

An efficient and mild protocol for the α -arylation of ketones mediated by an (imidazol-2-ylidene)palladium(acetate) system

Rohit Singh, Steven P. Nolan *

Department of Chemistry, University of New Orleans, New Orleans, LA 70148-2820, USA

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Abstract

The activity of well-defined *N*-heterocyclic carbene (NHC)-palladium acetate complexes has been studied in the α -arylation of ketones. The enolate was generated in situ via use of slight excess of sodium *tert*-butoxide as base. The results showed a high activity, allowing for the coupling of non-activated chlorides. The use of hindered substrates provided an avenue for convenient synthesis of various ketone derivatives. The first examples of α -arylation of ketones at room temperature mediated by an NHC-ligated catalyst are also presented.

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Keywords: Arylation; Ketones; Arylchlorides; *N*-heterocyclic carbenes; Palladium

1. Introduction

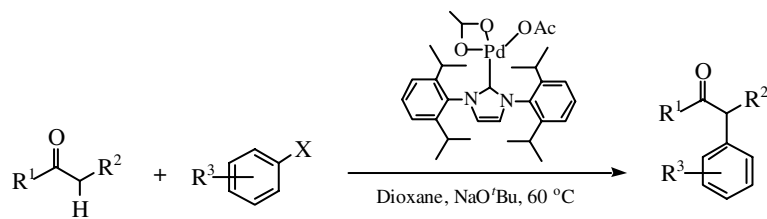
Transition metal catalyzed cross-coupling reactions are a popular means of adding a variety of carbon nucleophiles to aryl halides [1]. Development of efficient and selective catalytic reactions for C–C bond formation has been a subject of paramount interest in organic and organometallic chemistry. Catalytic conversion of C–H bond to a C–C bond is an important subgrouping of such transformations. During the past years, numerous reactions involving C–H bond transformations have been developed [2]. Among these, palladium-catalyzed conversion of C–H bonds to form C–C bonds via coupling of aryl halides or pseudo aryl halides with carbon nucleophiles is one of the most widely employed transition metal catalyzed reaction [3]. Finding an efficient and reliable catalytic method to form a bond between an arene and carbon α to a carbonyl group is a challenging problem [4]. The use of aryl halides for direct arylation of ketones

at the carbon α to the carbonyl group has proven to be a transformation of great utility in pharmaceutical, agrochemical and organic synthesis [5]. It has also found an increasing interest in the synthesis of fine chemicals [6].

The increased acidity of a proton on a carbon α to a carbonyl group helps in its abstraction and generation of an enolate. The simplicity in methodology offered by in situ generation of an enolate via deprotonation is an added advantage of this approach. Initially, the metal mediated coupling of enolates was achieved by use of stoichiometric amounts of metal complexes [7]. Moreover some of the procedures involved use of less readily available carbonyl alternatives [8]. However, in concurrent work, Buchwald [9], Hartwig [10] and Miura [11] reported the first examples of direct, catalytic, α -arylations of ketones in 1997. Since then, a myriad of reports from these and other groups have helped establish the catalytic α -arylation of ketones as an indispensable synthetic tool [12–15].

Since the discovery of stable *N*-heterocyclic carbenes (NHCs), a number of groups have utilized these in catalysis [16]. In the past several years, a number of NHC-metal complexes serving as efficient catalysts for a

* Corresponding author. Tel. +1 504 286 6311; fax: +1 504 280 6860.
E-mail address: snolan@uno.edu (S.P. Nolan).

Scheme 1. (NHC)Pd(OAc)₂ catalyzed α -arylation of ketones.

number of reactions have been reported [17]. Such examples include the palladium-catalyzed α -arylation of ketones [18]. More recently, we and others [19] have reported on the synthesis and characterization of (imidazol-2-ylidene)palladium acetate complexes. The complexes were tested for activity in the hydroarylation of alkynes [20] and in the Suzuki–Miyaura cross-coupling reaction [17a]. Encouraged by the very attractive reactivity profile in these transformations mediated by (NHC)Pd(OAc)₂ complexes, results of catalytic study dealing with α -arylation of ketones with various chlorides as coupling partners are reported here (see Scheme 1).

The model reaction involving propiophenone with 4-chlorotoluene revealed the complex (IPr)Pd(OAc)₂ [IPr = *N,N'*-(2,6-diisopropyl phenyl) imidazol-2-ylidene] to be an active mediator, furnishing quantitative yield of product in 3 h at 60 °C. This catalytic transformation is very appealing, especially since the catalyst is very easily synthesized [21]. With an aim to prove this protocol practical and amenable to wider laboratory and industrial applications we wish to provide a detailed report of our studies regarding the optimization, scope and applicability of α -arylation of ketones.

2. Results and discussion

For the initial optimization studies we chose to focus on reactions of propiophenone, since it provides only one site for a possible deprotonation by the base and avoids potential complications arising from multi-arylations. For halide coupling partner, we primarily made use of chlorides. This decision was motivated in part by our realization that so far very few reports have been published which employ chlorides [15c,12c,13e]. Although aryl chlorides have lower costs and are available in broader diversity as compared to bromides and iodides, as a general trend they tend to be less active towards oxidative addition in metal mediated couplings [22]. We therefore initiated an investigation of the utility of chlorides in α -arylation of ketones [18]. For optimization studies, 4-chlorotoluene was chosen as the halide coupling partner. Initially, an analysis of various solvents as reaction media was carried out (Table 1).

Table 1
Solvent screening^a

Entry	Solvent	Time (h)	Yield (%) ^b
1	Toluene	1	77
2	DME	2	85
3	Dioxane	1	87
4	THF	1	84
5	Isopropanol	–	NR
6	MTBE	1	82
7	DMAc	–	NR

^a Reaction conditions: 1 mol% of (IPr)Pd(OAc)₂, 1.2 mmol of propiophenone, 1 mmol of 4-chlorotoluene, 1.5 equiv. of NaO'Bu, 1.5 mL of solvent, 60 °C.

^b GC yields, average of two runs.

2.1. Solvent screening

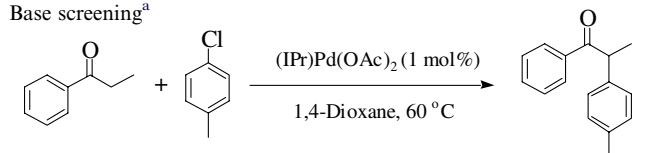
As a generic reaction, 4-chlorotoluene was reacted with propiophenone in the presence of 1 mol% of (IPr)Pd(OAc)₂ and 1.5 equiv. of base (sodium *tert*-butoxide) at 60 °C. Among various solvents tested for activity, isopropyl alcohol and *N,N*-dimethylacetamide failed to furnish appreciable quantities of product. However, excellent yields were obtained with other solvents and 1,4-dioxane was found to provide quantitative conversion in minimum time, making it the solvent of choice for our protocol [23].

2.2. Base screening

With the dual influence of base in mind (generation of active catalytic Pd species and deprotonation of ketone to generate the enolate), various commercially available standard alkali metal bases were investigated in the model reaction (Table 2). Among the productive bases, NaO'Bu was found to be the most affordable.

2.3. Reactions of various halides with propiophenone

With optimum conditions in hand, a survey of reactions between propiophenone and various aryl halides

Table 2
Base screening^a

Entry	Base	Time (h)	Yield (%) ^b
1	NaO ^t Bu	3	96
2	KO ^t Bu	4	85
3	NaH	2	85
4	KH	12	78
5	Cs ₂ CO ₃	3	10
6	KOMe	5	60
7	K ₃ PO ₄	3	27

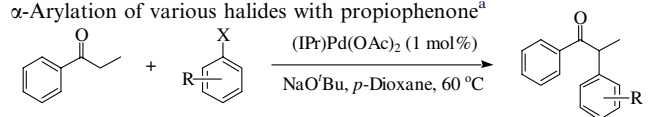
^a Reaction conditions: 1 mol% of (IPr)Pd(OAc)₂, 1.2 mmol of propiophenone, 1 mmol of 4-chlorotoluene, 1.5 equiv. of base, 1.5 mL of 1,4-dioxane, 60 °C.

^b GC yields, average of two runs.

under catalytic conditions was performed. The details are provided in Table 3. Reactions of *para*-bromo- and *para*-iodotoluene proceeded to furnish quantitative yields within 1 h (Table 3, entries 4 and 5). More difficult substrates, chlorobenzene and *para*-chlorotoluene also performed well giving good yields (Table 3, entries 1 and 2). A stronger C–F bond in aryl-fluorides prevents its oxidative addition to the palladium center. Therefore, the reaction of *para*-fluorotoluene with propiophenone under the standard conditions failed to furnish the product in appreciable quantity (Table 3, entry 3). Reaction of *ortho*-chlorotoluene proceeded to give complete conversion in less time than *para*-chlorotoluene (Table 3, entry 6), indicating a favorable effect of the presence of steric bulk around the reaction center. This increase in steric bulk (Scheme 2) expedites the reductive elimination [24]. Increase in steric bulk around the metal center increases the energy of the stable, higher co-ordinate species prompting it to undergo reductive elimination [25,13a]. Moreover, the presence of sterically hindering moiety in the final product can act as a deterrent for multi-arylations.

2.4. Study of *ortho*-, *meta*- or *para*-substitution on aryl chlorides with both electron-donating and electron-withdrawing groups

To obtain some insight into the substrate scope of this reaction, we investigated the effect of electron-donating and electron-withdrawing groups at various positions on the aryl chlorides. Hence, reactions of *ortho*-, *meta*- and *para*-substituted chloroanisoles and chloro(trifluoromethyl)phenyls were performed under the standard reaction conditions. The substrates with electron donating methoxy substituent performed exceedingly well, furnishing excellent yields in short

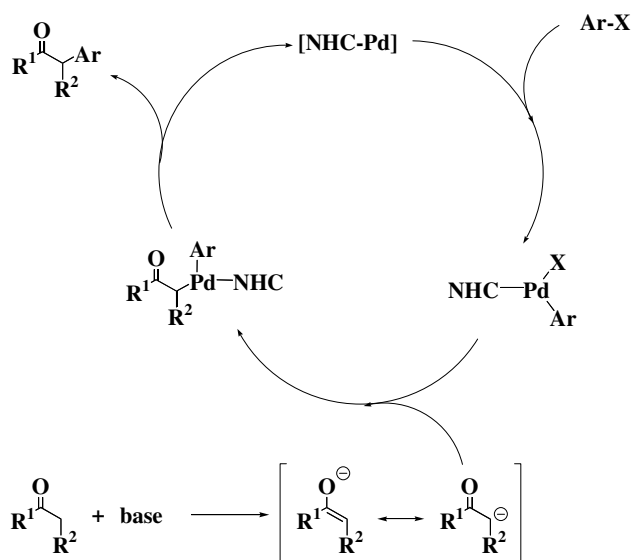
Table 3
 α -Arylation of various halides with propiophenone^a

Entry	Aryl halide	Time (h)	Yield (%) ^b
1		6	80 (71)
2		3	96 (92)
3		–	NR
4		1	92 (88)
5		1	96 (83)
6		2	96 (90)
7		–	NR
8		–	NR

^a Reaction conditions: 1 mol% of (IPr)Pd(OAc)₂, 1.2 mmol of propiophenone, 1 mmol of aryl halide, 1.5 equiv. of NaO^tBu, 1.5 mL of 1,4-dioxane, 60 °C.

^b GC yields (isolated yields in parentheses), average of two runs.

times (Table 4, entries 1–3). However, reactions involving the electron-withdrawing trifluoromethyl substituted chlorophenyls displayed poorer performance. While *ortho*- and *para*-chloro(trifluoromethyl)phenyls furnished moderate yields in longer time periods (Table 4, entries 4 and 6), the *meta*-substituted, 3-chloro(trifluoromethyl)phenyl failed to undergo coupling (Table 4, entry 5). These results represent an interesting trend, since it is known that usually electron-rich aryl halides are difficult to activate towards oxidative addition with palladium [25]. Conceivably, the oxidative addition does not affect the overall rate of the reaction and is not the rate determining step. Although in most cross-coupling reactions of haloarenes, the reaction rates are usually believed to be controlled by the rate of oxidative addition [22b] and usually the transmetalation and reductive elimination are more rapid [26], non-involvement of oxidative addition in dictating the rate of a reaction is not unprecedented [27]. Since the presence of electron withdrawing groups around the metal center should activate it towards transmetalation with an enolate, it is possible that the presence of elec-



Scheme 2. Proposed catalytic cycle for α -arylation of ketones in (NHC)Pd(OAc)₂ system.

Table 4
Substituent effect on aryl chlorides in α -arylation with propiophenone^a

Entry	Aryl halide	Time (h)	Yield (%) ^b
1		1	98 (94)
2		1	91 (81)
3		3	96 (90)
4		12	75 (71)
5		–	NR
6		12	71 (69)

^a Reaction conditions: 1 mol% of (IPr)Pd(OAc)₂, 1.2 mmol of propiophenone, 1 mmol of aryl halide, 1.5 equiv. of NaO^tBu, 1.5 mL of 1,4-dioxane, 60 °C.

^b GC yields (isolated yields in parentheses), average of two runs.

tron withdrawing group (especially at the *meta*-position) deactivates the substrates towards reductive elimination.

2.5. Study of effect of introduction of steric bulk on position α to carbonyl group in substituted cyclohexyl ketones

Given the fact that sterics play an important role in the α -arylation of ketones, an investigation of effect of bulk around the ketone, on the generation of enolate was carried out. To this effect, a limited study with various substituted cyclohexyl ketones was performed (Table 5). Unsubstituted, cyclohexyl ketone performed well under the standard conditions, furnishing good yield in 2 h. However, poor conversion due to the presence of methyl groups around the carbonyl carbons in 2,6-dimethylcyclohexanone and 2,2,6-trimethylcyclohexanone was observed. This is indicative of the sensitivity in generating an enolate in the presence of sterically hindering groups around the carbonyl group. Furthermore, 2-*tert*-butylcyclohexanone yielded a poor conversion while aryl fused cyclohexanone derivative (α -tetralone) fared better giving good conversion in 6 h. It is worth mentioning that both these substrates have an unsubstituted carbon α -to the

Table 5
Effect of steric bulk in generation of enolates in cyclohexyl ketone derivatives^a

Entry	Aryl halide	Time (h)	Yield (%) ^b
1		2	73 (67)
2		–	NR
3		–	NR
4		12	20
5		–	NR
6		6	90 (83)

^a Reaction conditions: 1 mol% of (IPr)Pd(OAc)₂, 1.2 mmol of ketone, 1 mmol of 4-chlorotoluene, 1.5 equiv. of NaO^tBu, 1.5 mL of 1,4-dioxane, 60 °C.

^b GC yields (isolated yields in parentheses), average of two runs.

carbonyl group. However, electronic effects come into play when 2-methoxycyclohexanone is used. In spite of an unsubstituted carbon α to the carbonyl group, the electron donating nature of the methoxy group attenuates acidity of the ketone, deactivating it towards deprotonation.

It is worthy of note that reactions involving cyclohexyl ketone derivatives demonstrated excellent regioselectivity. In spite of the availability of additional sites for arylation, only trace amounts of diarylations were observed in these reactions.

2.6. α -Arylation of various substrates including heterocyclic ketones and chlorides

With an aim to expand the scope of the reaction and broadening the base of usable substrates, we explored various chlorides in the α -arylation of ketones. Since synthesis of heterocyclic compounds is of significant importance to synthetic and medicinal chemists, we wished to explore the compatibility of heterocyclic substrates with the present protocol. Moderate success was achieved in this venture on coupling 2- and 3-chlorothiophene with propiophenone and 2-acetyl-1-methylpyrrole with 2-chlorotoluene (Table 6, entries 3–5). 2-Acetylthiophene did not furnish a good yield in the reaction with 2-chlorotoluene.

Table 6
 α -Arylation of various substrates including heterocyclic ketones and chlorides^a

Entry	Ketone	Aryl halide	Product	Time (h)	Yield (%) ^b
1				24	80 (75)
2				12	17
3				12	42
4				24	36
5				6	46
6				12	13

^a Reaction conditions: 1 mol% of (IPr)Pd(OAc)₂, 1.2 mmol of ketone, 1 mmol of aryl halide, 1.5 equiv. of NaO^tBu, 1.5 mL of 1,4-dioxane, 60 °C.

^b GC yields (isolated yields in parentheses), average of two runs.

2.7. α -Arylation of sterically hindered substrates and optimum reaction temperature

At this stage we were pleased that our objective of effecting couplings of non-activated chlorides in a synthetically oriented protocol could be accomplished. On the other hand, we were not satisfied with the scope of the process and aspired to further expand it. Given our past experience [17a,17f], we wished to pursue sterically hindered substrates as prospective coupling partners in this reaction. The use of bromomesitylene in arylating the ketone in excellent yield was achieved within a very short time (Table 7, entry 1). Unactivated, *ortho*-substituted chlorides performed well under our reaction protocol (Table 7, entries 2–4). In particular, bulky naphthylchloride gave quantitative yield within 1 h at 60 °C. Furthermore, on testing the performance of catalyst at optimum temperature in this reaction, we were pleased to observe formation of arylated product. Only few examples of α -arylation of ketones, performed at room temperature have been reported so far. However, elegant reports by Hartwig [13e] and Buchwald [12a] have only utilized more reactive bromides. To the best of our knowledge, no reports of room temperature α -arylation of ketones with chlorides have been reported to date [29]. To further explore this aspect of our reaction protocol, we carried out reactions of

Table 7
 α -Arylation of sterically hindered substrates^a

Entry	Aryl halide	Product	Temp (°C)	Time (h)	Yield (%) ^b
1			60	0.5	92 (83)
2			60	1	100 (93)
3			25	12	80 (75)
4			25	12	78 (71)
5			25	18	73 (67)
6			25	24	41
7			25	12	42
8			25	12	75 (70)

^a Reaction conditions: 1 mol% of (IPr)Pd(OAc)₂, 1.2 mmol of propiophenone, 1 mmol of aryl halide, 1.5 equiv. of NaO^tBu, 1.5 mL of 1,4-dioxane.

^b GC yields (isolated yields in parentheses), average of two runs.

various halides at room temperature. Herein, we wish to report the first examples of α -arylation of ketones with chlorides at room temperature. Reactions of propiophenone progress well with 1-chloronaphthalene, 2-chloroanisole and 4-chloroanisole (Table 7, entries 3–5). Reaction of 4-iodotoluene proceeds cleanly to provide the product in good yield (Table 7, entry 8). However, when 4-chlorotoluene and 4-bromotoluene are used, the product is obtained in moderate yields (Table 7, entries 6 and 7). Nevertheless, the activity of (IPr)Pd(OAc)₂ at room temperature provides a new dimension to the use of this protocol towards more universal laboratory and industrial applications.

3. Conclusions

In summary, we have described a convenient protocol for the α -arylation of ketones utilizing an easy to synthesize (imidazol-2-ylidene)palladium acetate complex as catalyst. The best reaction conditions obtained via optimization studies revealed compatibility with a commercially available, inexpensive and convenient base, as well as solvent making the reaction protocol amenable to large-scale synthesis. A wide array of functionalized halides has been investigated in an effort to better understand the bearings of electronics and sterics on the reaction. Coupling of heterocyclic substrates has also been achieved. In view of the paucity of examples of reactions at lower temperatures using unactivated aryl chlorides (particularly *ortho*-substituted chlorides), we believe these observations are noteworthy. Efforts aimed at developing effective catalyst systems for a broad range of substrates under mild conditions, as well as initiating investigations of mechanistic aspects at play are ongoing [28].

4. Experimental

4.1. General considerations

All aryl halides and ketones were used as received (Aldrich, Acros). Bases were stored under argon in an MBraun glovebox. All solvents were distilled from appropriate drying agents or were passed through an alumina column in an MBraun solvent purification system. The catalyst was prepared according to the reported procedures [17a,20,30]. All reactions were carried out under an atmosphere of argon in screw-cap vials. ¹H and ¹³C NMR spectra were recorded using a Varian-400 or Varian-300 MHz spectrometer at ambient temperature in CDCl₃ (Cambridge Isotope Laboratories, Inc.). The solvent for NMR spectroscopy was stored over molecular sieves. Flash chromatography was performed on silica gel (230–400 mesh) (Natland International Corporation).

4.2. Representative procedure for α -arylation of ketones

In a drybox, 1.5 mmol of base was added to a screw-cap vial charged with 1 mol% of (IPr)Pd(OAc)₂ complex. 1.5 mL of solvent was added and the vial sealed with a rubber septum. Outside the drybox, 1.2 mmol of ketone was injected in the vial with a syringe. 1 mmol of aryl halide was injected last. The reaction mixture was allowed to shake on a Lab-Line Orbit Shaker (set at 60 °C – J-Kem Scientific, Kem-Lab Controller) or stirred over a magnetic plate in an oil bath set at 60 °C for the indicated time. The reactions were monitored by gas chromatography. After reaching maximum conversion, the reaction mixture was allowed to cool to room temperature and it was then quenched with water. The organic layer was extracted with methyl *tert*-butyl ether or diethyl ether and dried over magnesium sulfate. The solvent was then evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel.

4.3. Screening of solvents in α -arylation of ketones

In a drybox, NaO^tBu (1.5 mmol, 144 mg) was loaded in a screw-cap vial charged with (IPr)Pd(OAc)₂ complex (0.01 mmol, 6.1 mg). 1.5 mL of solvent was added and the vial sealed with a rubber septum. Outside the drybox, propiophenone (1.2 mmol, 160 μ l) was injected in the vial with a syringe. Lastly, 4-chlorotoluene (1 mmol, 118 μ l) was injected into the vial. The reaction mixture was allowed to shake on a Lab-Line Orbit Shaker (set at 60 °C – J-Kem Scientific, Kem-Lab Controller) or stirred over a magnetic plate in an oil bath set at 60 °C for the indicated time. The reactions were monitored by gas chromatography.

4.4. Screening of bases in α -arylation of ketones

In a drybox, 1.5 mmol of base was loaded in a screw-cap vial charged with (IPr)Pd(OAc)₂ complex (0.01 mmol, 6.1 mg). 1.5 mL of dioxane was added and the vial sealed with a rubber septum. Outside the drybox, propiophenone (1.2 mmol, 160 μ l) was injected in the vial with a syringe. Lastly, 4-chlorotoluene (1 mmol, 118 μ l) was injected to the vial. The reaction mixture was allowed to shake on a Lab-Line Orbit Shaker (set at 60 °C – J-Kem Scientific, Kem-Lab Controller) or stirred over a magnetic plate in an oil bath set at 60 °C for the indicated time. The reactions were monitored by gas chromatography.

4.5. α -Arylation of various ketones with aryl halides

In a drybox, NaO^tBu (1.5 mmol, 144 mg) was loaded in a screw-cap vial charged with (IPr)Pd(OAc)₂

complex (0.01 mmol, 6.1 mg). 1.5 mL of dioxane was added and the vial sealed with a rubber septum. Outside the drybox, 1.2 mmol of ketone was injected in the vial with a syringe. 1 mmol of aryl halide was injected last. The reaction mixture was allowed to shake on a Lab-Line Orbit Shaker (set at 60 °C – J-Kem Scientific, Kem-Lab Controller) or stirred over a magnetic plate (at room temperature or in an oil bath set at 60 °C) for the indicated time. The reactions were monitored by gas chromatography. After the maximum conversion had been reached, the reaction mixture was allowed to cool to room temperature and quenched with water. The organic layer was extracted with methyl *tert*-butyl ether or diethyl ether and dried over magnesium sulfate. The solvent was then evaporated in vacuo. When necessary, the product was purified by flash chromatography on silica gel. Identity of products was confirmed by comparison with literature spectroscopic data.

Isolated products:

1,2-Diphenyl-propan-1-one [13e] (Table 3, entry 1): The procedure afforded 149 mg (71%) of the compound.

1-Phenyl-2-*p*-tolyl-propan-1-one [31] (Table 3, entry 2): The procedure afforded 206 mg (92%) of the compound.

1-Phenyl-2-*p*-tolyl-propan-1-one [31] (Table 3, entry 4): The procedure afforded 197 mg (88%) of the compound.

1-Phenyl-2-*p*-tolyl-propan-1-one [31] (Table 3, entry 5): The procedure afforded 185 mg (83%) of the compound.

1-Phenyl-2-*o*-tolyl-propan-1-one [31] (Table 3, entry 6): The procedure afforded 202 mg (90%) of the compound.

2-(2-Methoxy-phenyl)-1-phenyl-propan-1-one [32] (Table 4, entry 1): The procedure afforded 225 mg (94%) of the compound.

2-(3-Methoxy-phenyl)-1-phenyl-propan-1-one [13e] (Table 4, entry 2): The procedure afforded 194 mg (81%) of the compound.

2-(4-Methoxy-phenyl)-1-phenyl-propan-1-one [10] (Table 4, entry 3): The procedure afforded 216 mg (90%) of the compound.

1-Phenyl-2-(2-trifluoromethyl-phenyl)-propan-1-one [33] (Table 4, entry 4): The procedure afforded 197 mg (71%) of the compound.

1-Phenyl-2-(4-trifluoromethyl-phenyl)-propan-1-one [33] (Table 4, entry 6): The procedure afforded 192 mg (69%) of the compound.

2-*p*-Tolyl-cyclohexanone [34] (Table 5, entry 1): The procedure afforded 126 mg (67%) of the compound.

2-*p*-Tolyl-3,4-dihydro-2H-naphthalen-1-one [35] (Table 5, entry 6): The procedure afforded 196 mg (83%) of the compound.

1,2-Di-*o*-tolyl-ethanone [36] (Table 6, entry 1): The procedure afforded 168 mg (75%) of the compound.

1-Phenyl-2-(2,4,6-trimethyl-phenyl)-propan-1-one [37] (Table 7, entry 1): The procedure afforded 209 mg (83%) of the compound.

2-Naphthalen-1-yl-1-phenyl-propan-1-one [38] (Table 7, entry 2): The procedure afforded 242 mg (93%) of the compound.

2-Naphthalen-1-yl-1-phenyl-propan-1-one [38] (Table 7, entry 3): The procedure afforded 195 mg (75%) of the compound.

2-(2-Methoxy-phenyl)-1-phenyl-propan-1-one [32] (Table 7, entry 4): The procedure afforded 170 mg (71%) of the compound.

2-(4-Methoxy-phenyl)-1-phenyl-propan-1-one [10] (Table 7, entry 5): The procedure afforded 161 mg (67%) of the compound.

1-Phenyl-2-*p*-tolyl-propan-1-one [31] (Table 7, entry 8): The procedure afforded 156 mg (70%) of the compound.

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References

- [1] For reactions of aryl halides with carbon nucleophiles such as Grignard reagents, boronic acids and tin reagents see F. Diederich, P.J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 1998, p. 517.
- [2] (a) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* 345 (2003) 1077; (b) J.A. Labinger, J.E. Bercaw, *Nature* 417 (2002) 507; (c) M. Miura, M. Nomura, *Cross-Coupling Reactions*, Springer, Berlin, Germany, 2002, p. 211; (d) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* 35 (2002) 826; (e) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* 102 (2002) 1731; (f) R.H. Crabtree, *Dalton Trans.* (2001) 2437; (g) Y. Guari, S. Sabo-Etienne, B. Chaudret, *Eur. J. Inorg. Chem.* (1999) 1047; (h) R.H. Crabtree, *Chem. Rev.* 85 (1985) 245.
- [3] (a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* 102 (2002) 1359; (b) N. Miyaura, A. Suzuki, *Chem. Rev.* 95 (1995) 2457; (c) J.K. Stille, *Angew. Chem., Int. Ed. Engl.* 25 (1986) 508; (d) E. Negishi, *Acc. Chem. Res.* 15 (1982) 340.
- [4] (a) Catalytic reactions for synthesis of α -aryl ketones M. Durandetti, J.-Y. Nedelec, J. Perichon, *J. Org. Chem.* 61 (1996) 1748; (b) M. Kosugi, I. Hagiwara, T. Sumiya, T. Migita, *Bull. Chem. Soc. Jpn.* 57 (1984) 242; (c) I. Kuwajima, H. Urabe, *J. Am. Chem. Soc.* 104 (1982) 6831; (d) K. Tamao, M. Zembayashi, M. Kumada, *Chem. Lett.* (1976) 1239.

- [5] (a) D.R. Bhowmik, R.V. Venkateswaran, *Tetrahedron Lett.* 40 (1999) 7431;
(b) A. Srikrishna, T.J. Reddy, *Tetrahedron* 54 (1998) 8133;
(c) J. Morgan, J.T. Pinhey, B.A. Rowe, *J. Chem. Soc. Perkin Trans. I* (1997) 1005;
(d) S. Takano, K. Inomata, T. Sato, M. Takahashi, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* (1990) 290;
(e) V. Nair, G.A. Turner, S.D. Chamberlain, *J. Am. Chem. Soc.* 109 (1987) 7223.
- [6] M. Beller, A. Zapf, W. Magerlein, *Chem. Eng. Technol.* 24 (2001) 575.
- [7] (a) Intermolecular arylation of an ester enolate: A.A. Millard, M.W. Rathke, *J. Am. Chem. Soc.* 99 (1977) 4833;
(b) , Intramolecular arylation of an ester enolate: M.F. Semmelhack, R.D. Stauffer, T.D. Rogerson, *Tetrahedron Lett.* (1973) 4519.
- [8] (a) T. Mino, T. Matsuda, K. Murahashi, M. Yamashita, *Organometallics* 16 (1997) 3241;
(b) M.W. Rathke, D. Vogiazoglou, *J. Org. Chem.* 52 (1987) 3697;
(c) J.P. Marino, J.C. Jaen, *J. Am. Chem. Soc.* 104 (1982) 3165;
(d) H. Sakurai, A. Shirahata, Y. Araki, A. Hosomi, *Tetrahedron Lett.* 21 (1980) 2325;
(e) L.F. Kelly, A.S. Narula, A. Birch, *Tetrahedron Lett.* 21 (1980) 2455;
(f) I. Al Adel, B. Adeoti Salami, J. Levisalles, H. Rudler, *Bull. Soc. Chim. Fr.* (1976) 930;
(g) C.E. Sacks, P.L. Fuchs, *J. Am. Chem. Soc.* 97 (1975) 7372;
(h) L.S. Hegedus, R.K. Stiverson, *J. Am. Chem. Soc.* 96 (1974) 3250;
(i) H.C. Brown, H. Nambu, M.M. Rogic, *J. Am. Chem. Soc.* 91 (1969) 6855;
(j) H.C. Brown, H. Nambu, M.M. Rogic, *J. Am. Chem. Soc.* 91 (1969) 6852;
(k) P.R. Jones, J.R. Young, *J. Org. Chem.* 33 (1968) 1675;
(l) M.S. Newman, M. Farbman, *J. Am. Chem. Soc.* 66 (1944) 1550.
- [9] M. Palucki, S.L. Buchwald, *J. Am. Chem. Soc.* 119 (1997) 11108.
- [10] B.C. Hamann, J.F. Hartwig, *J. Am. Chem. Soc.* 119 (1997) 12382.
- [11] T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem. Int. Ed.* 36 (1997) 1740.
- [12] (a) T. Hamada, A. Chieffi, J. Ahman, S.L. Buchwald, *J. Am. Chem. Soc.* 124 (2002) 1261;
(b) , Vinylolation of enolates: A. Chieffi, K. Kamikawa, J. Ahman, J.M. Fox, S.L. Buchwald, *Org. Lett.* 3 (2001) 1897;
(c) J.M. Fox, X. Huang, A. Chieffi, S.L. Buchwald, *J. Am. Chem. Soc.* 122 (2000) 1360;
(d) . Asymmetric arylation of ketone enolates: J. Ahman, J.P. Wolfe, M.V. Troutman, M. Palucki, S.L. Buchwald, *J. Am. Chem. Soc.* 120 (1998) 1918.
- [13] (a) D.A. Culkin, J.F. Hartwig, *Acc. Chem. Res.* 36 (2003) 234;
(b) S. Lee, N.A. Beare, J.F. Hartwig, *J. Am. Chem. Soc.* 123 (2001) 8410;
(c) S. Lee, J.F. Hartwig, *J. Org. Chem.* 66 (2001) 3402;
(d) S.R. Stauffer, N.A. Beare, J.P. Stambuli, J.F. Hartwig, *J. Am. Chem. Soc.* 123 (2001) 4641;
(e) M. Kawatsura, J.F. Hartwig, *J. Am. Chem. Soc.* 121 (1999) 1473;
(f) K.H. Shaughnessy, B.C. Hamann, J.F. Hartwig, *J. Am. Chem. Soc.* 63 (1998) 6546.
- [14] T. Satoh, J. Inoh, Y. Kawamuro, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* 71 (1998) 2239.
- [15] (a) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* 127 (2005) 5936;
(b) O. Prieto, D.J. Ramon, M. Yus, *Tetrahedron: Asymmetry* 14 (2003) 1955;
(c) A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* 344 (2002) 209;
- (d) G. Pandey, M. Karthikeyan, A. Murugan, *J. Org. Chem.* 63 (1998) 2867;
(e) J.H. Ryan, P.J. Stang, *Tetrahedron Lett.* 38 (1997) 5061.
- [16] (a) H.-W. Wanzlick, E. Schikora, *Angew. Chem.* 72 (1960) 494;
(b) H.-W. Wanzlick, H.-J. Kleiner, *Angew. Chem.* 73 (1961) 493;
(c) H.-W. Wanzlick, *Angew. Chem.* 74 (1962) 129;
(d) A. Igau, H. Gruetzmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* 110 (1988) 6463;
(e) A. Igau, A. Baceiredo, G. Trinquier, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* 28 (1989) 621;
(f) A.J. Arduengo III, R.L. Harlow, M. Kline, *J. Am. Chem. Soc.* 113 (1991) 361;
(g) A.J. Arduengo, H.V.R. Dias, R.L. Harlow, M. Kline, *J. Am. Chem. Soc.* 114 (1992) 5530;
(h) , For comprehensive reviews on NHC see: M. Regitz, *Angew. Chem., Int. Ed. Engl.* 35 (1996) 725;
(i) A.J. Arduengo, R. Krafczyk, *Chem. Z.* 32 (1998) 6;
(j) D. Bourissou, O. Guerret, F.P. Gabbaï, G. Bertrand, *Chem. Rev.* 100 (2000) 39;
(k) W.A. Herrmann, *Angew. Chem., Int. Ed. Engl.* 41 (2002) 1290;
(l) B. Yong, S.P. Nolan, *Chemtracts* 16 (2002) 205;
(m) A.C. Hillier, S.P. Nolan, *Platinum Met. Rev.* 46 (2002) 50;
(n) L. Jafarpour, S.P. Nolan, *Adv. Organomet. Chem.* 46 (2002) 181.
- [17] (a) R. Singh, M.S. Viciu, N. Kramareva, O. Navarro, S.P. Nolan, *Org. Lett.* 7 (2005) 1829;
(b) O. Navarro, Y. Oonishi, R.A. Kelly, E.D. Stevens, O. Briel, S.P. Nolan, *J. Organomet. Chem.* 689 (2004) 3722;
(c) H. Kaur, F.K. Zinn, E.D. Stevens, S.P. Nolan, *Organometallics* 23 (2004) 1157;
(d) O. Navarro, H. Kaur, P. Mahjoor, S.P. Nolan, *J. Org. Chem.* 69 (2004) 3173;
(e) G.A. Grasa, R. Singh, E.D. Stevens, S.P. Nolan, *J. Organomet. Chem.* 687 (2003) 269;
(f) O. Navarro, R.A. Kelly, S.P. Nolan, *J. Am. Chem. Soc.* 125 (2003) 16194;
(g) M.S. Viciu, R.M. Kissling, E.D. Stevens, S.P. Nolan, *Org. Lett.* 4 (2002) 2229.
- [18] (a) α -Arylation of ketones with aryl chlorides: M.S. Viciu, R.A. Kelly, E.D. Stevens, F. Naud, M. Studer, S.P. Nolan, *Org. Lett.* 5 (2003) 1479;
(b) M.S. Viciu, R.F. Germaneau, S.P. Nolan, *Org. Lett.* 4 (2002) 4053.
- [19] (a) For examples of (NHC)palladium acetate systems see: M.J. Schultz, S.S. Hamilton, D.R. Jensen, M.S. Sigman, *J. Org. Chem.* 70 (2005) 3343;
(b) J.A. Mueller, C.P. Goller, M.S. Sigman, *J. Am. Chem. Soc.* 126 (2004) 9724;
(c) M.M. Konnick, I.A. Guzei, S.S. Stahl, *J. Am. Chem. Soc.* 126 (2004) 10212.
- [20] M.S. Viciu, E.D. Stevens, J.L. Peterson, S.P. Nolan, *Organometallics* 23 (2004) 3752.
- [21] The precursor for synthesis of catalyst, IPr·HCl is commercially available from: Strem Chemicals, Inc. and from Sigma/Aldrich.
- [22] (a) For a discussion, see: V.V. Grushin, H. Alper, in: S. Murai (Ed.), *Activation of Unreactive Bonds and Organic Synthesis*, Springer, Berlin, 1999, p. 193;
(b) V.V. Grushin, H. Alper, *Chem. Rev.* 94 (1994) 1047.
- [23] Although initially THF also performed equally well, on individual optimization of the reaction, it was found that 1,4-dioxane performs better.
- [24] R.H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, third ed., Wiley, New York, 2001.
- [25] A.F. Littke, G.C. Fu, *Angew. Chem. Int. Ed. Engl.* 41 (2002) 4176.

- [26] L.M. Alcazar-Roman, J.F. Hartwig, *J. Am. Chem. Soc.* 123 (2001) 12905.
- [27] For a recent example in palladium catalyzed arylation of indoles see: B.S. Lane, M.A. Brown, D. Sames, *J. Am. Chem. Soc.* 127 (2005) 8050.
- [28] Efforts to reduce catalyst loadings and include a wider array of non-activated chlorides (especially *ortho*-substituted) are being undertaken. Analysis of factors governing the mechanism at play is also being conducted.
- [29] G. Bertrand, *J. Am. Chem. Soc.* 127 (2005).
- [30] (a) For synthesis of carbenes see: M.S. Viciu, O. Navarro, R.F. Germaneau, R.A. Kelly, W. Sommer, N. Marion, E.D. Stevens, L. Cavallo, S.P. Nolan, *Organometallics* 23 (2004) 1629;
(b) A.J. Arduengo III, R. Krafczyk, R. Schmutzler, A. Craig, A. Hugh, J.R. Goerlich, J.M. William, M. Unverzagt, *Tetrahedron* 55 (1999) 14523;
(c) P.L. Arnold, F.G.N. Cloke, T. Geldbach, P.B. Hitchcock, *Organometallics* 18 (1999) 3228;
(d) A.J. Arduengo III, F. Davidson, R. Krafczyk, W.J. Marshall, M. Tamm, *Organometallics* 17 (1998) 3375;
(e) A.J. Arduengo III, S.F. Gamper, J.C. Calabrese, F.J. Davidson, *J. Am. Chem. Soc.* 116 (1994) 4391;
(f) A.J. Arduengo, R.L. Harlow, M. Kline, *J. Am. Chem. Soc.* 113 (1991) 361.
- [31] D.A. Culkin, J.F. Hartwig, *J. Am. Chem. Soc.* 123 (2001) 5816.
- [32] H.C. Bell, J.T. Pinhey, S. Sternhell, *Aust. J. Chem.* 35 (1982) 2237.
- [33] K.C. Nicolaou, T. Montagnon, P.S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* 124 (2002) 2245.
- [34] S. Nakamura, M. Kaneeda, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* 122 (2000) 8120.
- [35] K. Hino, Y. Nagai, H. Uno, Y. Masuda, M. Oka, T. Karasawa, *J. Med. Chem.* 31 (1988) 107.
- [36] P. Nilsson, M. Larhed, A. Hallberg, *J. Am. Chem. Soc.* 123 (2001) 8217.
- [37] P.J. Wagner, B. Zhou, *J. Am. Chem. Soc.* 110 (1988) 611.
- [38] S.S. Hecht, M. Loy, R. Mazzaresse, D. Hoffmann, *J. Med. Chem.* 21 (1978) 38.