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**Pd-Catalyzed  $\alpha$ -Arylation of Trimethylsilyl Enol Ethers with Aryl Bromides and Chlorides: A Synergistic Effect of Two Metal Fluorides as Additives\*\****Weiping Su, Steven Raders, John G. Verkade,\*  
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Ketone enolates are among the most common nucleophiles in organic chemistry, and transition-metal-catalyzed cross-coupling reactions are among the most commonly used catalytic processes.<sup>[1]</sup> However, the combination of these two chemistries—cross-coupling of enolate nucleophiles—has been developed only recently.<sup>[2–6]</sup> Moreover, coupling of silyl enol ethers, which temper the high basicity and nucleophilicity of alkali metal enolates,<sup>[7]</sup> is undeveloped.<sup>[8–11]</sup> The first example of the cross-coupling of silyl enol ethers was reported in 1982 by Kuwajima and Urabe, and the reactions of related tin enolates were reported by Kosugi and co-workers in 1984.<sup>[9]</sup> The reactions of silyl enol ethers were limited to the enolates of methyl ketones, and the activation of the silyl enol ether was conducted with stoichiometric tributyltin fluoride. Over the next twenty years, the scope and utility of the coupling of silyl or stannyl enol ethers has advanced only slightly.<sup>[10–12]</sup>

The cross-coupling of silyl enol ethers offers several advantages over the coupling of alkali-metal enolates of ketones. The reduced basicity should improve functional-group compatibility; the defined structure of the main-group enolate could allow coupling at the more hindered site of a ketone with two enolizable positions; and conditions for the coupling of silyl enol ethers could ultimately allow the development of enantioselective processes to form acidic tertiary stereocenters.

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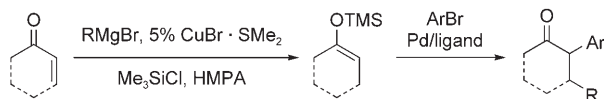
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We report two protocols for the coupling of several classes of ketones with aryl bromides catalyzed by palladium and  $\text{PrBu}_3$ . These reactions are conducted in toluene as the solvent with a combination of tributyltin fluoride and cesium fluoride as additives, or in  $N,N$ -dimethylformamide (DMF) with a combination of cesium fluoride and zinc fluoride as additives. The success of these procedures, which tolerate a variety of electrophilic functionalities and allow arylations at the more hindered position of dialkyl ketones, results from a synergistic effect<sup>[13]</sup> of two fluoride activators.

One set of studies focused on the arylation of silyl enol ethers formed by the addition of Grignard reagents to  $\alpha,\beta$ -unsaturated ketones in the presence of  $\text{CuBr} \cdot \text{Me}_2\text{S}$ , chlorotrimethylsilane, and hexamethylphosphoramide (HMPA; Scheme 1).<sup>[14]</sup> Studies of the model reaction of 2-trimethyl-



**Scheme 1.** Two approaches to  $\alpha$ -arylated carbonyl compounds.

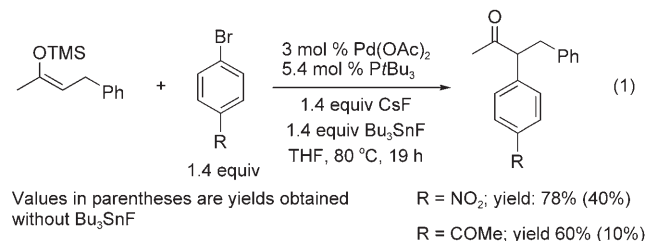
siloxy-4-phenyl-2-butene (**1**) with 1-bromo-4-*tert*-butylbenzene (**2**) were examined with a variety of additives, ligands, solvents, and palladium sources (Table 1). In the presence of catalytic amounts of  $\text{Pd}(\text{OAc})_2$  and  $\text{PrBu}_3$ , the reaction between 1.2 equivalents of **1** with limiting **2** in toluene in the absence of an additive did not afford the desired product in appreciable amounts (entry 1). The same reactions conducted with added  $\text{Bu}_3\text{SnF}$  formed some arylated product, but the yields were poor (entry 2). These reactions with added  $\text{CsF}$  or  $\text{ZnF}_2$  (entries 3 and 4) formed the product in low yield, and reactions conducted with the more soluble  $\text{Me}_4\text{NF}$  apparently caused only decomposition of silyl enol ether **1** (entry 6).

**Table 1:** Coupling of **1** with **2**.<sup>[a]</sup>

Entry	Additive (equiv)	Ratio of <b>1</b> / <b>2</b>	Yield [%] <sup>[b]</sup>
1		1.2:1	0
2	$\text{Bu}_3\text{SnF}$ (1.2)	1.2:1	34
3	$\text{CsF}$ (1.2)	1.2:1	18
4	$\text{Bu}_3\text{SnF}$ (1.2), $\text{CsF}$ (1.2)	1.2:1	81
5	$\text{ZnF}_2$ (1.2)	1.2:1	38 <sup>[c]</sup>
6	$\text{Me}_4\text{NF}$ (1.2)	1.2:1	0
7	$\text{Bu}_3\text{SnF}$ (1.2), $\text{CsF}$ (1.2)	1:1.2	65
8	$\text{Bu}_3\text{SnF}$ (1.4), $\text{CsF}$ (1.4)	1.4:1	98
9	$\text{Bu}_3\text{SnF}$ (0.14), $\text{CsF}$ (1.4)	1.4:1	67
10	$\text{CsF}$ (1.4)	1.4:1	81 <sup>[d]</sup>
11	$\text{Bu}_3\text{SnF}$ (1.4), $\text{CsF}$ (1.4)	1.4:1	93 <sup>[d]</sup>

[a] Reactions were run at 85 °C with 0.5 mmol **2** (0.25 M). [b] Yield of the isolated product (average of two runs). [c] DMF was used as the solvent. [d] THF was used as the solvent.

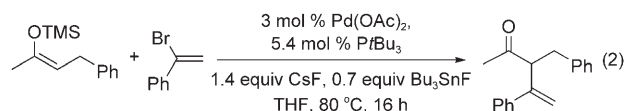
The reaction of 1.4 equivalents of **1** with **2** in THF containing  $\text{CsF}$  as the additive afforded the desired product in a high yield of 81 % (entry 10), but the functional-group tolerance of reactions with  $\text{CsF}$  alone was similar to that of reactions of alkali-metal enolates. For example, reactions of **1** with 1-bromo-4-nitrobenzene and 4'-bromoacetophenone in THF afforded only 40 and 10 % yields, respectively [Eq. (1)].



In contrast, reactions conducted with a combination of  $\text{Bu}_3\text{SnF}$  and  $\text{CsF}$  as additives occurred in high yields (entry 4) and with a broad scope (see below). Reactions conducted with a catalytic amount of  $\text{Bu}_3\text{SnF}$  (10 mol % based on the silyl enol ether) and 1 equivalent of  $\text{CsF}$  afforded the desired product in 67 % yield (entry 9). Altering the ligand, palladium precursor, and solvent did not further improve the reaction (reactions in toluene and THF occurred in comparable yields), but increasing the amount of the silyl enol ether and additive (1.4:1.4:1.4:1 ratio of the two additives, enol **1**, and aryl halide **2**) led to formation of the coupled product in 98 % yield (entry 8).

Table 2 illustrates the scope of the reactions under the conditions of entry 8 in Table 1 with  $\text{Bu}_3\text{SnF}$  and  $\text{CsF}$  as the additives. Both acyclic and cyclic silyl enol ethers smoothly underwent coupling at 85–90 °C with a wide variety of aryl bromides and chlorides to form  $\alpha$ -arylated ketones in good-to-excellent yields. These weakly basic conditions were compatible with ester, nitro, cyano, and keto substituents. Both sterically hindered aryl bromides and heterocyclic aryl bromides, such as 3-bromothiophene, served as coupling partners.

The coupling between a vinyl bromide and a silyl enol ether under these conditions was tested briefly [Eq. (2)].<sup>[15]</sup> The combination of 3 mol %  $\text{Pd}(\text{OAc})_2$  and 5.4 mol %  $\text{PrBu}_3$  catalyzed the coupling of  $\alpha$ -bromostyrene with **1** in THF in the presence of 1.4 equivalents of  $\text{CsF}$  and 0.7 equivalents of  $\text{Bu}_3\text{SnF}$  (based on the amount of silyl enol ether) in 66 % yield.



Considering the stoichiometric amounts of tin reagent in the couplings of Table 2 and the toxicity of tin, other combinations of metal fluorides were examined to promote the couplings of silyl enol ethers. One of us recently reported

**Table 2:** Scope of the arylation of a trimethylsilyl enol ether.<sup>[a]</sup>

Entry	Silyl enol ether	Halide	Products	Yield [%] <sup>[b]</sup>
1				89 <sup>[c]</sup>
2				84
3				96
4				97
5				97
6				93
7				91
8				55
9				80 <sup>[c]</sup>
10				80 <sup>[c]</sup>
11				70 <sup>[c]</sup>
12				84
13				77 <sup>[c]</sup>
14				85
15				78

[a] Reactions were run under the conditions of entry 8 in Table 1 for 12–20 h. [b] Yield of the isolated product (average of two runs). [c] Reaction run at 90 °C.

that the combination of CsF and ZnF<sub>2</sub> promotes the asymmetric iridium-catalyzed allylation of silyl enol ethers with allylic carbonates.<sup>[16]</sup> Thus, we investigated the combination of ZnF<sub>2</sub> with other metal fluorides as promoters for the

palladium-catalyzed coupling of silyl enol ethers with bromoarenes.

The results of experiments to develop reaction conditions with the metal fluoride additives are provided in the Supporting Information. Experiments on the coupling of **1** with 4-bromoacetophenone showed that conditions could be developed for the coupling of silyl enol ethers with aryl bromides in high yield and in the presence of the combination of stoichiometric amounts of ZnF<sub>2</sub> and either CsF or MnF<sub>2</sub> as additives. These reactions occurred in much higher yield in the polar DMF than the less polar toluene and with [Pd(dba)<sub>2</sub>] (dba = dibenzylideneacetone) as the precursor than Pd(OAc)<sub>2</sub>. Reactions carried out in DMF with [Pd(dba)<sub>2</sub>] and PrBu<sub>3</sub> as the catalyst with stoichiometric amounts of ZnF<sub>2</sub> and CsF occurred in lower yields than reactions with stoichiometric amounts of ZnF<sub>2</sub> and 0.4 equivalents of CsF. Reactions with stoichiometric ZnF<sub>2</sub> and substoichiometric CsF as additives occurred with high functional-group tolerance (see below). However, this combination of metal fluorides led to diarylation of the silyl enol ethers of methyl ketones. Selective monoarylation of silyl enol ethers of ketones was achieved instead when the reactions were carried out with the combination of ZnF<sub>2</sub> and MnF<sub>2</sub> as additives.

Several examples of the [Pd(dba)<sub>2</sub>]/PrBu<sub>3</sub>-catalyzed reactions of silyl enol ethers promoted by catalytic CsF or MnF<sub>2</sub> and stoichiometric ZnF<sub>2</sub> are shown in Table 3. Most generally, these data illustrate the same two beneficial effects of conducting the coupling of silyl enol ethers in the presence of these fluoride activators, as was observed from the use of Bu<sub>3</sub>SnF and CsF as additives: The product from the reaction of the silyl enol ether 2-siloxy-1-butene was formed by monoarylation of the methyl group with aryl halides that contained functionalities intolerant of the basic conditions of the couplings of alkali-metal enolates, and reactions of the more substituted silyl enol ethers of an alkyl ketone regioselectively formed the product from arylation at the more hindered enolizable position.

The first two examples (Table 3, entries 1 and 2) show that similar yields for reactions of electron-neutral and *ortho*-substituted bromoarenes are obtained for reactions containing tin fluoride as an additive. Entries 3 and 4 show that these conditions allow the coupling of bromoarenes with functionalities that are not tolerated by the basic alkali-metal enolates. Hydrolysis of the silyl enol ether during the reaction of bromophenol did limit the yield of entry 4, but substantial quantities of coupled product were formed. Entries 5–7 show examples of the selective monoarylation of the silyl enol ether of 4-phenyl-2-butanone with bromoarenes that are intolerant of alkali-metal enolates. Finally, entry 8 (Table 3) shows the first coupling of an enolate of acetone without tin reagents. Diarylation to form 1,1-diphenylacetone competed with the monoarylation in this case, but the use of excess silyl enol ether led to the formation of  $\alpha$ -aryl acetone in good yield.

In summary, the combination of two metal fluorides synergistically promotes the coupling of silyl enol ethers with aryl bromides and chlorides. Two procedures are presented, each with certain advantages: reactions containing CsF and tributyltin fluoride occur in nonpolar solvents, whereas the reactions containing either ZnF<sub>2</sub>/MnF<sub>2</sub> or ZnF<sub>2</sub>/CsF occur

**Table 3:** Scope of the palladium-catalyzed arylation of trimethylsilyl enol ethers in the presence of  $\text{ZnF}_2$  and CsF or  $\text{MnF}_2$ .

Entry	Silyl enol ether	Halide	Product	Yield [%]
1				89 <sup>[a]</sup>
2				87 <sup>[a]</sup>
3				90 <sup>[a]</sup>
4				53 <sup>[a]</sup>
5				78 <sup>[b]</sup>
6				71 <sup>[b,c]</sup>
7				64 <sup>[d,e]</sup>
8				68 <sup>[f,g]</sup>

[a] Reaction conditions: aryl halide (1.0 equiv), silyl enol ether (1.4 equiv), zinc fluoride (1.4 equiv), cesium fluoride (0.4 equiv),  $[\text{Pd}(\text{dba})_2]$  (3 mol %), and  $\text{PtBu}_3$  (5.4 mol %), 85 °C; DMF (1 mL) was added per 0.2 mmol of aryl halide. [b] Reaction conditions: aryl halide (1.0 equiv), silyl enol ether (1.5 equiv), zinc fluoride (1.0 equiv), manganese fluoride (0.4 equiv),  $[\text{Pd}(\text{dba})_2]$  (2 mol %), and  $\text{PtBu}_3$  (4 mol %), 70 °C; DMF (1 mL) was added per 0.2 mmol of aryl halide. [c] The ratio of mono/diarylation was 5.5:1. [d] Reaction conditions: aryl halide (1.0 equiv), silyl enol ether (1.5 equiv), zinc fluoride (1.4 equiv), manganese fluoride (1.4 equiv),  $[\text{Pd}(\text{dba})_2]$  (3 mol %), and  $\text{PtBu}_3$  (5.4 mol %), 60 °C; DMF (1 mL) was added per 0.2 mmol of aryl halide. [e] The ratio of mono/diarylation was 4:1. [f] Reaction conditions: aryl halide (1.0 equiv), silyl enol ether (5.0 equiv), zinc fluoride (1.4 equiv), manganese fluoride (1.4 equiv),  $[\text{Pd}(\text{dba})_2]$  (3 mol %), and  $\text{PtBu}_3$  (5.4 mol %), 70 °C; DMF (2 mL) was added per 0.2 mmol of aryl halide. [g] The ratio of mono/diarylation was 5.5:1.

without tin. All the reactions appear to occur without cleavage to form alkali-metal enolates, thus providing a mild and selective methodology for the preparation of  $\alpha$ -aryl ketones. Studies to determine the origin of the synergistic effect, which remains unclear at this time, will be the subject of future studies.

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- [1] a) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **2004**; b) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley, Hoboken, **2002**.
- [2] a) D. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, 36, 234; b) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, 219, 211.
- [3] a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, 119, 11108; b) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, 119, 12382; c) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, 121, 1473; d) J. M. Fox, X. H. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, 122, 1360; e) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem.* **1997**, 109, 1820; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1740; f) J. L. Rutherford, M. P. Rainka, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, 124, 15168; g) M. S. Viciu, R. F. Germaneau, S. P. Nolan, *Org. Lett.* **2002**, 4, 4053; h) D. Solé, L. Vallverdú, X. Solans, M. Font-Bardia, J. Bonjoch, *J. Am. Chem. Soc.* **2003**, 125, 1587; i) A. Ehrentauf, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, 344, 209; j) T. Satoh, Y. Kametani, Y. Terao, M. Miura, M. Nomura, *Tetrahedron Lett.* **1999**, 40, 5345; k) Y. Terao, Y. Kametani, H. Wuhui, T. Satoh, M. Miura, M. Momura, *Tetrahedron* **2001**, 57, 5967.
- [4] a) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, 124, 12557; b) W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, 123, 7996; c) S. Lee, N. A. Beare, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, 123, 8410.
- [5] a) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, 67, 541; b) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, 66, 3402; c) J. Cossy, A. Filippis, D. G. Pardo, *Org. Lett.* **2003**, 5, 3037.
- [6] T. Hamada, A. Chieffi, J. Ahman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, 124, 1261.
- [7] I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, 97, 2063.
- [8] I. Kuwajima, H. Urabe, *J. Am. Chem. Soc.* **1982**, 104, 6831.
- [9] M. Kosugi, I. Hagiwara, T. Sumiya, T. Migita, *Bull. Chem. Soc. Jpn.* **1984**, 57, 242.
- [10] For a recent coupling of a diphenyl bisenol ether, see: J. Chae, J. Yun, S. L. Buchwald, *Org. Lett.* **2004**, 6, 4809.
- [11] For coupling of silyl ketene acetals, see: a) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, 125, 11176; b) X. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, 126, 5182.
- [12] For activation of silyl ketene acetals of an acetate, see: F. Agnelli, G. A. Sulikowski, *Tetrahedron Lett.* **1998**, 39, 8807.
- [13] A synergistic effect of the combination of CsF and CuI as additives has been observed in the promotion of Stille coupling reactions; see: S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem.* **2004**, 116, 1152; *Angew. Chem. Int. Ed.* **2004**, 43, 1132.
- [14] S. Matsuzawa, Y. Horiguchi, E. Nakamura, I. Kuwajima, *Tetrahedron* **1989**, 45, 349.
- [15] For the palladium-catalyzed intermolecular vinylation of ketones, see: Ref. [6]; A. Chieffi, K. Kamikawa, J. Ahman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, 3, 1897; for the palladium-catalyzed intramolecular vinylation of ketones, see: a) T. Wang, J. M. Cook, *Org. Lett.* **2000**, 2, 2225; b) D. Solé, E. Peidró, J. Bonjoch, *Org. Lett.* **2000**, 2, 2225; c) D. Solé, F. Diaba, J. Bonjoch, *J. Org. Chem.* **2003**, 68, 5746; d) D. Solé, X. Urbaneja, J. Bonjoch, *Adv. Synth. Catal.* **2004**, 346, 1646.
- [16] T. Graening, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, 127, 17192.