ORGANIC LETTERS
2002
Vol. 4, No. 23
4053−4056

Well-Defined, Air-Stable (NHC)Pd(Allyl)Cl (NHC = N-Heterocyclic Carbene) Catalysts for the Arylation of Ketones

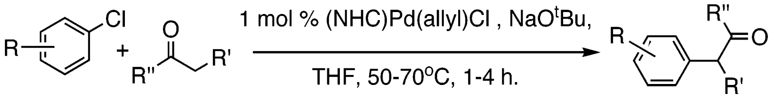
Mihai S. Viciu, Romain F. Germaneau, and Steven P. Nolan*

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

snolan@uno.edu

Received August 16, 2002

ABSTRACT



A number of palladium-N-heterocyclic carbene (NHC) complexes were found to be active catalysts for the arylation of ketones. A large number of substrates, both aryl halides and ketones, are compatible with the reaction conditions. The ketone arylation reactions are achieved with low catalyst loading in short reaction times using aryl chlorides and triflates as reactive partners.

The synthesis of α-aryl ketones has received renewed attention since the discovery of direct coupling between simple ketones and aryl halides without the use of tin or silicon intermediates.[1] The enolate form of the ketone can be generated efficiently in situ and acts as a transmetalating agent in catalytic transformation. The reaction leads to the formation of new sp^2−sp^3 bonds and can be conducted regioselectively.[2] With one exception,[3] the catalyst supporting ligands are tertiary phosphines. These ligands are susceptible to thermal degradation and are often difficult to remove from products.

Herein, we describe a new class of palladium catalysts bearing a N-heterocyclic carbene (NHC) ligand (where NHC is SIPr [*N*,*N*′-bis(2,6-diisopropylphenyl)4,5-dihydroimidazol)-2-ylidene], IPr [*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol)-2- ylidene], IMes [*N*,*N*′-bis(2,4,6-trimethylphenyl)-imidazole)-2-ylidene], or ItBu [*N*,*N*′-bis *tert*-butyl-imidazol)-2-ylidene]), capable of mediating the direct coupling of readily available ketones with aryl chlorides.

N-Heterocyclic carbenes have proven to be efficient ligands in numerous coupling reactions mediated by palladium and nickel.[4] The use of bulky substituents on the imidazole nitrogens and the important σ-donating properties of the NHC are beneficial to the oxidative-addition and reductive-elimination steps of the cross-coupling catalytic cycle.

The ability of the NHC to coordinate metal centers[5] strongly makes them excellent candidates for the design of well-defined catalysts. Recent studies have presented catalytic systems bearing different numbers (one[6] and two[7]) of ligands in palladium-mediated cross-coupling reactions. Jutand and

---

[1] (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1742. (d) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101−104. (e) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.

[2] (a) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919. (b) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261−1268.

[3] Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507−2516.

[4] For reviews see: (a) Herrmann W. A *Angew. Chem., Int. Ed.* **2002**, 41, 1290−1309. (b) Hillier, A. C.; Nolan, S. P. *Platinum Metals Rev.* **2002**, *46*, 50−64. (c) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69−82. (d) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2000**, *46*, 181−222. (e) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *600*, 12−22.

[5] (a) Voges, M. H.; Rømming, C.; Tilset, M. *Organometallics* **1999**, *18*, 529−533. (b) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163−2187.

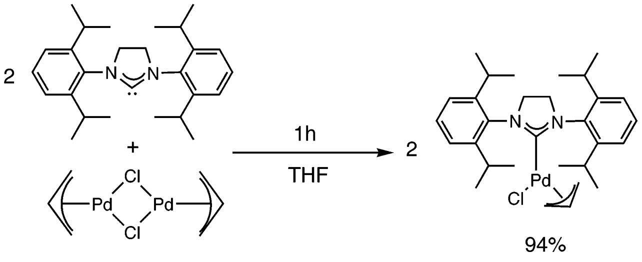
[6] (a) Jackstell, R.; Gomez A.; Frisch, A.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Rottger, D.; Briel, O.; Karch, R.; Beller, M., *Angew. Chem., Int.* Ed. **2002**, *41*, 986−989. (b) Lee, H.-M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053−2055. (c) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119−122. (d) Zhang, C.; Huang, J.; Trudell, M. T.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805.

10.1021/ol026745m CCC: $22.00

co-workers[8] have recently described palladium/phosphine systems that benefit from the presence of a single bulky tertiary phosphine ligand in the coordination sphere of palladium. These results, along with our early metal/ligand ratio optimization studies in palladium-mediated cross-coupling reactions, encouraged the design of catalysts bearing one NHC ligand and the examination of reactivity displayed by such complexes in various cross-coupling reactions.[9]

Recently, we observed that reaction of NHC with $[(\eta^3\text{-allyl})Pd(Cl)]_2$ led, with high yields, to the formation of monomeric species with the general formula (NHC)Pd(allyl)-Cl.[10] ^1H NMR and single-crystal X-ray structures confirmed the η^3 coordination of the allyl fragment and the distorted square planar geometry of the complex around the palladium center (Scheme 1).

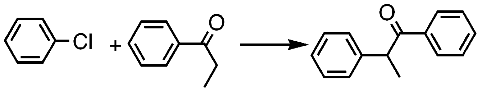
Scheme 1. Synthesis of (SIPr)Pd(allyl)Cl



The formal 16-electron configuration at the palladium center confers air-stability to the complexes. It is well-known in the literature that nucleophilic attack on the allyl moiety by a base, which should generate active species, is a very plausible catalyst activation step.[11] This active "NHC−Pd" species would then be able to oxidatively add aryl halides or pseudohalides. Beller and co-workers have also proposed the intermediacy of such a species in the palladium-mediated telomerization of butadiene.[6a] The product of this allylic attack by base, allyl *tert*-butyl ether, was unambiguously characterized by ^1H NMR spectroscopy.[12] Its formation is nearly quantitative based on the amount of palladium precursor. The trapping of a $(NHC)Pd{-}PR_3$ species[13] also confirmed the reduction of (NHC)Pd(allyl)Cl complexes to a (NHC)Pd species in the presence of base.

We investigated the use of (NHC)Pd(allyl)Cl complexes in cross-coupling of aryl halides and ketone enolates. Propiophenone and chlorobenzene were chosen as substrates for optimization studies. Propiophenone has the advantage of only having one available site for deprotonation. A strong base was required in order to abstract the acidic proton and to generate the enolate form of the ketone. NaO^tBu, 1.1 mmol, was found to be the most convenient and affordable base. The role of the base is twofold: to generate active Pd−NHC species and to deprotonate the ketone. No aryl-*tert*-butyl ether was detected by GC, indicating alkoxide anion attack to be occurring exclusively at the ketone and not on an oxidative adduct.[14] Hartwig and co-workers highlighted the need for the ketone to be in the enolate form to prevent side reactions.[15] In the present cases, an excess of base led to an increased amount of biarylated ketone. We concluded that monoarylated product is the subject of a second deprotonation due to the enhanced acidity of the methine proton.

Table 1. Catalyst Effect on α-Arylation of Propiophenone[a]



catalyst	yield(%)
(SIPr)Pd(allyl)Cl (**1**)	100
(IAd)Pd(allyl)Cl (**2**)	95
(IPr)Pd(allyl)Cl (**3**)	95
(IMes)Pd(allyl)Cl (**4**)	93
(I^tBu)Pd(allyl)Cl (**5**)	99

[a] Conditions: 1 mol % (NHC)Pd(ally)Cl, 1.1 mmol of NaO^tBu, THF, 70 °C, 1 h. GC yields are averages of two runs.

A survey of catalyst activity (Table 1) proved that steric properties of the ligand are important. The most effective catalyst was found to be (SIPr)Pd(allyl)Cl (**1**), although it is apparent that at 70 °C, all entries are very efficient catalysts for ketone arylation. The use of **1** leads to complete conversion of the substrates in 1 h at 70 °C. Other catalysts are slightly less active, and differences in reactivity, although not that significant at 70 °C, are notable at lower temperatures. For example, the difference in activity, at 50 °C in 1 h, between (SIPr)Pd(allyl)Cl (**1**) and its unsaturated relative (IPr)Pd(allyl)Cl (**3**) is noteworthy: **1** led to 97% conversion, while **3** yielded only 51% of the desired product. The reasons behind the difference in reactivity are not obvious at this time since only slight differences exist between steric and electronic properties of the saturated and unsaturated ligand

---

(7) (a) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309. (b) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363−1365.

(8) (a) Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1760−1763. (b) McGuiness, D.; Cavell, K. J. *Organometallics* **2000**, *19*, 741−748.

(9) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229−2231.

(10) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. Manuscript in preparation.

(11) (a) Vedernikov, A. N.; Sayakhov, M. D.; Solomonov, B. N. *Mendeleev Comm.* **1997**, *5*, 205−206. (b) Stanton, S. A.; Felman, S. W.; Parkurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964−1969.

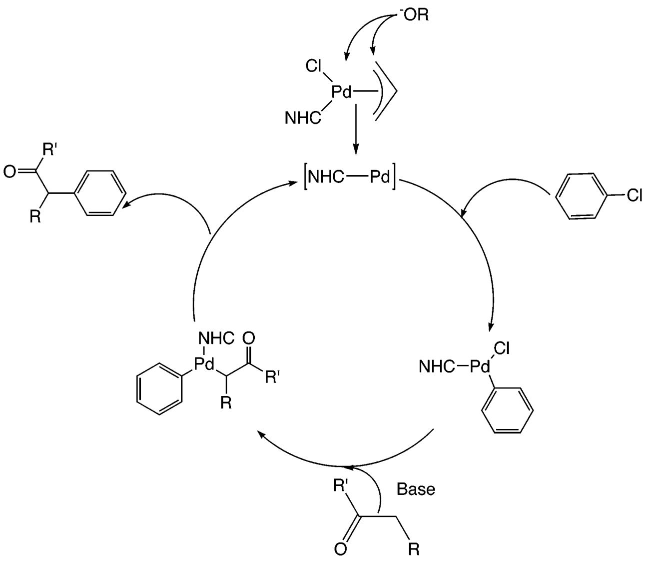
(12) The allyl ether could also be generated via halide replacement and reductive-elimination of the allyl alkoxy fragments on palladium. At this point, both routes are viewed as possible.

(13) Such species have been fully characterized. See: Titcomb, L. R.; Caddick, S.; Cloke, F. G. N.; Wilson, D. J.; McKerrecher, D. *Chem. Commun.* **2001**, 1388−1389.

(14) A reviewer suggested that it may be possible that the Pd(aryl)(OtBu) complex forms but reacts with free ketone to form the enolate or enolate complex faster than it does C−O bond-forming reductive elimination. This possibility also exists, and we thank the reviewer for his alternative explanation.

(15) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc*, **1999**, *121*, 1473−1478. (b) Hartwig has recently reported the use of a NHC palladium system generated in situ in reactions with esters: Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410−8411.

Scheme 2. Proposed Catalytic Cycle for the α-Arylation of Ketones Using a (NHC)Pd(allyl)Cl System



pair.[16] To investigate the scope and limitations of the palladium-allyl system, complex **1** was used as a catalyst.

A closer examination of the proposed catalytic cycle (Scheme 2) raises the question of possible β-hydrogen elimination from a tricoordinated species after a transmetalating step.

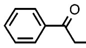
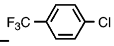
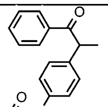
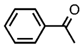
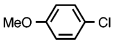
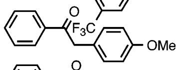
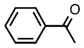
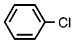
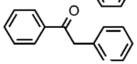
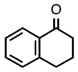
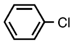
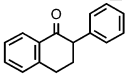
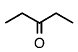
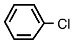
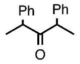
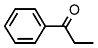
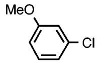
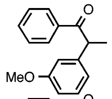
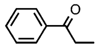
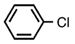
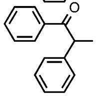
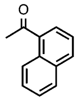
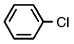
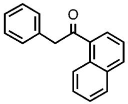
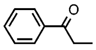
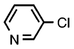
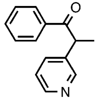
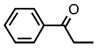
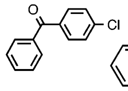
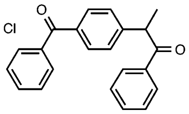
The availability of a vacant site on a species generated after oxidative addition could possibly facilitate β-hydrogen elimination. This reaction route appears to be quite sensitive to steric factors. We observed the formation of benzene in 6% yield when (IMes)Pd(allyl)Cl (**4**) was used as catalyst, but no benzene formation was observed when more sterically demanding catalysts were used.

A survey of reactivity of aryl and heteroaromatic halides with various alkyl−alkyl or aryl−alkyl ketones under catalytic conditions is provided in Table 2.

Operationally, the ketone was added to a mixture of catalyst, base, and solvent in order to induce the formation of the enolate. The aryl halides were injected last.

We focused our study on the use of aryl chlorides as reactive partners.[17] As a general trend of reactivity, aryl bromides are more reactive than chloride counterparts, but the amount of side-products is higher. The reactions of propiophenone with chloro- and bromobenzene reach completion within 1 h, but in the latter case, 10% benzene was observed. The presence of an aryl group α to the carbonyl minimizes the formation of multiarylated products, but it is not clear if either electronic or steric factors are essential. The reaction times are little or not affected by the electronics of substituents on the aryl halides. Unhindered dialkyl ketones have a tendency to react with more than 1 equiv of aryl halides. The reaction of chlorobenzene and 3-butanone gave an 80:20% mixture of mono- and diarylated products. By using 2 equiv of aryl halides per equivalent of 3-butanone, we were able to obtain pure diarylated product in less than 15 min. It was concluded that since the reaction was fairly rapid, base could deprotonate the product, thereby generating the second enolate, which would be involved in the subsequent reaction. We investigated the use of hindered substrates as a way to minimize the formation of diarylated byproducts. The results of coupling between hindered aryl halides and ketones are presented in Table 3.

Table 2. Palladium-Mediated α-Arylation of Ketones

substrates		product	temp(°C)	time(h)	yield(%)[a]
			70	1	97(81)
			70	1	95(78)
			70	1	98(93)
			70	6	50
			70	0.2	88[b]
			70	1	100(88)
			50	1	97(91)
			70	1	35
			50	1	86(60)
			70	4	95(71)

[a] Conditions: **1**, 1 mol %; THF, 4 mL; NaO^{t}Bu, 1.05 mmol; ketone, 1 mmol; aryl halide, 1 mmol; NMR yields, 95% pure compounds. Isolated yields reported in brackets. [b] Base (2 mmol) and aryl chloride.

The amount of diarylated and dehalogenated byproducts was effectively suppressed. One notable exception is the reaction of 2-bromomesitylene and propiophenone that led to 11% mesitylene and 80% isolated coupling product.

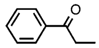
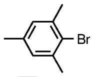
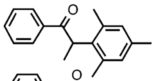
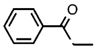
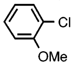
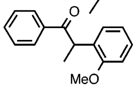
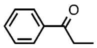
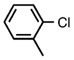
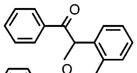
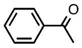
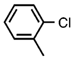
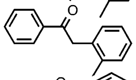
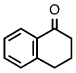
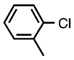
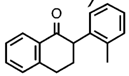
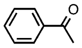
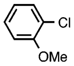
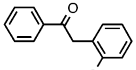
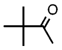
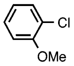
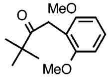
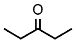
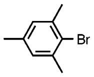
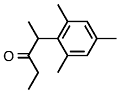
To test the generality of the catalytic system, a number of triflates were tested as substrates (Table 4). In initial attempts, using the reaction conditions described for the aryl chlorides, very poor or no yields of the desired coupling products were obtained. Only starting materials were observed under these conditions with no other product formed. However, changing the solvent from THF to toluene leads to facile arylation product formation in short reaction times. The reactions

---

(16) (a) Hillier, A. C.; Yong, B. S.; Sommer, W.; Petersen, J. L.; Nolan, S. P. *Organometallics*, manuscript submitted. (b) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39−92.

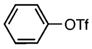
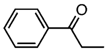
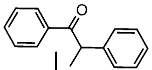
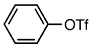
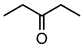
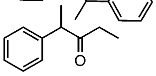
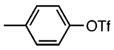
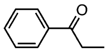
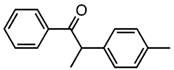
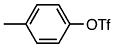
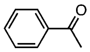
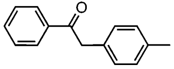
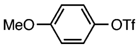
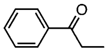
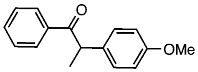
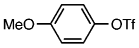
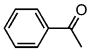
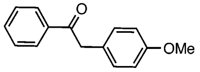
(17) For Pd−phosphine complexes able to mediate this transformation with aryl chlorides, see: Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209−217.

Table 3. α-Arylation of Ketones Using Hindered Aryl Halides[a]

substrates		products	temp(°C)	time(h)	yield(%)
			60	6	80(72)
			60	1	100(80)
			60	1	93(87)
			60	1	96(90)
			60	1	90
			60	1	82(80)
			60	1	91
			60	0.5	91(68)

[a] Conditions: **1**, 1 mol%; THF, 4 mL; NaO^{t}Bu, 1.05 mmol; ketone, 1 mmol; aryl halide, 1 mmol; NMR yields, 95% pure compounds. Isolated yields are reported in brackets.

Table 4. α-Arylation of Ketones Using Aryl Triflates

substrates		product	time(h)	yield(%)[a]
			1.5	91
			1.5	87[b]
			1	93
			1.5	88
			1	90
			1	87

[a] Reaction conditions: aryl triflates, 1 mmol; ketone, 1.1 mmol; 60 °C; NaO^{t}Bu, 100 mg; THF, 4 mL; isolated yields. [b] GC yield. All yields are averages of two runs.

conducted in toluene with aryl chlorides are kinetically slower than those performed in THF. The generality of the present catalytic system is presently being investigated on a larger number of aryl triflates and halides. The origin of the surprising solvent effect is also being examined.

In summary, a general and efficient protocol for coupling of aryl halides (and triflates) with ketones has been developed. The catalyst is part of a new generation of air-stable, well-defined palladium N-heterocyclic carbene systems. The activation of the catalyst is achieved by an alkoxide base acting as a nucleophile. The generality of the activation step makes this class of catalyst suitable for a large variety of cross-coupling reactions. The catalyst is very efficient in coupling aryl chlorides, bromides, or triflates with ketones, in terms of reaction temperature, reaction time, and catalyst loading. The regioselective reactions using catalysts based on chiral N-heterocyclic carbenes are currently under investigation.

Acknowledgment. We gratefully acknowledge financial support from the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Louisiana Board of Regents.

Supporting Information Available: Experimental details for the synthesis of (SIPr)Pd(allyl)Cl, the catalysis protocol, and the product isolation procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026745M