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Direct Hiyama Cross-Coupling of Enaminones With Triethoxy(aryl)silanes and Dimethylphenylsilanol

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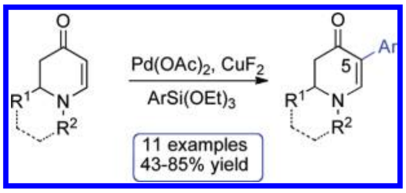
ABSTRACT



2,3-Dihydropyridin-4(1H)-ones undergo direct C–H functionalization at C5 in the palladium(II)-catalyzed Hiyama reaction, using triethoxy(aryl)silanes and dimethylphenylsilanol. The reagent CuF_2 has a dual role in the reactions with triethoxy(aryl)silanes. It is a source of fluoride to activate the silane in the Hiyama reaction and also serves as the reoxidant to convert Pd(0) to Pd(II) in the catalytic cycle.

Cross-coupling reactions that directly convert C–H to C–C bonds are valuable atom-efficient chemistry processes when compared with conventional cross-coupling reactions.[1,2] A transition metal-catalyzed C–H functionalization obviates the need for a preactivation step to set up the substrate for the cross-coupling reaction. As a C–C bond-forming strategy, direct arylation of C–H bonds has attracted considerable attention.[3] However, the majority of these reactions have been performed employing aromatic C–H bonds and often involve a directing group.[4] We have recently shown that enaminones (2,3-dihydropyridin-4(1*H*)-ones) can be substrates for direct C–H functionalization in Pd(II)-catalyzed Suzuki-type reactions.[5] We have proposed that the innate nucleophilicity of C5 of enaminones allows for the direct reaction with electrophilic Pd(II), which is followed by deprotonation of the palladium intermediate, transmetalation, and reductive elimination (Figure 1).[6] The catalytic cycle is completed by reoxidation of Pd(0) to Pd(II) with an appropriate oxidant such as $Cu(OAc)_2$.

We have recently demonstrated the utility of this chemistry for the concise enantiospecific synthesis of the phenanthropiperidine alkaloids ipalbidine and antofine,[7] tylocrebrine,[8] and boehmeriasin A.[9]

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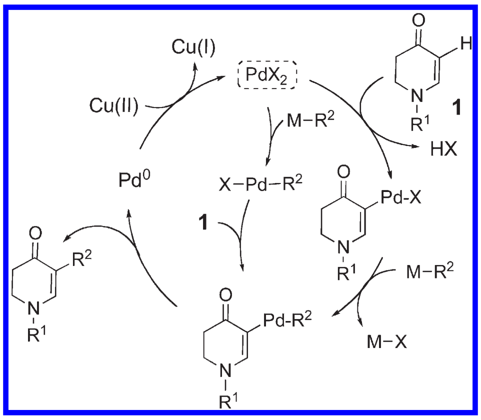
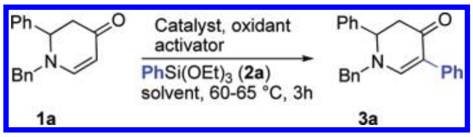


Figure 1. Proposed catalytic cycle for the direct arylation of enaminones **1**.

On the basis of our results with the Suzuki-type reactions, we hypothesized that the palladated enaminone intermediate could participate in other cross-coupling reactions, such as the Hiyama coupling. Hiyama reactions typically take place between organohalides (alkyl, aryl, and alkenyl) and organosilanes.[10] Organosilanes have a number of advantages that make them desirable organic reagents for cross-coupling reactions in comparison to organoboranes or organostannanes. They are stable, relatively nontoxic, and can be easily prepared. Nonetheless, only a few cases of direct C−H arylation with organosilane coupling partners have been reported. Yang et al.[11] described the direct Hiyama ortho arylation of acetanilides and Zhou et al.[4k] described the reaction of cyclic *N*-acetyl enamides with arylsilanes. In both cases, the palladation is believed to be dependent upon neighboring group assistance. To explore whether enaminones could participate directly in the Hiyama reaction, we selected 1-benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (**1a**) as the substrate, $Pd(OAc)_2$ as the catalyst, $Cu(OAc)_2$ as the reoxidant, and TBAF to activate the triethoxy(phenyl)silane (**2a**) (Table 1, entry 1). The initial result was quite discouraging because only a trace amount of the desired reaction product **3a** could be identified, accompanied by the biphenyl homocoupled product. Similar results were obtained when potassium fluoride was employed (Table 1, entry 2). Silver(I) fluoride appeared to be a better activator, compared to the more commonly used TBAF and KF, possibly due to the oxidative effect of silver(I) (Table 1, entry 3).

Table 1. Reaction Optimization for the Hiyama Coupling Reaction of Enaminone **1a**



entry[a]	catalyst	oxidant/activator	solvent	yield (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$/TBAF	THF	0[c]
				trace
2	$Pd(OAc)_2$	$Cu(OAc)_2$/KF	dioxane	trace
3	$Pd(OAc)_2$	$Cu(OAc)_2$/AgF	dioxane	30
4	$Pd(OAc)_2$	$Cu(OTf)_2$/AgF	dioxane	0[d]
5[e]	$Pd(OAc)_2$	AgF_2	dioxane	50
				62[f]
6	White catalyst[g]	AgF_2	dioxane	40
7	$Pd(TFA)_2$	AgF_2	dioxane	48
8	$PdCl_2$	AgF_2	dioxane	trace
9	PdI_2	AgF_2	dioxane	0
10	$NiBr_2$	AgF_2	dioxane	0
11	NiF_2	AgF_2	dioxane	trace
12	$Pd(OAc)_2$	CuF_2	dioxane[h]	0
			^{t}BuOH/AcOH (4:1)[i]	82
13[j]	$Pd(OAc)_2$	$Cu(OAc)_2$/TBAF	DMF	80
14[j]	$Pd(OAc)_2$	$Cu(OAc)_2$/KOTMS	DME	77

[a] Reaction conditions unless otherwise specified: enaminone **1a** (0.1 M), siloxane **2a** (2 equiv), catalyst (0.3 equiv), oxidant (2 equiv), activator (2 equiv), 3 h. [b] Isolated yield. [c] $PhSiMeCl_2$ was used. [d] Enaminone **1a** decomposed. [e] Typical reaction was completed within 1 h when AgF_2 was used. [f] Siloxane **2a** (3.5 equiv). [g] 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate. [h] Enaminone **1a** was recovered. [i] $Pd(OAc)_2$ (0.25 equiv), CuF_2 (2.5 equiv), siloxane **2a** (2.5 equiv), 65 °C, 3 h. [j] $PhSiMe_2OH$ (**2b**) was used instead of **2a**.

Since copper and silver are both in group 11 in the periodic table, we next explored Ag(II) in this reaction because it is expected to possess chemical properties similar to Cu(II). We selected AgF_2, which contains two equivalents of fluoride and is also an oxidant to test the proposition that AgF_2 could not only provide the necessary fluoride atoms for the activation of the silane but also function as the reoxidant in the palladium catalytic cycle. Gratifyingly, the Hiyama coupling reaction proceeded smoothly and with a satisfactory yield (Table 1, entry 5). When different catalysts were examined in this reaction, $Pd(TFA)_2$ exhibited comparable activity while other Pd(II) or Ni(II) salts showed inferior catalytic capabilities (Table 1, entries 6−11). The reaction with AgF_2, however, required the use of a large excess of organosilane. Therefore, we decided to replace AgF_2 with CuF_2. An initial attempt with CuF_2, using dioxane as the solvent, did not provide the reaction product (Table 1, entry 12). However, when the solvent was changed to a 4:1 mixture of *tert*-butyl alcohol and acetic acid, the yield of the Hiyama coupling product increased to 82% (Table 1, entry 12). We also examined dimethylphenylsilanol (**2b**), an organosilanol

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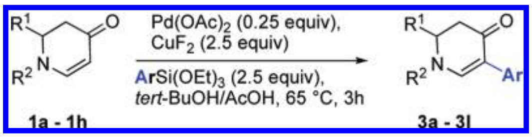
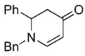
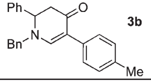
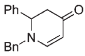
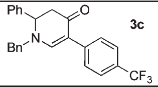
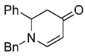
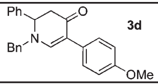
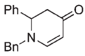
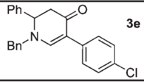
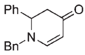
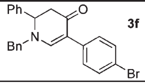
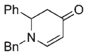
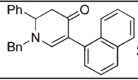
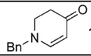
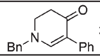
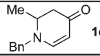
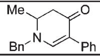
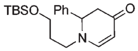
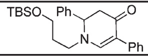
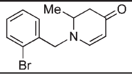
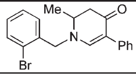
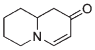
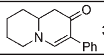
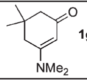
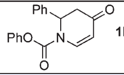
Table 2. Substrate Scope of Hiyama Coupling Reactions



entry[a]	enaminone	product	yield (%)[b]
1	 1a	 3b	85
2	 1a	 3c	73
3	 1a	 3d	50
4	 1a	 3e	65
5	 1a	 3f	61
6[c]	 1a	 3g	43
7	 1b	 3h	62
8	 1c	 3i	81
9	 1d	 3j	75
10	 1e	 3k	68
11	 1f	 3l	72
12[d]	 1g	not observed	0
13[d]	 1h	not observed	0

[a] Reaction conditions: enaminone (0.1 M), Pd(OAc)$_2$ (0.25 equiv), CuF$_2$ (2.5 equiv), ArSi(OEt)$_3$ (2.5 equiv) in ^{t}BuOH/AcOH (4:1), 65 °C, 3 h. [b] Isolated yield. [c] α-Naphthyltrimethoxysilane was used. [d] Starting material recovered.

introduced by Denmark, as a potential coupling partner.[12] Both fluoride-containing (Table 1, entry 13) and fluoride-free (Table 1, entry 14) conditions gave excellent results with this reactant. The clean, complete conversion clearly demonstrated the utility of these reagents as alternative coupling partners. To the best of our knowledge, this is the first case where an organosilanol has been used in a direct C−H cross-coupling reaction.

The optimized reaction conditions from Table 1, entry 12, were next used to examine the scope of the reaction with different enaminones and substituted triethoxy(aryl)silanes (Table 2). The Hiyama coupling reactions of enaminone **1a** worked well with substituted triethoxy(phenyl)silanes that carry a 4-methyl group (Table 2, entry 1), the electron-withdrawing 4-trifluoromethyl group (Table 2, entry 2), and the electron-donating 4-methoxy group (Table 2, entry 3). The sterically hindered α-naphthyltrimethoxysilane was also a suitable coupling partner (Table 2, entry 6).

Both monocyclic and bicyclic enaminones were sufficiently active in the direct coupling reactions (Table 2, entries 7, 8 and 11). TBAF, often used in Hiyama coupling reactions to activate the organosilicon reagent, also deprotects silyl protecting groups and thus presents a limitation of this method. It is of note that the TBS group was stable in the presence of CuF$_2$ (Table 2, entry 9). We observed that halides on both the enaminone and organosiloxane remained intact, presenting positions for further derivatization (Table 2, entries 4, 5 and 10). Steric (Table 2, entry 12) or electronic factors (Table 2, entry 13) are presumably responsible for the lack of reactivity of enaminones **1g** and **1h**.

In summary, effective protocols for the Hiyama coupling reaction with enaminones have been developed. In the case of triethoxy(aryl)silanes as the coupling partner, AgF$_2$ and CuF$_2$ were employed for the first time as bifunctional activator/reoxidants. Dimethylphenylsilanol was successfully used as well, without fluoride activation. All reactions took place in open air. To the best of our knowledge, this is the first direct Hiyama coupling reaction to take place without neighboring group assistance and with an organosilanol. The reaction conditions are compatible with the TBS protecting groups and, thus, could find utility in multistep organic syntheses.

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Supporting Information Available. Representative experimental procedures, characterization data and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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