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Cross-Coupling Reactions

General and Mild Ni^0-Catalyzed α-Arylation of Ketones Using Aryl Chlorides

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Abstract: A general methodology for the α-arylation of ketones using a nickel catalyst has been developed. The new well-defined [Ni(IPr*)(cin)Cl] (**1c**) pre-catalyst showed great efficiency for this transformation, allowing the coupling of a wide range of ketones, including acetophenone derivatives, with various functionalised aryl chlorides. This cinnamyl-based Ni–N-heterocyclic carbene (NHC) complex has demonstrated a different behaviour to previously reported NHC-Ni catalysts. Preliminary mechanistic studies suggest a Ni^0/Ni^{II} catalytic cycle to be at play.

α-Arylated carbonyl compounds are recognizable structural motifs in biologically active molecules and are of interest to the pharmaceutical industry.[1] Therefore, over the last few years significant efforts have been devoted to the development of more efficient and milder methodologies for their preparation. For example, the use of transition-metal catalysts has allowed one to dispense with the use of stoichiometric amounts of toxic reagents and harsh reaction conditions typically required by more conventional approaches.[2] Since initial reports of the intermolecular palladium-catalyzed α-arylation of ketones by the groups of Miura,[3] Buchwald[4] and Hartwig,[5] this reaction has rapidly become one of the most powerful and atom-economical strategies for the formation of C–C bonds.[1d,6] Moreover, this reaction generates little side-products and makes use of simple and widely available substrates.[1d,6b]

Although palladium-based catalysts are very active in this transformation, the development of new catalytic systems that use less expensive and more earth-abundant metals is a crucial challenge for modern chemists. Despite the importance of this challenge, only a handful of non-palladium systems have been described for this purpose.[7] In recent years, nickel catalysis has received significant attention as a palladium surrogate, and has been employed in a plethora of transformations.[8,9] Since Buchwald and co-workers described the enantioselective nickel-catalyzed α-arylation of α-substituted butyrolactones,[10] nickel has become a valuable (and possibly viable) alternative to the established palladium catalytic systems for the α-arylation of ketones. In spite of this early result, nickel–phosphine systems have shown narrow reaction scope,[11] as only α-substituted cyclic ketones were found to be suitable substrates.[10,11] Two examples of well-defined NHC-based (NHC: N-heterocyclic carbenes) nickel complexes have been reported as active pre-catalysts for this transformation.[12] Despite the improvement that these protocols provide, both suffer from several shortcomings, particularly regarding a narrow reaction scope limited to the coupling of aryl bromide derivatives with propiophenone.

Very recently, Itami and co-workers have described a challenging α-arylation of ketones with aryl pivalates using a $[Ni(cod)_2]$/biphosphine catalytic system.[13] However, the use of high catalyst loading (10 mol%), a large excess of the ligand (20 mol%) and high temperatures (150 °C), hamper the general use of this methodology. Studies conducted by Ritleng and co-workers showed that the [Ni(NHC)CpCl]-catalyzed (NHC = N-heterocyclic carbene; Cp = cyclopentadienyl) reaction might proceed via a radical pathway.[12b] However, the mechanism regarding the nickel-catalyzed α-arylation of ketones is not yet clearly defined and might, in the end, be dependent on the Ni source used.

Taking into account the state-of-the-art, we took up the challenge of developing a general nickel-catalyzed α-arylation of ketones using easily accessible, widely available and inexpensive aryl chlorides, under significantly milder reaction conditions. Our approach made use of our prior experience with more easily initiated palladium cinnamyl NHC-based catalysts[14] and of the reported high activity displayed by [(dppf)Ni(cin)Cl] in the Suzuki–Miyaura cross coupling.[15] We describe here the synthesis of [Ni(NHC)(cin)Cl] complexes and their application in the α-arylation of ketones, in a general and efficient nickel-catalyzed procedure for this transformation using aryl chlorides.

The synthesis of [Ni(NHC)(cin)Cl] complexes with SIPr, IPr, IPr* and IPr^{*OMe} as NHC ligands,[16] was accomplished following the protocol described by Sigman for the IPr derivative.[17] This straightforward, one-pot procedure provided the desired Ni complexes in good yields (Scheme 1).

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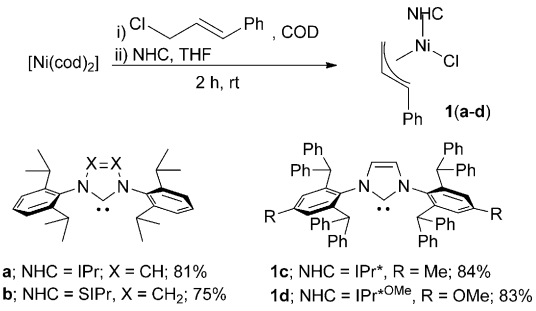


Scheme 1. Synthesis of the well-defined [Ni(NHC)(cin)Cl] (**1**)complexes.

All complexes (**1**) were fully characterized by NMR spectroscopy, and their purity was confirmed by elemental analysis. To unequivocally establish the atom connectivity in **1**, the molecular structures of **1c**[18] and **1d**[19] (see the Supporting Information) were elucidated by X-ray diffraction analysis of single crystals (Figure 1).

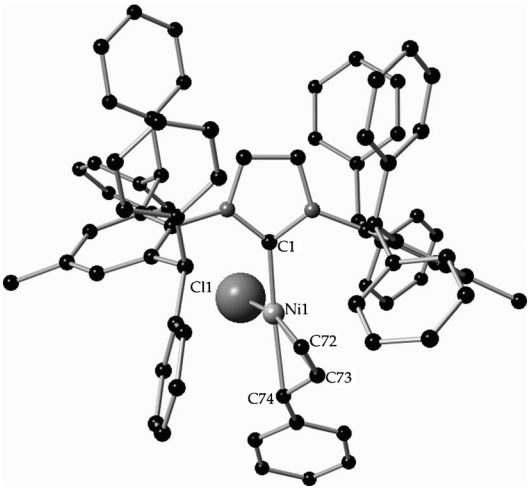
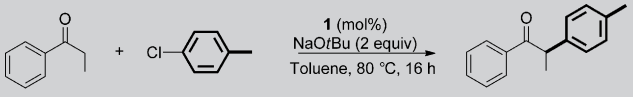


Figure 1. Molecular structure of **1c**. Selected bond lengths [Å] and angles [°]: Ni1–Cl1 2.1684(9), Ni1–C72 1.997(3), Ni1–C74 2.123(4), Ni1–C1 1.903(3), Ni1–C73 1.982(4); Cl1-Ni1-C1 96.16(8), Cl1-Ni1-C74 96.66(10), C1-Ni1-C74 70.58(14).

Complete optimization studies defining best solvent, base and temperature for the coupling of propiophenone (**2a**) and *p*-chlorotoluene (**3a**) as model reaction, using the nickel catalyst bearing the IPr* ligand (**1c**) were next performed (see Supporting Information for details). The use of NaO*t*Bu in toluene provided optimum results, giving full conversion at 80 °C after 16 h. It should be noted that 2 equivalents of NaO*t*Bu are required, as lower amounts of base reduce the yield. Then, the role of the ligand (**1a–d**) was tested (Table 1). Less sterically demanding NHCs (IPr and SIPr) afforded low conversion to the desired product in both cases (entries 1 and 2). The bulkier IPr*-based ligands (IPr* and IPr*^{OMe}) were required to obtain full conversion (entries 3 and 4). Only at low catalyst loadings (1 mol%) was it possible to observe a difference in the reactivity between IPr* and IPr*^{OMe}, the former being slightly more

Table 1. Nickel-catalyzed α-arylation of propiophenone optimization.[a]



2a 3a 4a

Entry	**1** [mol%]	Conv. [%][b]	Yield [%][c]
1	[Ni(IPr)(cin)Cl] (**1a**) (3 mol%)	35	–
2	[Ni(SIPr)(cin)Cl] (**1b**) (3 mol%)	30	–
3	**[Ni(IPr*)(cin)Cl] (1c) (3 mol%)**	**99**	**92 (90)**[d]
4	[Ni(IPr*^{OMe})(cin)Cl] (**1d**) (3 mol%)	99	89
5	[Ni(IPr*^{OMe})(cin)Cl] (**1d**) (1 mol%)	70	–
6	[Ni(IPr*)(cin)Cl] (**1c**) (1 mol%)	80	–
7	[Ni(IPr*)(cin)Cl] (**1c**) (2 mol%)	92	84
8[e]	[Ni(IPr*)(cin)Cl] (**1c**) (3 mol%)	99	80

[a] Reaction conditions: propiophenone (**2a**) (1 mmol, 2 equiv), 4-chlorotoluene (**3a**) (0.5 mmol, 1 equiv), NaO*t*Bu (1 mmol, 2 equiv), **1** (mol%), in toluene (2.5 mL). [b] Conversion of the 4-chlorotoluene (**3a**), as measured by GC. [c] NMR yields using dimethyl malonate as internal standard. [d] Isolated yield in parentheses. [e] Using 4-bromotoluene as coupling partner.

active than the latter (entries 5 and 6). Under the optimized conditions, 3 mol% of **1c** were sufficient to obtain full conversion (entry 3 vs. 7). Notably, the use of *p*-bromotoluene as coupling partner consistently gave lower yields compared to reactions involving its chloride analogue (entry 3 vs. 8). These results suggest that a different mechanism might be involved in the NHC cinnamyl-based nickel-catalyzed reaction compared to the previously reported Cp-based family of complexes, which are not reactive with aryl chlorides.[12b] Under the optimized reaction conditions, a wide variety of ketones (**2**) and aryl chlorides (**3**) were examined (Table 2). Firstly, several aryl chorides with varied electronic and steric properties were tested. Electron-donating groups in either *para* or *meta* position led to the arylated ketones in excellent isolated yields (**4a**, **4b** and **4g**), whereas electron-withdrawing groups such as CF_3 (**4c**) proved to be less suitable for this transformation. Hindered aryl chlorides (**4e** and **4f**) were coupled less efficiently, although reasonable yields (60% and 68%, respectively) could be obtained. Additionally, 1-chloronaphtalene led to the desired product in 77% (**4j**). These coupling reaction outcomes represent the best results so far when using hindered aryl chlorides for the nickel-catalyzed α-arylation of ketones, even when aryl bromides are considered as coupling partners.[12] Ketone- and methylsulfone-containing aryl chlorides, despite their relative sensitivity towards basic conditions, led to the corresponding aryl ketones with 89% and 65% yields, respectively (**4i**, **4d**). A benzodioxole chloride derivative reacted very efficiently (**4h**), and nitrogen- or sulfur-containing heterocycles were tolerated (**4k** and **4l**). The nature of the ketone was also studied. Electron-rich propiophenone derivatives proved suitable for this transformation (**4m**, 79%). Moreover, the analogous cyclohexanone derivative led to the formation of **4n** in high yield. In contrast, electron-poor ketones proved inadequate and no conversion to the desired product was observed using *p*-CF_3-substituted propiophenone (see the Supporting Information). To our delight, aliphatic ketones were also suitable

for the reaction, leading to the desired mono-arylated product in good yield (**4o**). These results encouraged us to further extend the scope of the system and test the challenging mono arylation of acetophenone derivatives. We were pleased to find that electron-rich acetophenones were well tolerated, giving good (67%) and very good yields (86%) for the *p*-NMe_2 (**4q**) and *p*-OMe (**4p**) substituted derivatives, respectively, without any observable formation of bis-arylated products. However, non-activated acetophenones led to complex mixtures (see the Supporting Information). An electron-rich naphthalene derivative led successfully to the desired adduct (**4t**). *p*-OMe acetophenone was also tested in the presence of electron-rich aryl chlorides (**4r** and **4u**), showing good efficiency. The coupling with a hindered 2,6-disubstituted chloroarene was also possible (**4s**).

Several experiments were carried out in order to gain insight into the reaction mechanism. Stoichiometric reactions involving [Ni(IPr*)(cin)Cl] (**1c**) and NaO*t*Bu, in the presence ([Eq. (1)]) or absence of chlorotoluene ([Eq. (2)]), did not proceed, and in both cases the starting materials were recovered. To our delight the stoichiometric reaction of [Ni(IPr*)(cin)Cl] with propiophenone and NaO*t*Bu, in the absence of the aryl chloride ([Eq. (3)]), gave, as major species (84% isolated yield), the regioisomeric mixture (75:25) of the allylic substitution products between the propiophenone nucleophile and the cinnamyl ligand **5** and **5′**.

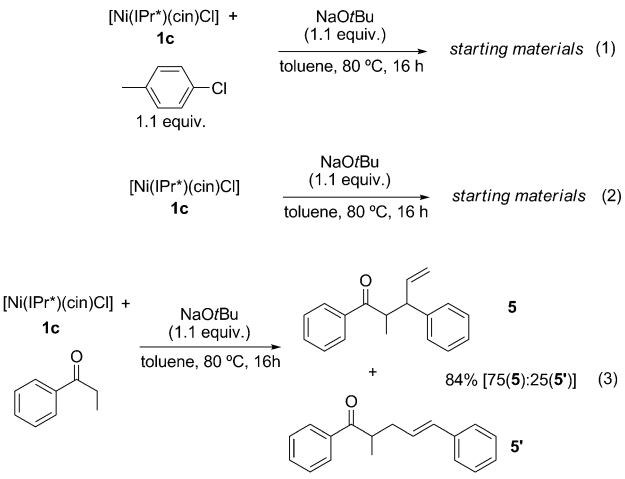
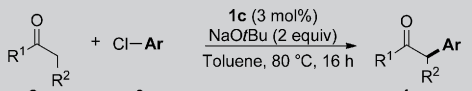
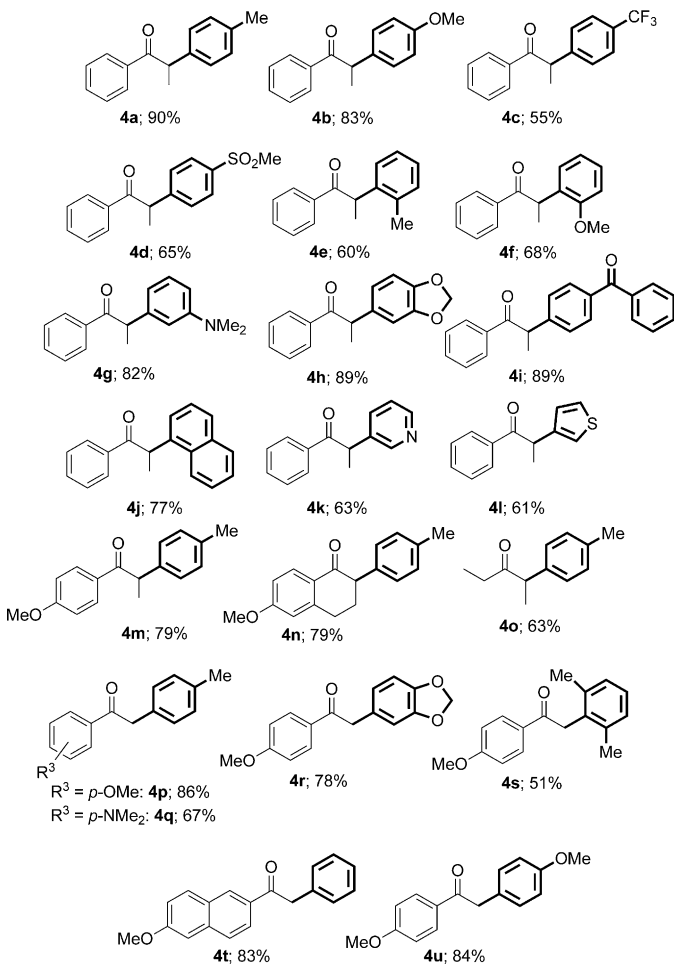


Table 2. Substrate scope for the [Ni(IPr*)(cin)Cl] catalyzed α-arylation of ketones.[a]

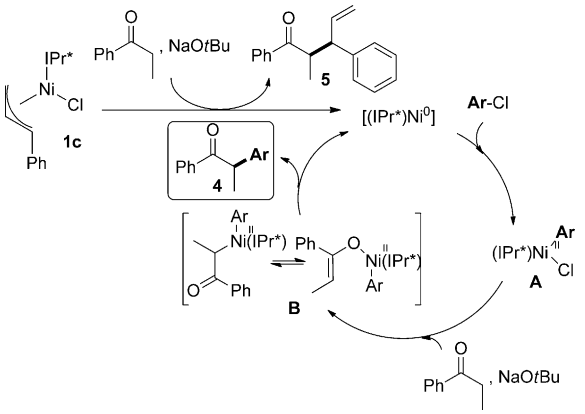




[a] Reaction conditions: ketone (**2**) (1 mmol, 2 equiv), chloroarene (**3**) (0.5 mmol, 1 equiv), NaO*t*Bu (1 mmol, 2 equiv), **1c** (3 mol%), in toluene (2.5 mL). Isolated yields.

The isolation of these products (**5** and **5′**), together with the fact that chloride derivatives performed comparably to bromide analogues, suggest to us that the activation of the Ni^{II} pre-catalyst takes place via a nucleophilic attack of the enolate formed in situ,[20] generating a Ni^0 active species, which may involve the formation, if only as a transient species, of [(η^6-toluene)Ni(IPr*)] under catalytic conditions.[21] Oxidative addition leads to Ni^{II} intermediate **A**, which transmetalates in the presence of another molecule of enolate (**B**), allowing the final reductive elimination to achieve the C–C bond formation (Scheme 2). Further investigations are currently ongoing in our laboratory to completely elucidate the mechanism of this coupling reaction using nickel catalysts and to expand the scope of this reaction to other carbonyl-containing compounds.

In summary, we have described, for the first time, a general nickel-catalyzed methodology for the α-arylation of ketones using aryl chlorides as coupling partners at relatively low loadings of Ni (3 mol%). Various coupling partners, including challenging acetophenone derivatives and functionalized aryl chlorides, were successfully coupled. In addition, stoichiometric reactions permitted the isolation of the pre-catalyst activation products (**5** and **5′**), strongly suggesting that a Ni^0/Ni^{II} catalytic cycle is responsible for the unique reactivity displayed by this catalyst.



Scheme 2. Ni^0/Ni^{II} proposed catalytic cycle.[1d,6a]

Acknowledgements

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Keywords: aryl chlorides · cross-coupling reactions · ketone arylation · N-heterocyclic carbenes · nickel · synthetic methods

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[16] SIPr = 1,3-bis- (2,6-diisopropylphenyl)imidazolin-2-ylidene; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; IPr* = *N*,*N*-bis[2,6-bis(diphenylmethyl)-4-methylphenyl]imidazole-2-ylidene; IPr^{*OMe} = *N*,*N*-bis[2,6-bis(diphenylmethyl)-4-methoxyphenyl]imidazol-2-ylidene.

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[18] CCDC 1030283(**1c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] CCDC 1030284 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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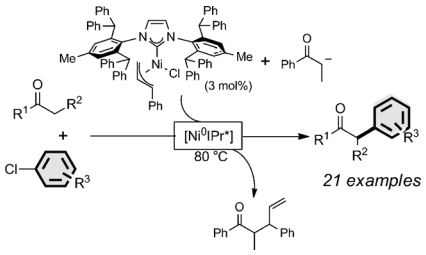
A Ni–N-heterocyclic carbene pre-catalyst was shown to be very active in the α-arylation of ketones, coupling a broad range of aryl chlorides and ketones. The isolation of the activation product resulting from the nucleophilic attack of the enolate onto the nickel pre-catalyst suggests a Ni^0/Ni^{II} catalytic cycle is at play.



Cross-Coupling Reactions

*J. A. Fernández-Salas, E. Marelli, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan**

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General and Mild Ni^0-Catalyzed α-Arylation of Ketones Using Aryl Chlorides