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Nickel-Catalyzed Mono-Selective α-Arylation of Acetone with Aryl Chlorides and Phenol Derivatives

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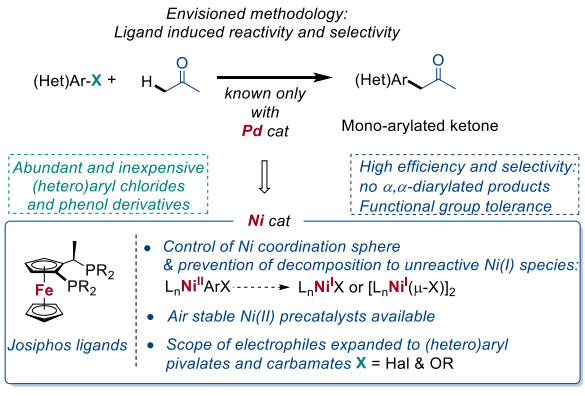
Abstract: The challenging nickel-catalyzed mono α-arylation of acetone with aryl chlorides, pivalates and carbamates has been achieved for the first time. A nickel/Josiphos-based catalytic system is shown to feature unique catalytic behavior allowing highly selective formation of the desired mono α-arylated acetone. The developed methodology was applied to a variety of (hetero)aryl chlorides including biologically relevant derivatives. The methodology has been extended to the unprecedented coupling of acetone with phenol derivatives. Mechanistic studies allowed the isolation and characterization of key Ni(0) and Ni(II) catalytic intermediates. The Josiphos ligand is shown to play a key role in the stabilization of Ni(II) intermediates to allow a Ni(0)/Ni(II) catalytic pathway. Mechanistic understanding was then leveraged to improve the protocol using an air-stable Ni(II) pre-catalyst.

Direct functionalization of ubiquitous carbonyl compounds represents a very powerful class of carbon-carbon bond forming reactions.[1] In this respect, significant advances have been achieved in the development of efficient catalytic methods for the α-arylation of substituted carbonyl compounds, particularly with transition metal catalysts, *via* the formation of enolate intermediates.[1,2] This methodology has proven applicable to various CH-acidic nucleophiles such as ketones, nitriles, esters, aldehydes and amides.

In striking contrast, the functionalization of simple and readily accessible compounds such as acetone has been under-developed and appears much more challenging.[3] Most of the catalytic systems developed for the α-arylation of carbonyl moieties are not active with acetone which bears much less acidic C–H bonds. To date, only very few efficient catalytic systems, all based on noble palladium catalysts, have been recently reported for the selective mono-arylation of acetone, using aryl halide electrophiles.[4] From an economic point of view, especially when considering the industrial interest in employing the monoarylation of acetone for the synthesis of pharmaceutically relevant substrates,[5] the development of more sustainable and cost-effective transition metals, such as nickel, would provide a highly valuable alternative. However, the transposition of this technology to nickel catalysis has proven highly challenging. Recently, only a few examples of nickel catalyzed α-arylation of substituted ketones have been reported,[6,7,8] but arylation of acetone remains yet undocumented using nickel catalysts. To fill this methodological gap, we aimed to develop a nickel-catalyzed mono-selective α-arylation of acetone with aryl chlorides as well as phenol derivatives. The use of nickel catalysts for this challenging transformation may raise some problems to be overcome. The main problem to address stands in the documented propensity of Ni species to readily transmute from Ni(II) to inefficient Ni(I) species.[9] The exclusive mono-arylation of acetone is also challenging. The resulting mono-arylated ketone products featuring more acidic CH bonds are prone to further arylation, making the selective mono α-arylation of acetone difficult.[10] In the present work, we show that these challenges could be addressed thanks to the use of an appropriate ancillary ligand, and report the development of an efficient Ni/Josiphos based catalytic system for the challenging monoarylation of acetone (Scheme 1).

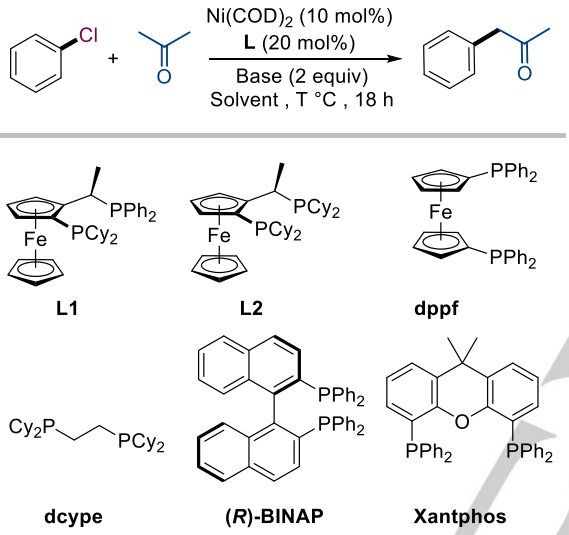


Scheme 1. Current development of nickel catalyzed α-arylation of acetone.

The development of this catalytic system relied on mechanistic studies guided by several isolated key intermediates. Comparative studies with other nickel complexes afforded some rationale to the unique reactivity of nickel/Josiphos combination. From the mechanistic rationale gained in this study, we were able to develop an air stable Ni(II)/Josiphos complex for a simplistic and practical methodology.

We initially set out to investigate the feasibility of nickel-catalyzed α-arylation of acetone with chlorobenzene under various conditions (base, solvents, temperature) (Table 1 and SI). The reaction was examined using a selection of chelating phosphine ligands reported to favor Ni(0)/Ni(II) catalysis.[6,8b,11]

Table 1. Optimization of reaction conditions.[a]



Entry	Ligand	Solvent	Base	Yield (%)[b]
1	**L1**	1,4-dioxane	CsF	43
2	**L1**	Diglyme	CsF	36
3	**L1**	DME	CsF	59
4	**L1**	Toluene	CsF	62
5	**L1**	**$PhCF_3$**	**CsF**	**72**
6	**L2**	$PhCF_3$	CsF	22
7	**–**	$PhCF_3$	CsF	0
8	**dppf**	$PhCF_3$	CsF	trace
9	**dcype**	$PhCF_3$	CsF	trace
10	**(*R*)-BINAP**	$PhCF_3$	CsF	0
11	**Xantphos**	$PhCF_3$	CsF	trace
12[c]	**L1**	$PhCF_3$	CsF	40
13	**L1**	$PhCF_3$	Cs_2CO_3	70
14	**L1**	$PhCF_3$	NaO*t*Bu	33
15	**L1**	$PhCF_3$	K_3PO_4	48
16[d]	**L1**	$PhCF_3$	CsF	41

[a] Reactions were performed with PhCl (0.3 mmol, 1equiv), acetone (9 mmol, 30 equiv), Base (0.6 mmol, 2 equiv), $Ni(COD)_2$ (0.1 equiv), ligand (0.2 equiv) and solvent (1 mL). The reaction mixture was stirred, unless otherwise noted, for 18 hours at 120 °C. [b] Determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction performed with 10 mol% of ligand L1. [d] Reaction performed at 100 °C.

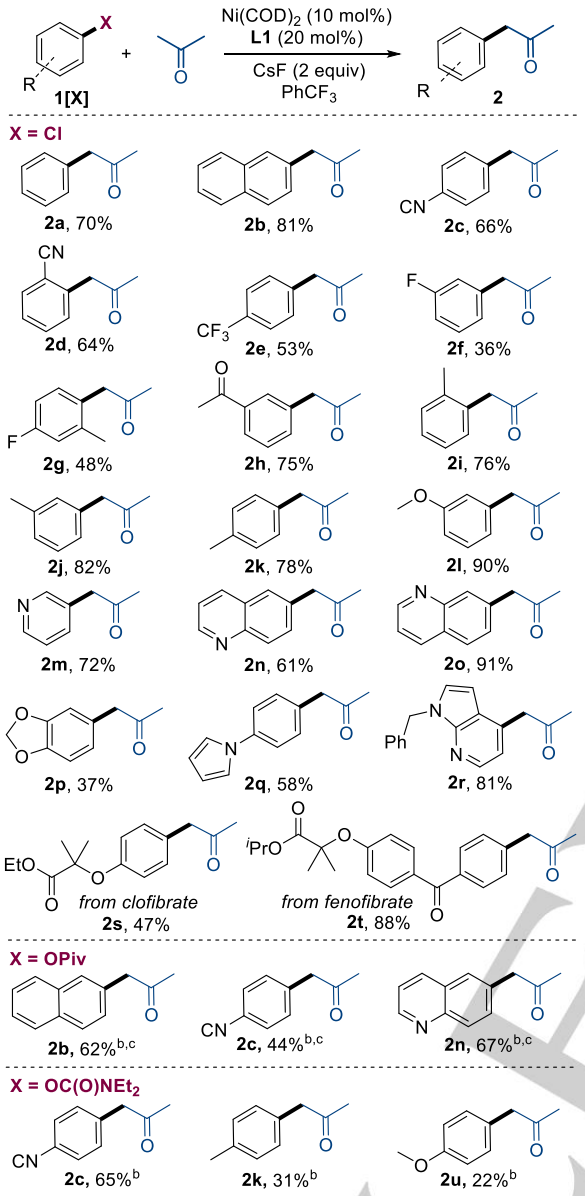
We found to our delight that the combination of $Ni(COD)_2$ and Josiphos ligands is an efficient catalytic system for this transformation. Such class of ligands has been recently shown to be efficient for Ni-catalyzed cross-coupling of small molecules including ammonia,[12] but they have not been used for nickel-catalyzed arylation of carbonyl derivatives.

The best result was obtained when the reaction was carried out in trifluorotoluene using CsF as a base, 10 mol% of $Ni(COD)_2$ and 20 mol% of Josiphos (**L1**). Under these conditions the desired product was obtained in 72% isolated yield (Table 1, entry 5). Remarkably, the mono α-arylation product was obtained selectively without any traces of bis-arylation product. The yield of the reaction is significantly reduced when an equimolar amount instead of 2 equiv of ligand **L1** is used (Table 1, entry 12). Decreasing the temperature to 100 °C led to significant diminution of the yield (Table 1, entry 16). Control experiment carried out in the absence of the ligand resulted in no product formation (Table 1, entry 7). More strikingly, all the other ligands evaluated, including diphosphine type ligands such as dppf, BINAP and Xantphos, were ineffective under these reaction conditions.

With optimal conditions in hand, the scope of the reaction was examined with a wide range of aryl chlorides, including extended π-electron 2-chloronaphtalene, chloroarenes bearing electron-withdrawing or electron-donating substituents, and heteroarenes. In each case examined, mono-arylated product was obtained selectively as the sole product of the reaction (Table 2). The arylation of acetone with electron-poor aryl chlorides could be achieved in moderate to good yields. *Para*- and *ortho*-substituted cyano aryl chlorides were converted selectively with good yields (**2c**, **2d**). Fluorinated compounds were also obtained in 30% yield (**2e–2g)**. Full selectivity toward the arylation of acetone was achieved with 3-chloroacetophenone affording compound **2h** in a very good isolated yield. Interestingly, employment of electron-rich aryl chlorides delivered the corresponding products in excellent yields (**2i-2l**). The cross-coupling could tolerate pyridines, quinolines (**2m**–**2o**), benzodioxoles (**2p**)**,** pyrroles (**2q**), and azaindoles (**2r**), allowing the isolation of heteroarylation products in good to excellent yields. Furthermore, the developed methodology was also amenable to the functionalization of biologically relevant aryl chlorides. Indeed, Clofibrate (Atromid-S®) as well as Fenofibrate (TriCor®), both used for treatment of abnormal blood lipid levels, were successfully converted to the corresponding mono α-arylated products with moderate to excellent yields (**2s** and **2t**).

In order to further emphasize the complementarity of this nickel-catalyzed process with the precedent methods using palladium catalysts,[4] the scope of the electrophiles was expanded to phenol derivatives.[13] Very satisfyingly, a primary selection of aryl pivalates as well as aryl carbamates were found to be suitable substrates for arylation providing the corresponding products in moderate to good yields (X = OPiv, **2b, 2c, 2n;** X = $OC(O)NEt_2$, **2c**, **2k, 2u**). Although the conditions have not been optimized with phenol derivatives, it is worth noting that the coupling reaction is not limited to π-extended aryl substrates.[14]

Table 2. Substrate scope.[a]



[a] Reactions were performed with ArCl (0.3 mmol, 1 equiv), acetone (9 mmol, 30 equiv), CsF (0.6 mmol, 2 equiv), $Ni(COD)_2$ (0.1 equiv), ligand (0.2 equiv) and $PhCF_3$ (1 mL). The reaction mixture was stirred for 18 hours at 120 °C. Yields shown are those of isolated products. [b] Yields determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Cs_2CO_3 instead of CsF.

Having examined the scope and the complementarity of the nickel-catalyzed acetone α-arylation methodology, we turned our attention to the reaction mechanism. We were particularly interested in delineating the key influence of the ancillary ligand. Based on previous mechanistic work on nickel-catalyzed cross-coupling reactions with diphosphine ligands,[6,11a] it is reasonable to envision a Ni(0)/Ni(II) pathway. However, the feasibility of such a mechanism for the challenging α-arylation of acetone under the developed catalytic conditions raises some questions about *(i)* the exact structure and the reactivity of Ni(0) species toward aryl chloride and pivalate substrates in the presence of an excess of coordinating and non-sterically hindered acetone and *(ii)* the stability and reactivity of Ni(II) intermediates at high temperature (Figure 1). The reaction of $Ni(COD)_2$ with an excess of chelating Josiphos ligands, as carried out in our catalytic protocol, may result in the formation of 4-coordinate $(Josiphos)_2Ni(0)$ species, raising the question of its reactivity in catalysis.[15]]

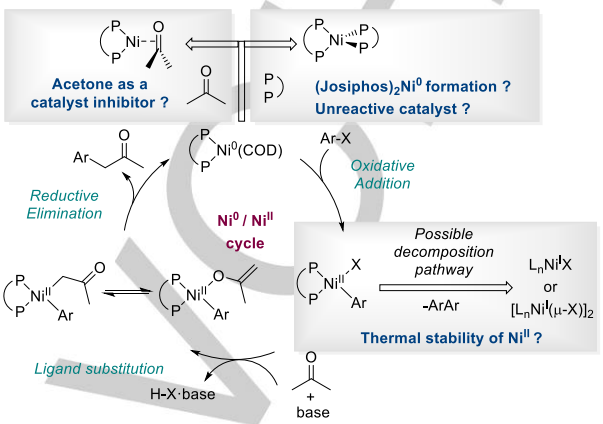


Figure 1. Proposed catalytic cycle with potential side reactions.

Using the same conditions as in the catalytic protocol, we performed the reaction between $Ni(COD)_2$ and 2 equivalents of the ligand **L1** in trifluorotoluene. The reaction occurred at room temperature and resulted in the rapid precipitation of complex **I** [(**L1**)Ni(COD)]. Consistently, treatment of $Ni(COD)_2$ with 1.1 equivalent of the ligand also afforded rapid precipitation of complex **I** from trifluorotoluene, which was isolated in 88% yield. The complex was fully characterized in solution and in the solid state. Both NMR spectroscopic data and X-Ray diffraction analysis revealed the exclusive formation of a 4-coordinate nickel(0) species surrounded by the bidentate Josiphos ligand and the COD ligand featuring κ^4 coordination (Figure 2A). The excess of the ligand remained free in the solution, as indicated by $^{31}P\{^1H\}$ NMR analysis of the reaction mixture at room temperature. However, heating the solution of $Ni(COD)_2$ and 2 equivalents of **L1** in trifluorotoluene at 90°C for several hours resulted in the formation of complex **I** and a new species corresponding to $(Josiphos)_2Ni$, as indicated by $^{31}P\{^1H\}$ NMR spectroscopy and HRMS analysis, in a 1:1 ratio (Figure S6).[16]

Then, we evaluated the reactivity of complex **I** with 4-chlorobenzonitrile, chlorobenzene and 4-cyanophenyl pivalate. These smoothly and quantitatively converted to the desired oxidative addition complexes **IIa**, **IIb** and **IIc**, which have been isolated in 98%, 65% and 62% yields, respectively, and structurally characterized (Figure 2B, S2, S3).[16] As expected, the less active unsubstituted chlorobenzene required heating at 80 °C to obtain similar yields. Of note, the same results were observed when the reaction of complex **I** with chlorobenzene was carried out in the presence of high excess of acetone, showing that acetone does not inhibit the oxidative addition process.[17] Moreover, addition of chlorobenzene to a 1/1 mixture of **I** and $(\mathbf{L1})_2Ni(0)$ led to quantitative formation of the oxidative addition product **IIb** (Figure S7), indicating that $(\mathbf{L1})_2Ni(0)$ is a reactive species.[15, 18]

In all cases, the ensuing Ni(II) aryl complexes were found to be stable both in the solid state and in solution. Remarkably, in

contrast with previously reported Ni(II) aryl complexes featuring BINAP,[6,19] dppf,[11a,20] or Xantphos[21] ligands, complexes **IIa,b,c** are stable in solution even upon heating at 80 °C for several hours.[16] Of note, bisphosphine ligated Ni(II) aryl intermediates generally require *ortho*-substituted aryl moieties to feature enhanced stability,[22] and very rapid decomposition to Ni(I) species is observed with non-substituted phenyl moieties.[11a,19,21] Very satisfyingly, Nickel(II) complex **IIa** proved to be a reactive intermediate for the coupling with acetone affording the corresponding product in high yield (Figure 2C).

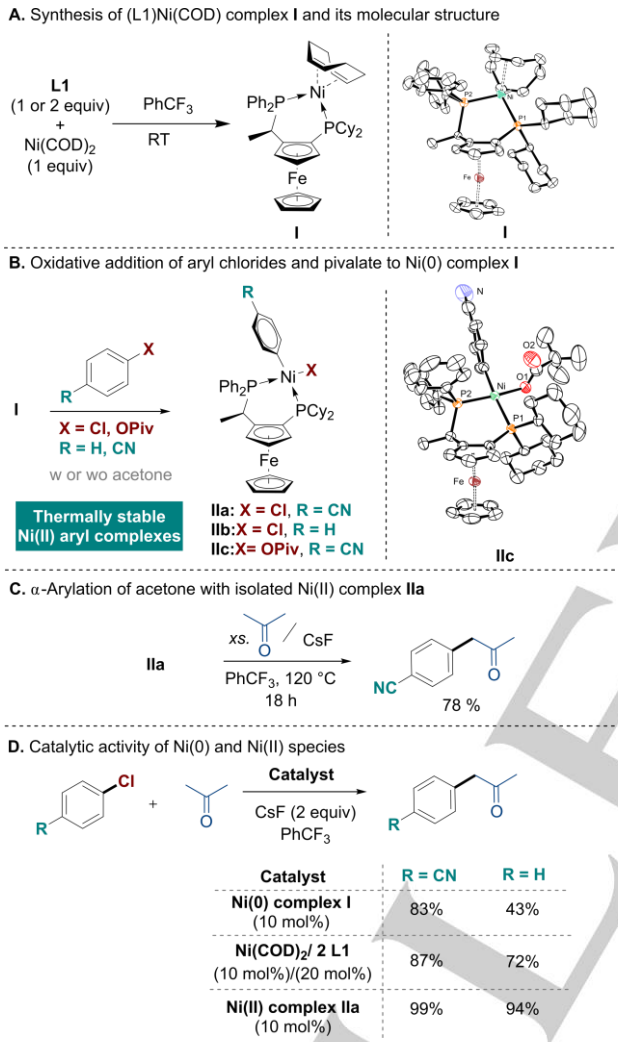
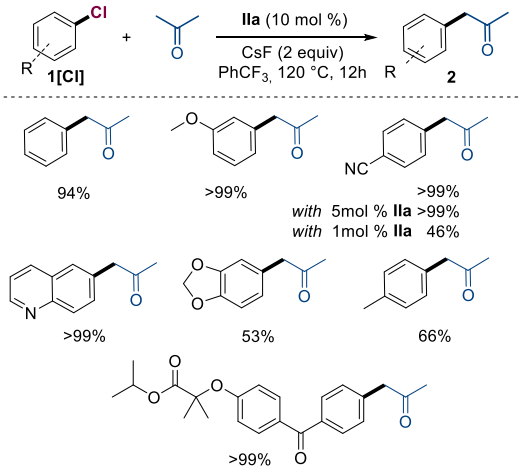


Figure 2. (A) Synthesis of (L1)Ni(COD) complex **I** (left) and molecular structure of **I** (right; hydrogen atoms are omitted for clarity). (B) Oxidative addition of aryl chlorides and pivalate to Ni(0) complex **I** with and without excess of acetone (left) and molecular structure of **IIc** (right; hydrogen atoms and Et_2O solvent molecule are omitted for clarity). (C) Isolated reactivity of Ni(II) complex **IIa** with acetone in the presence of CsF. (D) Comparative catalytic activities of nickel species.

These results emphasize that chelating Josiphos ligand **L1** plays a key role in the stabilization of the Ni(II) aryl intermediates towards decomposition to Ni(I) species. Therefore, the higher propensity of Josiphos ligand to stabilize Ni(II) intermediates compared to other diphosphines such as dppf or BINAP, is likely to be the key difference to achieve the challenging coupling reaction of aryl halides and pivalates with acetone. Finally, we evaluated the catalytic behavior of Ni(0) and Ni(II) species for the coupling of acetone with 4-chlorobenzonitrile and chlorobenzene (Figure 2D). In both cases, monitoring of the reactions by $^{31}P\{1H\}$ NMR spectroscopy indicated the presence of L1Ni(II)-Aryl species as the catalysts resting state.[16] Overall, mechanistic studies support the occurrence of Ni(0)/Ni(II) catalytic cycle as the main pathway. The influence of the second equivalent of ligand *vs.* Ni was analyzed by comparing the catalytic activity of complex **I** and $Ni(COD)_2$/2Josiphos (Figure 2D). While very similar results were obtained with 4-chlorobenzonitrile, the reaction yield is higher with electron neutral chlorobenzene with $Ni(COD)_2$/2Josiphos (72% yield *vs* 43% with **I**). These results indicate that $(\mathbf{L1})_2$Ni(0) intermediate, generated in-situ during catalysis with an excess of ligand, is catalytically active and suggest that the second equivalent of ligand may enhances the stability of Ni(0) species.[16] In the case of 4-chlorobenzonitrile, the stability and activity of the Ni(0) species can be improved by the η^2-coordination of the cyano group of the substrate.[11a,12a]

Remarkably, the mono α-arylation product was obtained selectively without any traces of bis-arylation product. The selectivity of the catalytic systems may arise from the sterically hindered Josiphos ligand that prevent coordination of bulky ketones to the **L1**Ni(II)-aryl intermediate. In line with this hypothesis, the reaction of 4-chlorobenzonitrile with *1-(p*-tolyl)propan-2-one **2k** catalyzed by Josiphos/Ni system did not occur. The catalytic system was also unreactive with a series of bulky ketones (table S12).[16] The nickel(II) complex **IIa** was also evaluated as a catalyst under the standard conditions using 10 mol% catalytic loading. Interestingly, compared to nickel(0) species, the aryl nickel complex **IIa** presented enhanced catalytic activity, leading to quantitative coupling reactions with both aryl chlorides. Based on these observations, the catalytic cross-coupling of a set of aryl chlorides was re-evaluated using complex **IIa** as a pre-catalyst (Scheme 2).[12c] From a practical point of view, Ni(II) complex **IIa** offers several advantages: it is air stable, commercially available and features enhanced catalytic efficiency. Furthermore, the reaction can proceed at lower temperature (95% yield at 80 °C), at shorter reaction time (65% yield after 1h) and the catalyst loading could be reduced down to 1 mol% while maintaining substantial activity.[18]



Scheme 2. Improved reaction conditions and catalytic efficiency with air stable nickel (II) complex **IIa**. Reactions were performed under the standard conditions on 0.3 mmol scale. Yields determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

In conclusion, we present herein an unprecedented methodology for the selective mono-α-arylation of acetone with (hetero)aryl chlorides and phenolic derivatives using earth abundant and cost effective nickel complexes as efficient catalysts. Key to implementing this methodology was the privileged structure of Josiphos ligand **L1**. The catalytic system demonstrated a high compatibility with several functional groups and the desired products are usually obtained in good to excellent yields. Interestingly, complex structures could also be encompassed in the substrate scope. Furthermore, the methodology has been extended to the unprecedented coupling of acetone with phenol derivatives. Mechanistic studies allowed the isolation and characterization of key Ni(0) and Ni(II) catalytic intermediates. The difference in the reactivity between Ni/Josiphos systems and other Ni/diphosphine catalyst systems likely results from enhanced stabilization of Ni(II)-aryl intermediates with Josiphos ligands. Finally, we demonstrate that air and thermally stable Ni(II) aryl complexes display enhanced catalytic activity providing a very practical protocol. Future developments with this catalytic system are under investigation in our laboratory.

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Keywords: Synthetic method • Oxidative addition • Nickel intermediates • Josiphos ligands • Mechanism

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[16] See Supporting Information for details.

[17] The presence of carbonyl moiety has been shown to possibly inhibit the oxidative addition of aryl halides to Ni(0) species by leading to thermodynamically stable carbonyl ligated nickel species, see: A. K. Cooper, D. K. Leonard, S. Bajo, P. M. Burton, D. J. Nelson, *Chem. Sci.* **2020**, *11*, 1905–1911.

[18] While many $Ni(bis\text{-}phosphine)_2$ species are unreactive in catalysis, a recent comprehensive study has shown that depending on the steric and electronic properties of the bis-phosphine ligands, the corresponding $Ni(bis\text{-}phosphine)_2$ complex may be susceptible to ligand exchange (see ref 15). The steric bulk of the Josiphos ligand, combined with the specific stereoelectronic properties imparted by the ferrocene backbone could be destabilizing for $(Josiphos)_2Ni$ and induces facile displacement of one Josiphos ligand by chlorobenzene.

[19] S. Ge, R. A. Green, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 1617–1627.

[20] S. Bajo, G. Laidlaw, A. R. Kennedy, S. Sproules, D. J. Nelson, *Organometallics* **2017**, *36*, 1662–1672.

[21] J. B. Diccianni, J. Katigbak, C. Hu, T. Diao, *J. Am. Chem. Soc.* **2019**, *141*, 1788–1796.

[22] Enhanced stability of *ortho*-substituted aryl nickel complexes is believed to originate from a combination of electronic and steric factors, see: J. Chatt, B. L. Shaw, *J. Chem. Soc.***1960**, 1718–1729.

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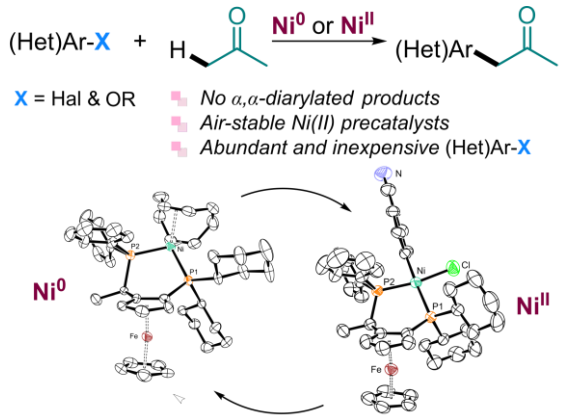

Thermally stable Ni^{II}/Josiphos complexes ensure Ni^{0}/Ni^{II} cycle

Nickel/Josiphos-based catalytic system is shown to be very efficient for the mono α-arylation of acetone with (hetero)aryl chlorides and phenols derivatives for the first time. Broad functional group tolerance was observed and the desired products are usually obtained in good to excellent yields. Mechanistic studies allowed the isolation of catalytic intermediates and provided rationale for the key role of the ligand.

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