromotoluene gave high to excellent yields with various ketones, including substituted propiophenones and dialkyl ketones. Thus, *p*-chloro-propiophenone, the electron-poor *p*-fluoro-propiophenone and the electron-rich *p*-methoxy-propiophenone were arylated in good to excellent yields in 24 and/or 48 h (entries 13-17). In addition, the reaction of 3-pentanone with 4-bromotoluene gave the monoarylated product selectively with up to 79% isolated yield (entries 21 and 23). This latter result is rather surprising and contrasts with the 2:1 mixture of coupling products obtained with 2-methyl-pentan-3-one (entry 23). As observed with propiophenone and 2-bromotoluene (entries 5, 6), the more sterically encumbered *iso*-butyrophenone gave poor yields (entries 18, 19). The *cyclic* indanone yielded no conversion at all (entry 20), probably also for steric reasons. This

Table 2 α-Arylation of ketones with arylhalides catalyzed by **6**.[a]



Entry	Ketone	Aryl halide	Coupling product	Time (h)	Yield (%)[b]
1				24	73
2				24	< 1[c]
3				24	92
4				24	65
5				24	10
6				48	17
7				24	89
8				24	53
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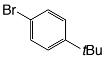
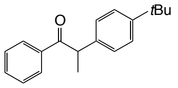
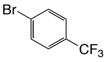
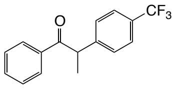
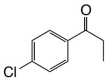
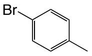
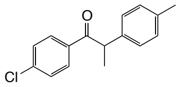
10				24	52
11				48	85
12				24	42
13				24	66
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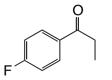
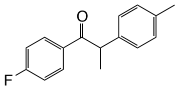
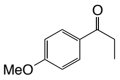
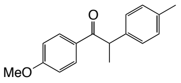
15				24	71
16				24	84
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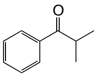
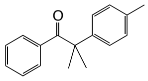
18				24	13
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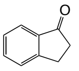
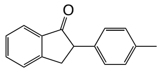
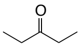
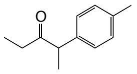
20				24	< 1[d]
21				24	68
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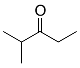
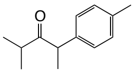
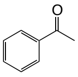
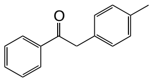
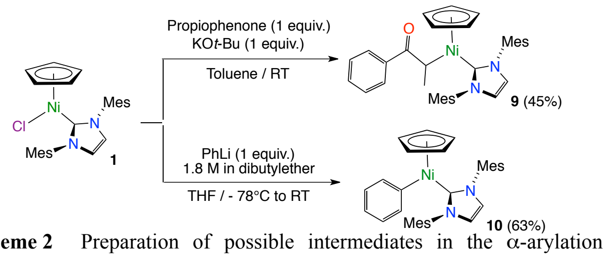
23				24	55[d]
24				24	<1[e]

[a] Reaction conditions: ketone (1.2 mmol), aryl halide (1 mmol), NaO*t*Bu (1.5 mmol), **6** (3 mol%) in toluene (3 mL) at 110 °C for 24 or 48 h. [b] Isolated yields; average value of two runs. [c] Yield determined by GC; average value of two runs. [d] A 2:1 mixture of 2-(*p*-tolyl)-4-methyl-pentan-3-one and 2-(*p*-tolyl)-2-methyl-pentan-3-one was obtained. [e] Aldol condensation products were observed.



Scheme 2 Preparation of possible intermediates in the α-arylation process: the nickel C-bound enolate complex **9** and the nickel–phenyl complex **10**

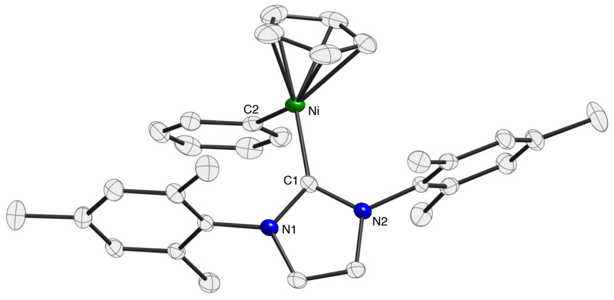
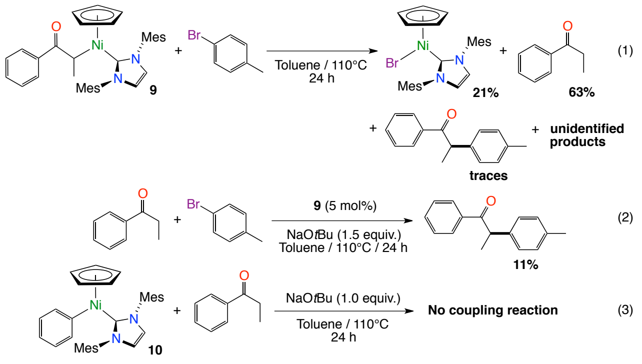


Fig. 2 Molecular structure of **10** showing all non-H atoms. Ellipsoids are shown at the 50% probability level and key atoms are labelled. Selected distances (Å) and angles (°) with esd's in parenthesis: Ni–C1, 1.875(2); Ni–C2, 1.908(2); Ni–Cp$_{cent}$, 1.785; C1–Ni–C2, 95.35(9); C1–Ni–Cp$_{cent}$, 136.45; C2–Ni–Cp$_{cent}$, 128.18.

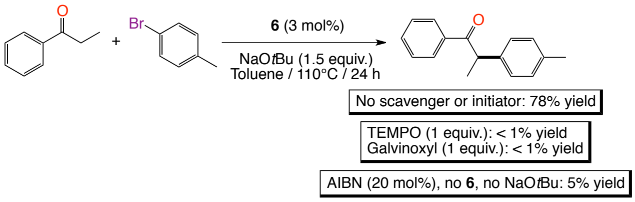
latter result makes our system complementary to Ni(COD)$_2$/ligand-based catalysts, which only achieve the α-arylation of *cyclic* ketones.[7] Finally, acetophenone gave only aldol condensation products (entry 24), as observed by Matsubara et al. with [Ni{(iPr$_2$Ph)$_2$NHC}(PPh$_3$)Cl$_2$].[8]

To get an insight into the mechanism, we first checked whether the α-arylation process was the result of a true homogeneous catalysis by conducting the coupling of propiophenone and 4-bromotoluene in the presence of 100 equivalents of Hg (relative to the nickel – see ESI†). No inhibition was observed, and thus a process catalyzed by nickel particles is unlikely.[21] This being established, we then checked whether a nickel C-bound enolate analogue of **3** could be prepared by the base-induced metalation of propiophenone. Thus, complex **1** was treated with propiophenone in the presence of KO*t*Bu, and [Ni(Mes$_2$NHC){CH(CH$_3$)C(O)Ph}Cp] **9** was isolated as an air- and thermally-sensitive reddish solid in 45% yield (Eq. 1, Scheme 2).‡ Additionally, the phenyl derivative of **1**, [Ni(Mes$_2$NHC)PhCp] **10**, was also prepared as a possible intermediate of the arylation process by reaction of **1** with phenyllithium. It was isolated as air-stable brown crystals in 63% yield (Eq. 2, Scheme 2). Both complexes were fully characterized, and an X-ray diffraction study confirmed the structure of **10** (Fig. 2 and ESI†).

To assess the viability of complexes **9** and/or **10** as intermediate(s) in the catalytic process, we conducted the series of experiments depicted in Scheme 3. The stoichiometric reaction of **9** with 4-bromotoluene in toluene at reflux gave a complicated mixture from which a violet complex, which we have identified as [Ni(Mes$_2$NHC)BrCp] (see ESI†), was isolated in 21% yield (Eq. 1, Scheme 3). The latter would mostly result from the dehalogenation of 4-bromotoluene, as propiophenone was the major organic product, but could also partly result from the coupling of the C-bound propiophenone enolate and 4-bromotoluene, as traces of the expected coupling product were identified by ^{1}H NMR spectroscopy in one organic fraction. To verify this latter hypothesis, we then conducted the coupling of propiophenone and 4-bromotoluene in the presence of a catalytic amount of **9**; an 11% yield of 1-phenyl-2-(*p*-tolyl)-propan-1-one was measured by GC (Eq. 2, Scheme 3). Thus, complex **9** is a possible intermediate in the nickel-catalyzed α-arylation, but the higher yield observed with **1** as a catalyst precursor (Table 1, entry 1) suggests that, at least, some of the product is formed *via* another intermediate and/or *via* a different type of mechanism.



Scheme 3 Assessment of the potential of complexes **9** and/or **10** as intermediate(s) in the catalytic process



Scheme 4 Effect of radical inhibitors and initiators

To assess the possibility of **10** being an intermediate in the α-arylation process, we reacted it under stoichiometric conditions with propiophenone in the presence of NaO*t*Bu in toluene at reflux (Eq. 3, Scheme 3). No coupling product was observed and most of the propiophenone was recovered, thus ruling out **10** as an intermediate.

These results led us to suspect a competing radical mechanistic pathway.[22] Experiments performed in the presence of radical scavengers supported this hypothesis. Thus, the addition of 1 equiv. of TEMPO or galvinoxyl completely inhibited the reaction (Scheme 4). Moreover, a metal-free version of the reaction using AIBN as a radical initiator – although far less efficient – indeed led to some α-arylation (Scheme 4, and Table S3–ESI†). Consequently, we believe that the principal mechanism at work in this nickel-catalyzed α-arylation process is of a radical nature, and that a C-bound ketone enolate derivative of **6**, if involved, has only a minor role.

In summary, we have demonstrated that the inexpensive and easy-to-handle complex, [Ni{(iPr$_2$Ph)$_2$NHC}ClCp] **6**, is an efficient pre-catalyst for the α-arylation of acyclic ketones, and the most productive nickel-based catalyst reported to date. Mechanistic evidence suggests a radical pathway. However, a nickel C-bound ketone enolate intermediate generated by base-promoted metalation may also be involved. Current investigation to achieve the α-arylation of nitriles is underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Synthesis and full characterization of complexes **7**, **9** and **10**, experimental details of all control experiments, catalytic procedure, spectroscopic data and ^{1}H and ^{13}C{^{1}H} spectra of all α-arylation products. CCDC 983811 (**7**) and 983818 (**10**). See DOI: 10.1039/b000000x/

‡ The $(iPr_2Ph)_2$NHC analogue of **9** (*i.e.*: the C-bound propiophenone enolate derivative of **6**) could not be isolated, most probably for steric reasons.

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