ORGANIC LETTERS

2000
Vol. 2, No. 10
1423−1426

High Turnover Number and Rapid, Room-Temperature Amination of Chloroarenes Using Saturated Carbene Ligands

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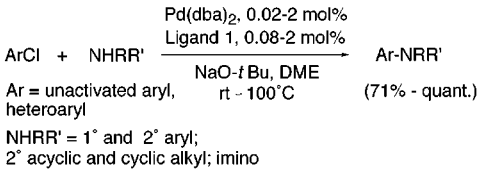
Received March 3, 2000

ABSTRACT



A catalytic system for the mild amination of aryl chlorides is described. This system consists of a Pd(0) precursor and a dihydroimidazoline carbene ligand, which is generated in situ from its protonated tetrafluoroborate salt (2). Using this catalyst, aryl and heteroaryl chlorides react with secondary amines and anilines within hours at room temperature. Turnover numbers as high as 5000 are obtained at elevated temperatures for reaction of morpholine with an unactivated aryl chloride.

The palladium-catalyzed amination of aryl halides[1−3] has experienced remarkable advances in substrate scope and reaction rates in recent years. Koie et al. reported the use of tri-*tert*-butylphosphine to obtain high turnover numbers for reactions of bromoarenes with piperazine and diarylamines at elevated temperatures.[4,5] We initially reported the use of sterically hindered alkylphosphines to observe room-temperature amination reactions with aryl bromides and to allow these reactions to be conducted under milder conditions with aryl chlorides and tosylates.[6]

More recently, our group and that of Buchwald's have reported the use of alkylmonophosphines to allow mild amination of aryl chlorides, including the room-temperature amination of unactivated aryl chlorides with several classes of amines.[7,8] Concurrent with this work, several groups have explored the use of Arduengo's heterocyclic carbene ligands[9−11] as phosphine analogues for cross-couplings. Hermann[12−15] initially reported the synthesis of palladium complexes of heterocyclic carbene ligands and their use for Heck reactions. Nolan has demonstrated that sterically hindered versions of these ligands, such as the chloride salt of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, are ef-

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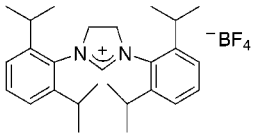
10.1021/ol005751k CCC: $19.00
Published on Web 04/27/2000

fective for the amination of aryl chlorides, albeit at elevated temperatures.[16] Trudell and Nolan have also studied their use in Kumada and Suzuki coupling of aryl chlorides,[17−19] at elevated temperatures. Most recently, Grubbs showed that ruthenium complexes of the saturated, and therefore more electron donating, analogues of Nolan and Trudell's ligands create highly active olefin metathesis catalysts based on ruthenium.[20]

As part of an effort to develop high-throughput screening methods for cross-coupling activity with libraries of phosphines and related ligands,[21] we found that the saturated carbene ligands used by Grubbs, specifically ligand **1** (Figure 1),[20] provide unusually fast reactions for the palladium-



1

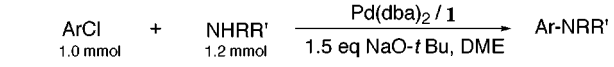
Figure 1. Dihydroimidazolium salt **1** for the amination reaction of aryl chlorides.

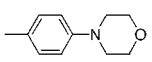
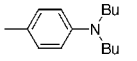
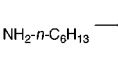
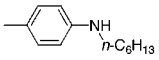
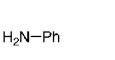
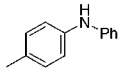
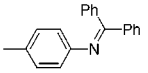
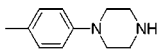
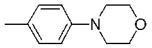
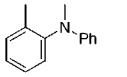
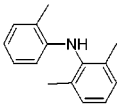
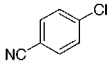
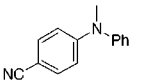
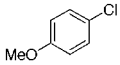
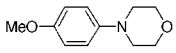
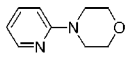
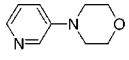
catalyzed coupling of aryl chlorides with amines at room temperature. This reactivity, presumably, results from the combination of strong electron donating ability and severe steric demands of **1**. We report herein the scope of the amination chemistry using remarkably active catalysts bearing these dihydroimidazoline ligands. In most cases, these reactions are faster or equal in rate to those using any previously reported catalyst system.[7,8] Use of ligand **1** in these reactions also allows for the first room-temperature coupling of chloropyridines and the highest reported turnovers for the amination of unactivated aryl chlorides. Protonated imidazoline ligands, such as **1**, are air stable and easily prepared from inexpensive components: 2,6-diisoproylaniline, glyoxal, sodium borohydride, triethyl orthoformate, and ammonium tetrafluoroborate.

Table 1 provides results on the room-temperature amination of aryl chlorides using the optimized conditions, which consisted of 0.02−2 mol % of the tetrafluoroborate salt of the protonated carbene and bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) as catalyst, sodium *tert*-butoxide as base, and DME as solvent.[22]

The dimeric precatalyst $Pd_2(dba)_3$ in place of $Pd(dba)_2$ was equally effective in these reactions. In addition, $Pd(OAc)_2$ can be used;[22] however, reaction times are slightly longer. DME or dioxane was comparable as the solvent and gave the fastest reaction times, followed by reactions in THF and

Table 1. Amination of Aryl Chlorides Using $Pd(dba)_2$/**1**[a]



entry	ArCl	amine	product	T / °C	time	yield[b]
1				rt	3h	quant.
2				rt	20h	86%[c]
3				70	8h	40%[c]
4				rt	18h	82%[c,d]
5				55	18h	94%[c]
6				100	3h	71%[c,e]
7				100	7h	quant.[f]
8				rt	16h	97%[c]
9				rt	4h	88%
10				rt	3h	97%
11				rt	5h	96%
12				rt	3h	98%
13				rt	20h	93%[c]

[a] performed at 1 mol% Pd / **1** (1/1) and 1.0 M unless indicated otherwise; see [22] for further details. [b] isolated yields are average of at least two runs; products >95% pure as judged by ^{1}H NMR and GC [c] 2 mol% Pd / **1** [d] substrate conc. 2.0 M. [e] 4 equiv of amine. [f] substrate conc. 2.9 M, 0.02 mol% Pd and 0.08 mol% ligand **1**.

toluene. Milder bases such as Cs_2CO_3 and K_3PO_4 were not effective in these reactions and resulted in low conversion of the arylated product. This finding is in accord with observations made by Grubbs and co-workers that alkoxides are required to deprotonate **1**.[20]

Using the optimal conditions, reactions of cyclic secondary amines with unactivated or even deactivated chloroarenes occurred within 5 h at room temperature with only 1 mol %

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(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(21) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123.

(22) **Representative Procedure:** In a drybox, aryl halide (1.00 mmol), amine (1.20 mmol), $Pd(dba)_2$ (0.01 mmol), 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene HBF_4 (0.01 mmol, **2**), and sodium *tert*-butoxide (144 mg, 1.50 mmol) were weighed directly into a screw cap vial. A stir bar was added followed by 1.0 mL of ethylene glycol dimethyl ether (DME). The vial was removed from drybox and allowed to stir at room temperature. The reaction was monitored by GC and after complete consumption of aryl halide the mixture was adsorbed onto silica gel and purified by flash chromatography. All products in Table 1 have been previously characterized.

of catalyst (entries 1 and 11). In all cases with this substrate combination, yields exceeded 95%. Reactions to form sterically hindered diarylamines also occurred in short reaction times at room temperature. 2-Chlorotoluene reacted with 2,6-dimethylaniline (entry 9) in only 4 h at room temperature with 1 mol % of catalyst. It should be noted, however, that sterically hindered *secondary* amines, such as diphenylamine and dicyclohexylamine (not shown), did not provide coupling products, even at higher catalyst loadings (2 mol %) and higher temperatures (70 °C).

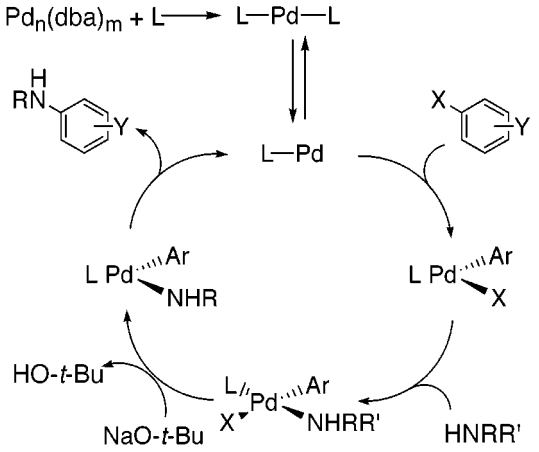
Reactions of acyclic secondary amines and less hindered anilines occurred at room temperature using 2 mol % of catalyst with rates that were comparable to those with *tert*-butylphosphine ligands. Dibutylamine and *N*-methylaniline reacted with 4- and 2-chlorotoluene, respectively (entries 2 and 8), to form the coupled product in 86−97% yield, and aniline reacted with 4-chlorotoluene in 82% yield (entry 4). *N*-Methylaniline reacted with the activated aryl chloride, 4-chlorobenzonitrile, in only 3 h with 1 mol % of catalyst (entry 10).

This catalyst system was less effective for reactions of primary alkylamines with aryl chlorides than others reported previously (entry 3).[8,16] Reaction rates were slower, and substantial amounts of hydrodehalogenation product were observed. Even aryl chlorides with *ortho* substituents reacted poorly, resulting in low conversion of the coupled product. For this class of amine, Nolan's unsaturated imidazolium ligand and hindered phosphine ligands appear to be more favorable, although not ideal.

Arylpiperazines are an important class of medicinal compound and have been prepared using the palladium-catalyzed amination reaction with primarily aryl bromides and iodides as coupling partners.[4,23] One reaction of an aryl chloride was reported by Koie et al. using $P(t\text{-Bu})_3/Pd(dba)_2$ as catalyst resulting in an 88% conversion by GC analysis.[4] Using the carbene system, 4-chlorotoluene coupled with piperazine to form the *N*-aryl product in moderate yield (entry 6); higher temperatures than those used for dialkyl monoamines were necessary.

Coupling of bromopyridines using aryl bisphosphines has been reported,[24] and the reaction of bromopyridines using *tert*-butyl monophosphines has been accomplished.[4] However, when monophosphines are used, the reaction of pyridine substrates is typically slower than reactions using simple aromatic substrates.[8b] The pyridine substrate may compete with the phosphine for coordination to palladium,[25,26] thereby inhibiting the coupling reactions. Thus, the activity of the palladium/carbene catalyst for reactions of chloropyridines is remarkable (entries 12 and 13). Morpholine reacted with 2-chloropyridine in only 3 h at room temperature with 1 mol % of catalyst. Reaction with the less electron deficient 3-chloropyridine also occurred at room temperature, this time after 20 h when using 2 mol % of catalyst. These reaction

Scheme 1. Proposed Catalytic Cycle for Amination Reaction



temperatures are roughly 80 °C lower than those for reactions involving sterically hindered monophosphines as ligands.[8b] Thus, it appears that the strong binding of the carbene ligands to the metal center[27] prevents competitive inhibition by the pyridine substrates. Benzophenone imine, which might also compete with a monodentate ligand for coordination to palladium, also reacted to give good yields of coupled product; at 55 °C complete conversion occurred after 18 h using 2 mol % of catalyst. This reaction is also milder than those involving sterically hindered monophosphines.[8b]

Although drybox procedures were used for the substrates examined in Table 1, a drybox is *not* required to successfully perform these reactions. In one set of experiments all of the solid components (1 mol % of $Pd(dba)_2$, 1 mol % of **1**, and 2.0 equiv of NaO-*t*-Bu) were weighed in air. In these experiments an additional half equivalent of alkoxide was used in case quenching of the base occurred due to adventitious moisture. The reaction flask was then evacuated and placed under an atmosphere of N_2. Aryl chloride, reagent grade DME (Aldrich), and amine were then added without degassing from bottles stored in air. Under these conditions, the coupling of morpholine with 4-chlorotoluene gave a 95% isolated yield, which was indistinguishable from that observed when drybox procedures were used.

The fast reaction rates for this catalyst system led us to determine the activity at higher temperatures with a lower catalyst loading. When using 0.02 mol % of catalyst and 0.08 mol % of **1**, reactions of morpholine with chlorotoluene occurred in essentially quantitative yields after 7 h at 100 °C. This reaction provides 5000 turnovers. At this catalyst loading, the catalyst cost is roughly one tenth the cost of the other reaction components, even with these structurally simple reagents. In fact, the alkoxide is the most expensive reaction component when this catalyst loading is used. The value of a system that would display higher turnover numbers for this class of amination reaction is limited, unless it provides similar activity with a less costly base.

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The mechanism for this reaction is likely to follow that for previously reported systems, as shown in Scheme 1.[1,28] The catalyst resting state and the turnover limiting step are not known at this time. However, the dependence of rate on the identity of the amine suggests either that reaction of the catalyst with amine, not aryl chloride, is rate limiting or that catalyst lifetime depends strongly on the type of amine used. Mechanistic studies to evaluate these issues with both highly active phosphine ligands and these saturated carbene ligands are in progress.

Acknowledgment. We thank the NIH (R29-6 M-55382) for support of this work. S.R.S. acknowledges the NIH (GM-20191-01) for a postdoctoral fellowship. S.L. acknowledges the Korea Science and Engineering Foundation (KOSEF) for a postdoctoral fellowship.

OL005751K

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