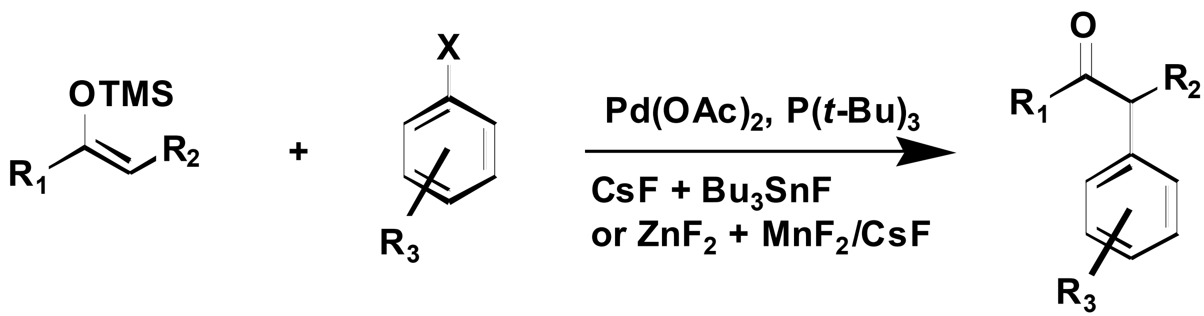
Pd-Catalyzed α-Arylation of Trimethylsilyl Enol Ethers with Aryl Bromides and Chlorides



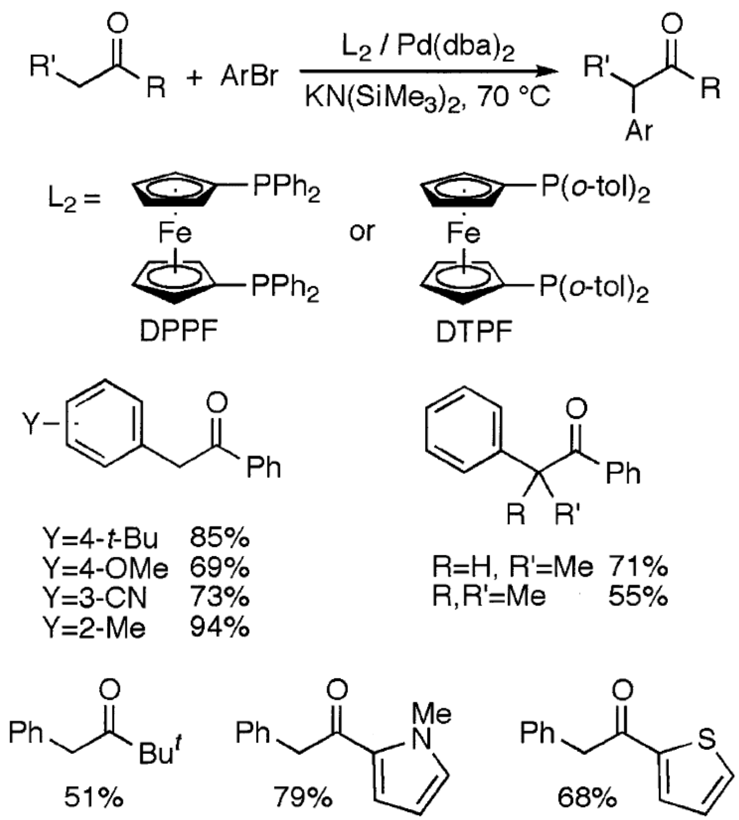
Weiping Su, Steven Raders, John G. Verkade,

Xuebin Liao, and John F. Hartwig

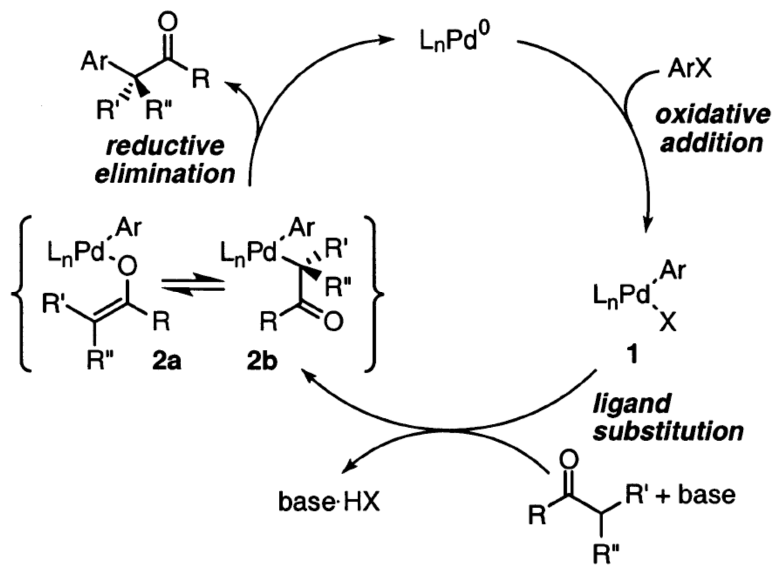
Angew. Chem. Int. Ed. ASAP

Current Literature
Chenbo Wang @ Wipf Group
August 12th, 2006

Pd-catalyzed Arylation of Enolates: Ketone Initial Works



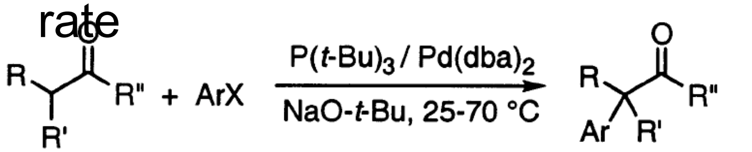
Mechanism:

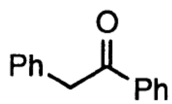


Hamann, B. C. and Hartwig, J. F. *J. Am. Chem. Soc.* **1997,** *119,* 12382
Culkin, D. A. and Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234

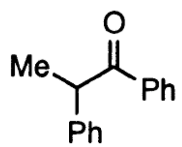
Pd-catalyzed Arylation of Enolates: Ketone Improvements

P(t-Bu)$_3$: faster reaction rate

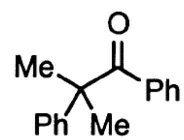




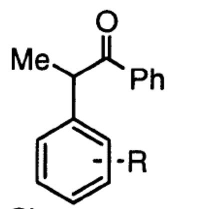
X=Br 96%



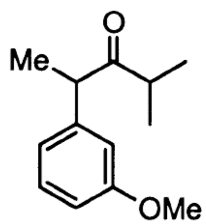
X=Br 98% (0.005 mol%)
X=Cl 90%



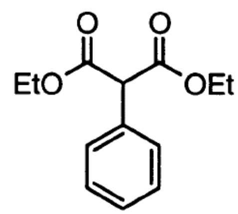
X=Br 92%
X=Cl 82% (3-OMe)



X=Cl
R=4-PhC(O) 95%
R=4-OMe 91%
R=2-Me 80%

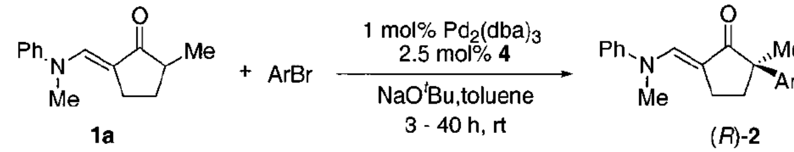


X=Br 83% (3:1 in THF)
X=Cl 82% (12:1 in toluene)



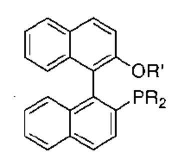
X=Br 80%

Asymmetric arylation:



ArBr	(*S*)-**4b**	(*S*)-**4d**	(*S*)-**4e**
(2-Me)-C_6H_4-Br	40%[b] **42% ee**[c]	53% 23% ee	43% 22% ee
(3-Me)-C_6H_4-Br	72% 87% ee	82% 89% ee	85% **94% ee**
(4-Me)-C_6H_4-Br	70% 86% ee	83% 87% ee	84% **93% ee**
(3-MeO)-C_6H_4-Br	79% 80% ee	81% 84% ee	80% **89% ee**
(4-MeO)-C_6H_4-Br	77% 83% ee	82% 87% ee	80% **94% ee**
(4-*t*-Bu)-C_6H_4-Br	88% 86% ee	79% 88% ee	84% **93% ee**

[a] Reaction conditions: 1.0 equiv ketone, 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, 0.25 M toluene, **3**/Pd = 1.25/1. [b] Isolated yield. [c] % ee detemined by HPLC (Daicel Chiralcel OD).



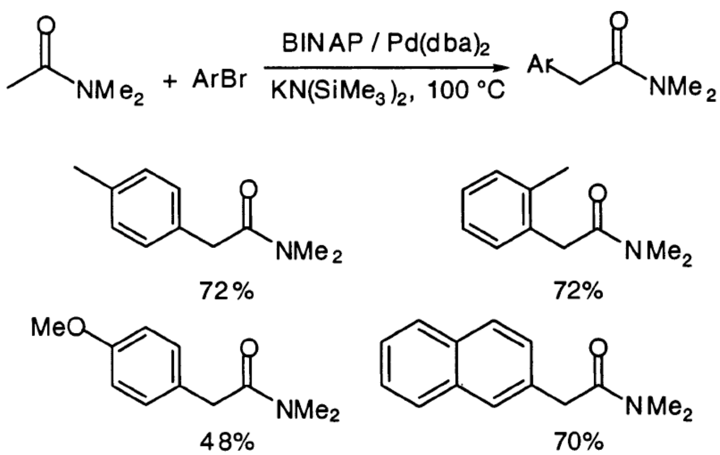
4a-g

4a,	R=Cy, R'=Me
4b,	R=^{i}Pr, R'=Me
4c,	R=^{i}Pr, R'=^{i}Pr
4d,	R=^{i}Pr, R'=Bn
4e,	R=^{i}Pr, R'=CH_2(1-napth)
4f,	R=^{i}Pr, R'=CH_2(2-napth)
4g,	R=^{i}Pr, R'=CH_2(9-phen)

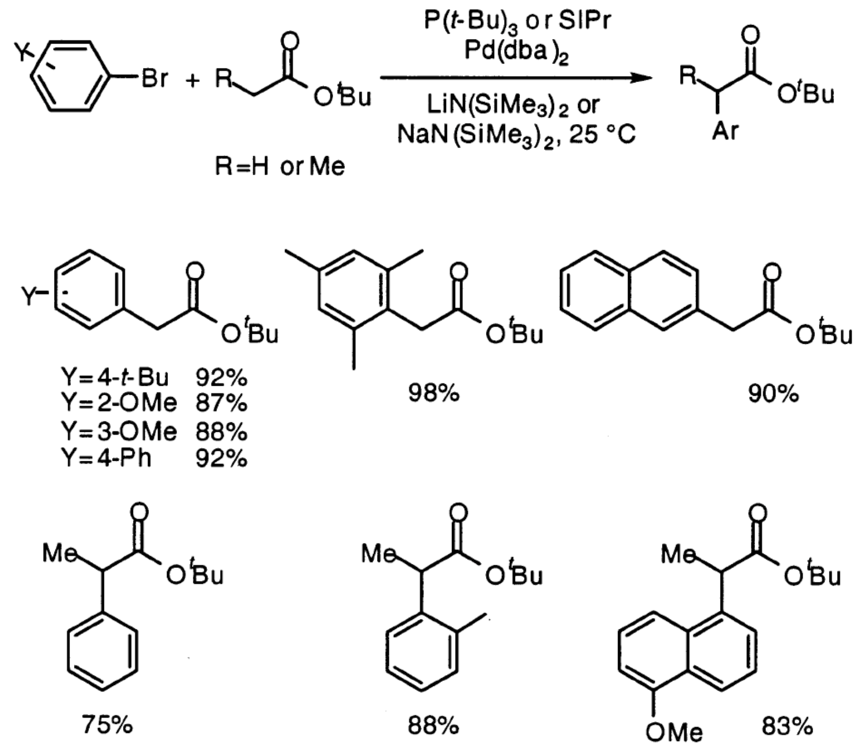
Kawatsura, M. and Hartwig, J. F. *J. Am. Chem. Soc.* **1999,** *121,* 1473
Hamada, T.; Chieffi, A.; Ahman, J. and Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** *124,* 1261

Pd-catalyzed Arylation of Enolates: Amides and Esters

Amides:



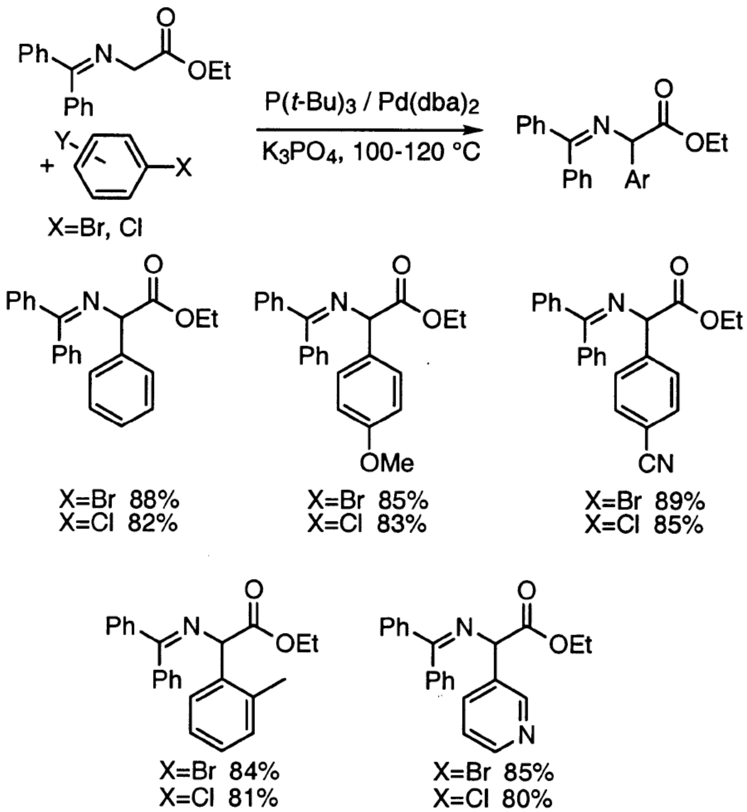
Esters:



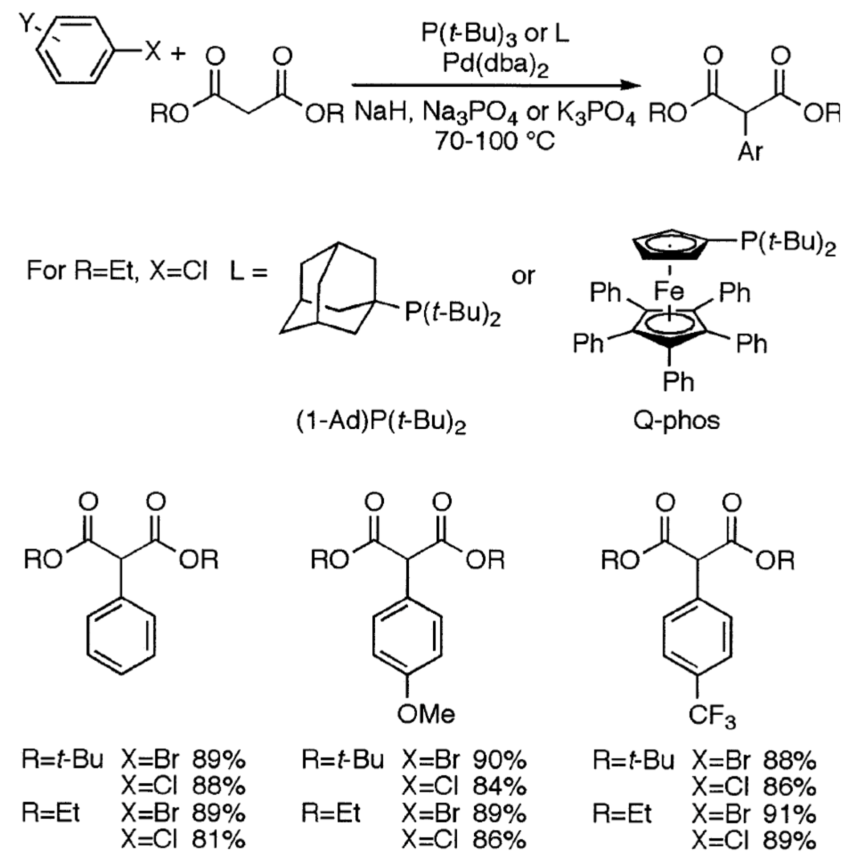
Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.
Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410

Pd-catalyzed Arylation of Enolates: Amino Acids and Malonates

Protected Amino Acids:



Malonates :



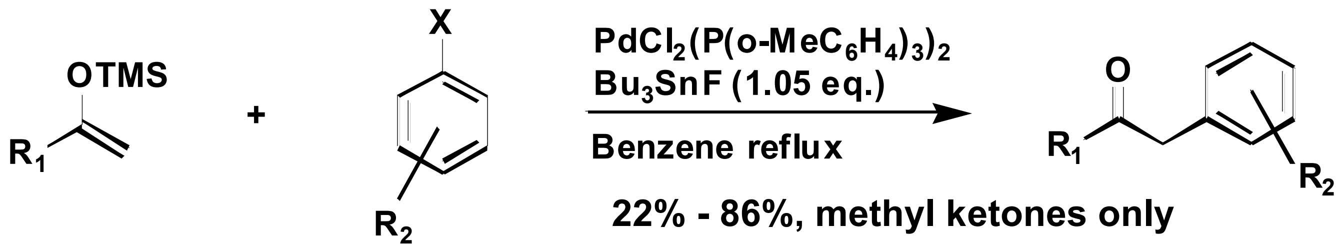
Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410
Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541

Pd-catalyzed Arylation of Enolates: Problems

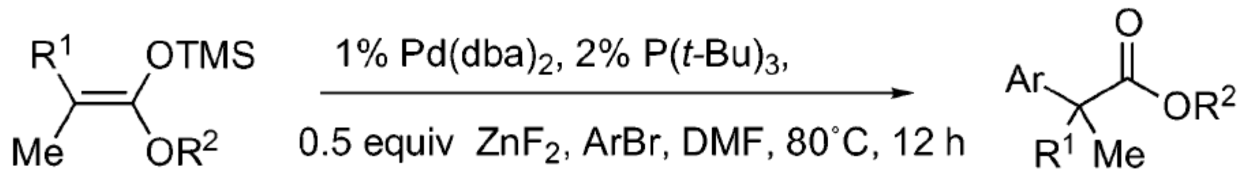
- Regioselectivity of ketone enolates: less hindered side is favored
- Strong basicity:
  - Functional group compatibility
  - Product's α-proton is more acidic than starting material:
    - Double arylation
    - Product may racemize under the reaction conditions

Su, S.; Raders, S. Verkade, J. G.; Liao, X. and Hartwig, J. F. *Angew. Chem. Int. Ed.* ASAP
Chae, J.; Yun, J. and Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809

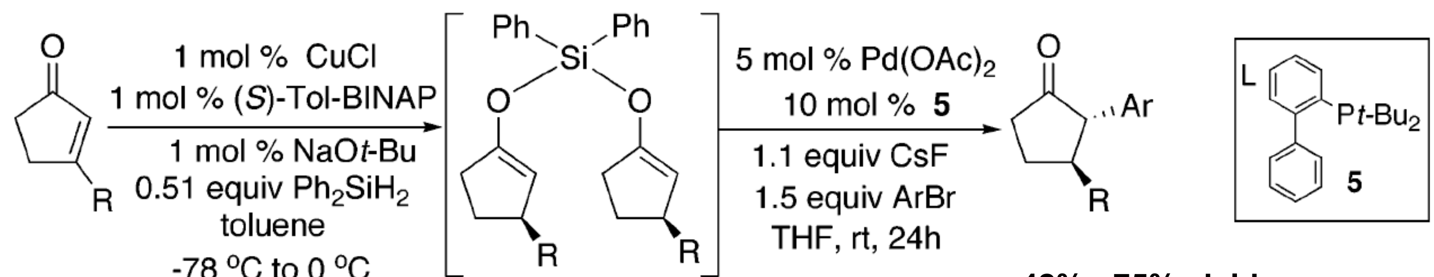
Pd-catalyzed Arylation of Silyl Enol Ethers: Previous Works



22% - 86%, methyl ketones only



67% - 96%

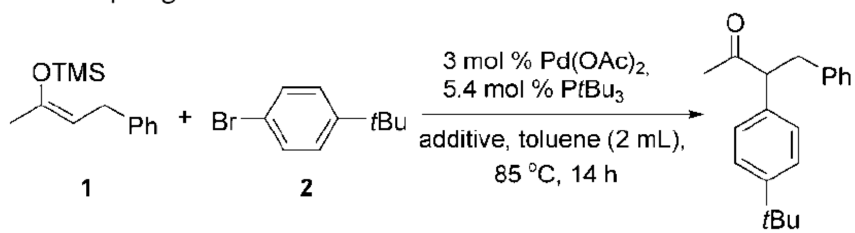


42% - 75% yield
92% - 98% de
Limited substrate scope

Kuwajima, I. and Urabe, H. *J. Am. Chem. Soc*. **1982**, *104*, 6831
Liu, X. and Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182
Chae, J.; Yun, J. and Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809

Pd-catalyzed Arylation of Silyl Enol Ethers with Two Metal Fluorides as Additives: Optimizing Reaction Conditions

Table 1: Coupling of **1** with **2**.[a]



Entry	Additive (equiv)	Ratio of **1**/**2**	Yield [%][b]
1		1.2:1	0
2	Bu_3SnF (1.2)	1.2:1	34
3	CsF (1.2)	1.2:1	18
4	Bu_3SnF (1.2) CsF (1.2)	1.2:1	81
5	ZnF_2 (1.2)	1.2:1	38[c]
6	Me_4NF (1.2)	1.2:1	0
7	Bu_3SnF (1.2) CsF (1.2)	1:1.2	65
8	Bu_3SnF (1.4) CsF (1.4)	1.4:1	98
9	Bu_3SnF (0.14) CsF (1.4)	1.4:1	67
10	CsF (1.4)	1.4:1	81[d]
11	Bu_3SnF (1.4) CsF (1.4)	1.4:1	93[d]

[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.

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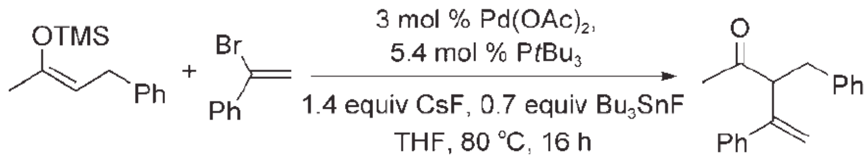
Pd-catalyzed Arylation of Silyl Enol Ethers with Two Metal Fluorides as Additives: Substrate Scope

Coupling to vinyl bromide:



66%

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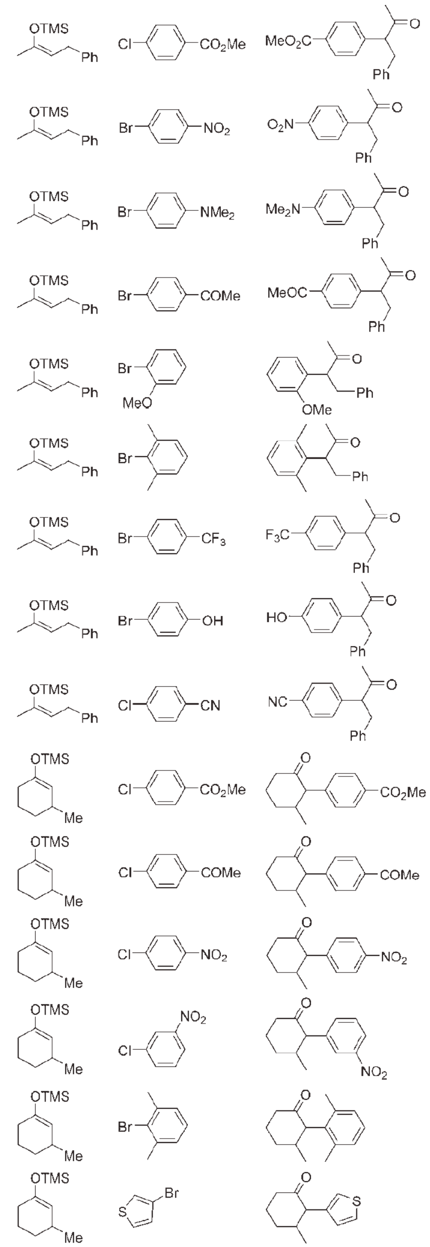
Table 2: Scope of the arylation of a trimethylsilyl enol ether.[a]

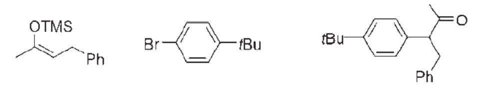
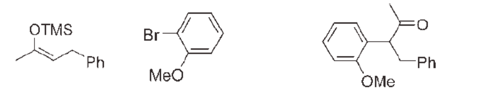
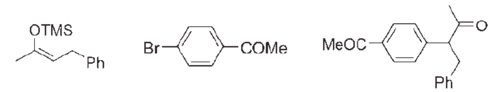
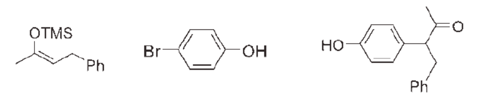
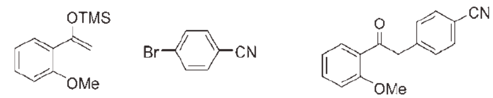
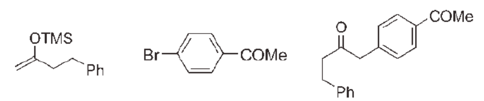
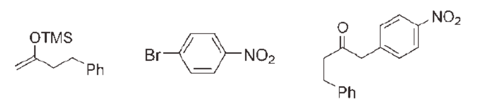
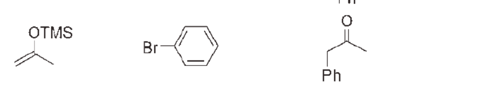


Entry	Yield [%][b]
1	89[c]
2	84
3	96
4	97
5	97
6	93
7	91
8	55
9	80[c]
10	80[c]
11	70[c]
12	84
13	77[c]
14	85
15	78

[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.

Pd-catalyzed Arylation of Silyl Enol Ethers with Two Metal Fluorides as Additives: Tin-free Conditions

Table 3: Scope of the palladium-catalyzed arylation of trimethylsilyl enol ethers in the presence of ZnF_2 and CsF or MnF_2.

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

[a] Reaction conditions: aryl halide (1.0 equiv), silyl enol ether (1.4 equiv), zinc fluoride (1.4 equiv), cesium fluoride (0.4 equiv), $[Pd(dba)_2]$ (3 mol%), and $PtBu_3$ (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), $[Pd(dba)_2]$ (2 mol%), and $PtBu_3$ (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), $[Pd(dba)_2]$ (3 mol%), and $PtBu_3$ (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), $[Pd(dba)_2]$ (3 mol%), and $PtBu_3$ (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.

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Summary

- Pd-catalyzed coupling of silyl enol ethers with aryl bromides and chlorides was realized by the combination of two metal fluorides ("synergistic effect"):
  - CsF+ Bu_3SnF: non-polar solvent
  - ZnF_2/MnF_2 or ZnF_2/CsF: Tin-free
- Future Work:
  - Origin of the synergistic effect
  - Milder conditions
  - Monoarylation
  - Asymmetric version