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COMMUNICATIONS

Published on Web 11/02/2006

Palladium-Catalyzed Synthesis of Aryl Ketones by Coupling of Aryl Bromides with an Acyl Anion Equivalent

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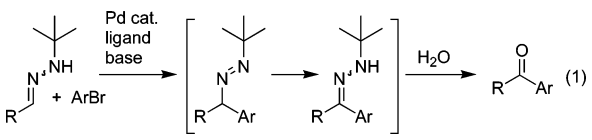
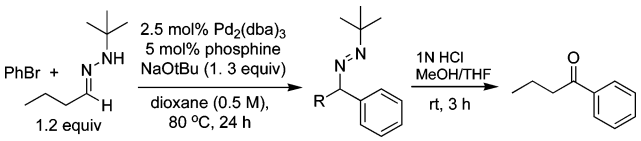
Palladium-catalyzed coupling reactions[1,2] to form carbon−carbon bonds have recently been expanded to include the coupling of aryl halides with carbonyl compounds to form α-aryl ketones,[3,4] esters,[5] and amides.[6,7] We envisioned a related reaction between an aryl halide and an acyl anion equivalent to form the acyl aryl carbon−carbon bond in aryl ketones by combining methods to couple aryl halides with substrates containing acidic C−H bonds and methods to convert electrophilic aldehydes into nucleophiles. Compared to the conventional preparation of aryl ketones from aldehydes by addition of Grignard reagents, followed by oxidation, the coupling of an acyl anion equivalent would avoid the conversion of the organic halide to a Grignard reagent, would alleviate the relative intolerance of organomagnesium reagents toward functional groups, and would eliminate the need for redox processes. There are only a few reports of direct coupling reactions between aryl halides and aldehydes to form ketones,[8,9] and they form alkyl aryl ketones in low yield or require a metal-binding group on the aldehyde.

Several acyl anion equivalents could be envisioned to undergo cross-coupling. Dithianes[10] and cyanohydrins[11] are often used in purely organic transformations, and an acyl anion equivalent is generated during the Stetter reaction.[12] However, the acyl anion equivalents based on hydrazones developed by Baldwin[13−15] seemed more amenable to cross-coupling (eq 1) because their acidity is closer to that of the carbonyl compounds that undergo palladium-catalyzed arylation in the presence of alkoxide base. As shown in eq 1, if the *N-tert*-butylhydrazones underwent coupling at the carbon of the diazaallyl unit, isomerization of the initial azo product to the corresponding hydrazone, followed by hydrolysis, would yield the arylketone.[14] The direct reaction of *N-tert*-butylhydrazones with organic electrophiles is known,[16,17] but the use of hydrazones as acyl anion equivalents in metal-catalyzed reactions is not. Moreover, the addition of the deprotonated hydrazone to a metal center would be likely to form a diazaallyl intermediate, and the chemistry of such compounds is unexplored. We report the development of a palladium-catalyzed coupling of aryl bromides with *N-tert*-butylhydrazones to form alkyl aryl ketones or diaryl ketones from aryl halides and alkyl or aryl aldehydes (eq 1). These reactions occur in the presence of a number of electrophilic functional groups, and preliminary data imply that they occur through η^1-diazaallyl intermediates.



To develop the coupling of aryl halides with the *N-tert*-butylhydrazones of aldehydes, we studied the reactions of bromobenzene with the *N-tert*-butylhydrazone of butyraldehyde in the presence of NaO-^{t}Bu as base and $Pd_2(dba)_3$ and several phosphines as catalyst precursors. The reactions were conducted in dioxane solvent and were heated for 24 h at 80 °C. The results of reactions conducted with several ligands are shown in Table 1.

Table 1. Palladium-Catalyzed Coupling of Bromobenzene with *N-tert*-Butylhydrazone



entry	phosphine	conversion of PhBr[a] (%)	yield of ketone[a] (%)
1	DPEphos[b]	100	99
2	Xantphos[c]	100	93
3	BINAP[d]	91	61
4	DPPF[e]	54	trace
5	DPPB[f]	59	28
6	PPh_3 (10 mol %)	77	7
7	P^{t}Bu$_3$	100	56
8	Q-phos	100	37

[a] Determined by GC with an internal standard. [b] Bis(2-diphenylphosphinophenyl)ether. [c] 9,9-Dimethyl-4,5-bis(diphenylphoshino)xanthene. [d] 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. [e] 1,1′-Bis(diphenylphosphino)ferrocene. [f] 1,4-Bis(diphenylphosphino)butane.

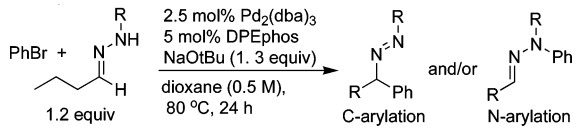
The reaction with $Pd_2(dba)_3$ and DPEphos as catalyst occurred to form the desired butyrophenone in nearly quantitative yield after hydrolysis (entry 1). Reactions conducted with $Pd_2(dba)_3$ and Xantphos also gave the desired ketone in good yield (entry 2). The similarity of the results of these two reactions is consistent with the comparable bite angle of DPEphos and Xantphos. Reactions conducted with bidentate phosphines containing smaller bite angles than DPEphos resulted in lower conversions (entries 3−5). The reactions catalyzed by $Pd_2(dba)_3$ and a monodentate arylphosphine formed complex mixtures (entry 6), and reactions conducted with sterically hindered monodentate ligands formed both C- and N-arylation products and ultimately a moderate yield of the desired ketone (entries 7 and 8). No reaction was observed in the presence of Cs_2CO_3 as base, and the yield of desired ketone was lower (87%) when the reactions with $Pd_2(dba)_3$ and DPEphos as catalyst were conducted in toluene.

We also tested reactions of several hydrazones containing different substituents on nitrogen. As summarized in Table 2, this group strongly influenced the extent of reaction and the selectivity for C- versus N-arylation. The reaction of bromobenzene with *N-tert*-butylhydrazone gave the desired C-arylated product selectively in good yield (entry 1). In contrast, the *N*-Boc and *N*-benzoylhydrazone, which have more acidic N−H protons and less nucleophilic conjugate bases, did not react (entries 2 and 3). Although the *N*-phenylhydrazone did react with PhBr, it formed the product from N-arylation (entry 4). Only trace amounts of the product of C-arylation were formed.

The scope of the coupling of different aliphatic and aromatic *N-tert*-butylhydrazones with a variety of bromoarenes is summarized

10.1021/ja064782t CCC: $33.50

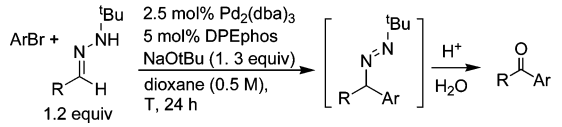
Table 2. Palladium-Catalyzed Coupling of Bromobenzene with Various Hydrazones



entry	R	yield[a] (%)
1	^{t}Bu	98 (C-arylation)[b]
2	Boc[c]	no reaction
3	Bz[d]	no reaction
4	Ph	91 (N-arylation)

[a] Isolated yield. [b] Yield of corresponding ketone after hydrolysis. [c] *tert*-Butoxycarbonyl. [d] Benzoyl.

Table 3. Palladium-Catalyzed Coupling of Aryl Bromides with *N-tert*-Butylhydrazones



entry	Ar	R	*T* (°C)	yield (%)[a]
1	Ph	*n*-propyl	80	98
2	Ph	cyclohexyl	80	81
3	Ph	benzyl	80	96
4	Ph	Ph	80	85
5	4-OMeC$_6$H$_4$	*n*-propyl	80	94
6	4-OMeC$_6$H$_4$	cyclohexyl	80	79
7	4-OMeC$_6$H$_4$	benzyl	80	91
8	4-CNC$_6$H$_4$	*n*-propyl	80	70
9	4-CNC$_6$H$_4$	cyclohexyl	70	46
10	4-CNC$_6$H$_4$	benzyl	70	73
11	4-CF$_3$C$_6$H$_4$	*n*-propyl	70	90
12	4-CF$_3$C$_6$H$_4$	cyclohexyl	70	66
13	4-CF$_3$C$_6$H$_4$	benzyl	70	80
14	4-PhCOC$_6$H$_4$	*n*-propyl	70	87
15	4-PhCOC$_6$H$_4$	cyclohexyl	70	52
16	4-PhCOC$_6$H$_4$	benzyl	70	95
17	4-^{t}BuO$_2$CC$_6$H$_4$	*n*-propyl	70	75
18	4-^{t}BuO$_2$CC$_6$H$_4$	benzyl	70	91
19	4-morpholino-COC$_6$H$_4$	*n*-propyl	50	83
20	4-morpholino-COC$_6$H$_4$	cyclohexyl	50	60
21	4-morpholino-COC$_6$H$_4$	benzyl	50	88
22	4-TBSO(CH$_2$)$_2$C$_6$H$_4$	*n*-propyl	50	78[b]
23	4-TBSO(CH$_2$)$_2$C$_6$H$_4$	benzyl	50	97[b]
24	3-pyridyl	*n*-propyl	70	98
25	3-pyridyl	cyclohexyl	70	85
26	3-pyridyl	benzyl	70	71
27	1-cyclohexenylOTf[c]	benzyl	70	52
28	4-MeCOC$_6$H$_4$	*n*-propyl	50	N.D.

[a] Isolated yield. [b] Free alcohol was obtained as product. [c] 1-Cyclohexenyl trifluoromethanesulfonate was used as a substrate instead of aryl bromide. TBS = *tert*-butyldimethylsilyl. N.D. = not detected.

in Table 3.[18] These reactions were conducted under the optimized conditions of entry 1 in Table 2. The reactions of hydrazones containing primary and secondary alkyl groups gave the desired ketones in good yield after hydrolysis (entries 1 and 2). Even the reaction of the hydrazone containing acidic benzylic hydrogens underwent reaction as an acyl anion to form the corresponding benzyl ketone in high yield (entry 3). In addition to hydrazones from alkyl aldehydes, the hydrazone from benzaldehyde reacted, in this case to form a diaryl ketone (entry 4).

The reaction also occurred with aryl bromides containing various substituents. Both electron-rich (entries 5−7) and electron-poor (entries 8−21) aryl bromides gave the desired ketones in high yield after hydrolysis. Further, the reaction occurred in the presence of several classes of functional groups. As shown in entries 14−16, the reactions of the three hydrazones occurred with 4-bromobenzophenone. The reaction also occurred in the presence of a *tert*-butyl ester (entries 17 and 18) and in the presence of a morpholine amide (entries 19−21). Aryl bromides containing TBS-protected alcohols also reacted to form the ketone. In this case, the free alcohol was obtained after hydrolysis (entries 22 and 23). In addition, the reaction occurred with some heteroaryl halides (entries 24−26). Likewise, reactions of vinyl triflates with the acyl anion equivalent formed α,β-unsaturated ketones (entry 27). However, 4-bromoacetophenone, which contains enolizable hydrogens, did not react to give the desired ketone (entry 28).

The most likely mechanism for this process would parallel the mechanism for coupling of aryl halides with amines and ketones. After oxidative addition to form an arylpalladium halide complex, a diazaallyl intermediate would form by reaction of this complex with the combination of hydrazone and base. The diazaallyl ligand in this complex could be bound in an η^1 mode through carbon or nitrogen, or it could be bound in an η^3 mode through the acyl carbon and the two nitrogen atoms. Although more detailed mechanistic studies are needed to define the binding mode of this ligand, the C−C bond-forming reductive elimination appears to occur from an η^1-diazaallyl complex because the reaction occurred faster with catalysts containing bidentate ligands that would enforce an η^1 binding mode of the allyl ligand than with catalysts containing monodentate ligands that would accommodate an η^3 binding mode.

In summary, we have developed an efficient cross-coupling reaction of aryl bromides using *N-tert*-butylhydrazones as acyl anion equivalent. These hydrazones are readily accessible from aldehydes and *N-tert*-butylhydrazine, and the coupling occurred under mild conditions at the C-position of the diazaallyl group when the hydrazone contained a *tert*-butyl group on nitrogen. Studies of the mechanism of this coupling reaction, including efforts to observe a diazaallyl intermediate, will be the focus of future work.

Acknowledgment. We thank the NIH (NIGMS GM-58108) for support of this work. A.T. thanks Mitsubishi Pharma Corporation for financial support.

Supporting Information Available: Reaction procedures and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Studies on the reactions of chloroarenes will be reported in due course.

JA064782T