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A facile, microwave-assisted, palladium-catalyzed arylation of acetone

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Abstract—We report an expedient method for the heteroarylation of acetone under tin-free conditions. The coupling is performed using the commercially available enol silane of acetone (2-trimethylsilyloxypropene) and a corresponding aryl bromide, chloride or triflate under microwave-assisted conditions, with tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) or palladium acetate ($Pd(OAc)_2$) and 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine (S-Phos) as the catalyst system.
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High-speed synthesis with microwaves has attracted a great deal of attention, particularly with regard to palladium mediated couplings.[1] Recently, we became interested in synthesizing an α-heteroaryl acetone derivative from a heteroaryl chloride under microwave conditions. We had previously reported thermal conditions to affect this transformation.[2] However, the use of a full equivalent of tributyltin methoxide is of concern during scale-up. While there are methods in the literature to ease the removal of tin residue,[3] we sought to avoid the use of tin altogether. Inspired by the work of Hartwig[4] and Kuwajima,[5] we postulated that the requisite acetone enolate may be generated from a silyl enol ether in the presence of a fluoride source.

Guided by our previously published results, we began our studies by examining the reaction between 4-bromoisoquinoline and 2-trimethylsilyloxypropene (Table 1), using ZnF_2 as the fluoride source. The first ligand examined was Xanthphos (Fig. 1), which has been widely used (Table 1, entry 1).[4] Unfortunately, upon microwave heating at 150 °C in DMF, very little conversion (<10%) was observed. Switching the ligand to either dppf (Table 1, entry 2) or 2-(di-*t*-butylphosphino) biphenyl (Table 1, entry 3) with the same solvent, temperature and fluoride source also led to poor conversion. Our next attempt was to use the S-Phos ligand, developed by Buchwald and co-workers, which has been shown to be very effective in catalyzing Suzuki–Miyaura couplings[6,7] and cyanations.[8] Excellent conversion (86%) was observed after 15 min of microwave irradiation (Table 1, entry 4). $Pd_2(dba)_3$ can be replaced with $Pd(OAc)_2$ to afford a comparable yield of the desired product (78%) (Table 1, entry 6). In contrast, acetonitrile is a poor solvent for this reaction, and the use of CsF is ineffective as the fluoride source (Table 1, entry 8). The conversion of **1** to **2** under the optimized conditions was also performed thermally with a comparable yield. However, it required 10 h for the reaction to complete (Table 1, entry 5).

Armed with the optimized conditions, we decided to examine the scope by probing an array of electronically

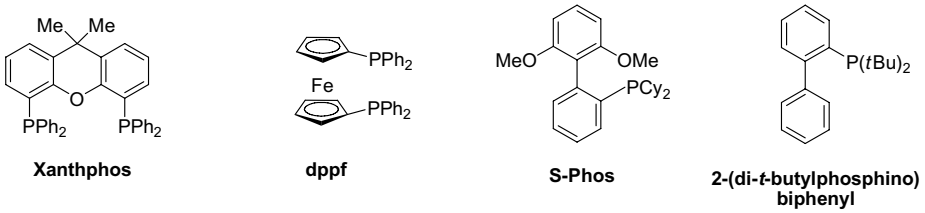

Figure 1. Structures of ligands used.

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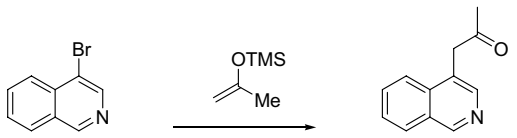
Table 1. Acetone heteroarylation of 4-bromoisoquinoline using various conditions



1 **2**

Entry	Ligand	Palladium source	Solvent	Fluoride source	T[a] (°C)	t	Yield (%)
1	Xanthphos	$Pd_2(dba)_3$	DMF	ZnF_2	150	15 min	<10
2	dppf	$Pd_2(dba)_3$	DMF	ZnF_2	150	15 min	<10
3	2-(Di-*t*-butylphosphino)biphenyl	$Pd_2(dba)_3$	DMF	ZnF_2	150	15 min	<10
4	S-Phos	$Pd_2(dba)_3$	DMF	ZnF_2	150	15 min	86
5	S-Phos	$Pd_2(dba)_3$	DMF	ZnF_2	120	10 h[b]	86
6	S-Phos	$Pd(OAc)_2$	DMF	ZnF_2	150	15 min	78
7	S-Phos	$Pd_2(dba)_3$	ACN	ZnF_2	150	15 min	<20
8	S-Phos	$Pd_2(dba)_3$	DMF	CsF	150	15 min	<10

[a] All microwave reactions were run using Biotage Initiator.
[b] Reaction was run thermally.

Table 2. Palladium/S-Phos microwave-assisted arylation of acetone

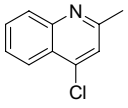
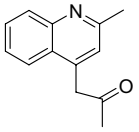
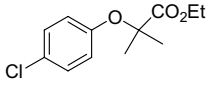
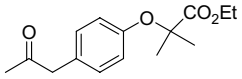
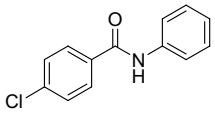
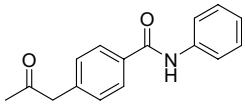
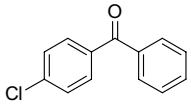
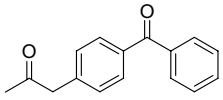
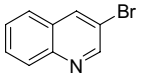
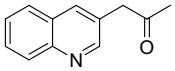
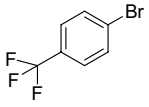
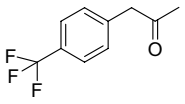
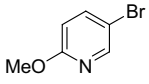
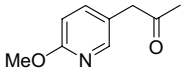
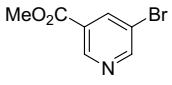
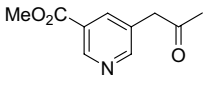
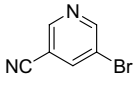
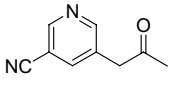
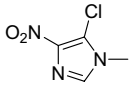
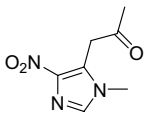
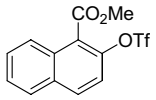
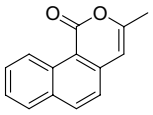
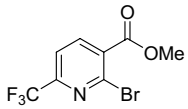
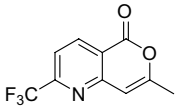
Entry	Ar–X	Product[a]	Yield[b] (%)
1			82
2			88
3			63
4			76
5			32
6			59
7			25
8			48
9			71
10			55

Table 2 (*continued*)

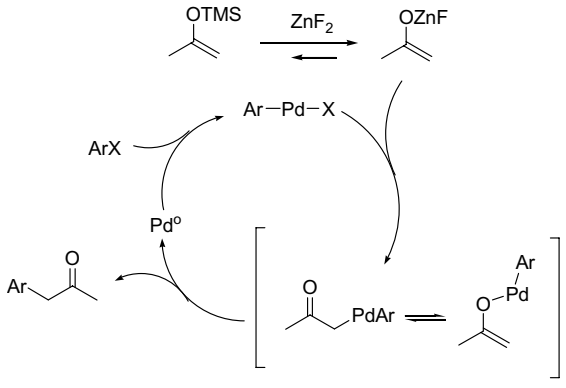
Entry	Ar–X	Product[a]	Yield[b] (%)
11			70
12			55

[a] All products gave satisfactory NMR and MS data.
[b] Isolated microwave yield after column chromatography on silica.

and structurally diverse substrates. The procedure proved to be quite general and well tolerated for both aryl and heteroaryl chlorides. Good isolated yields were realized in all cases (55–88%, Table 2, entries 1–4). For some substrates, however (entries 5 and 7), a side product was identified as the dimer of the aryl ring. An aryl triflate was also a viable substrate for this reaction (entry 11). Interestingly, a subsequent cyclization occurred after the arylation reaction to afford an isocoumarin derivative under the described reaction conditions. A similar cyclization was also observed in entry 12.[9]

In comparison with our previous work utilizing the Bu_3SnOMe/isopropenyl acetate conditions,[2] the current procedure afforded comparable yields in most cases, and superior in the case of aryl or heteroaryl chloride. The utilization of microwave irradiation has shortened reaction times from an average of 2–14 h down to 15 min. The catalyst loading is comparable with previously published results (6 mol %).[10] One significant advantage was the benign byproducts, which could be easily removed through aqueous work-up and silica gel chromatography.

Mechanistically, we postulate the Pd-catalyzed arylation of acetone as commencing with in situ generation of the zinc enolate via reaction of the silyl enol ether (2-trimethylsilyloxypropene) and ZnF_2.[11] Reaction of the zinc enolate with Ar–Pd–X would produce the transmetallated palladium species, which would then undergo reductive elimination then undergo reductive elimination giving rise to the desired arylation product and regeneration of the Pd^0 species (Scheme 1).



Scheme 1.

In summary, we describe another entry into the arena of palladium-catalyzed arylation of acetone that can be performed readily under microwave-mediated or thermal conditions. The reaction is shown to be general for a wide array of aryl and heteroaryl substrates. In certain cases, spontaneous cyclization yields potentially useful isocoumarin pharmacophores.

References and notes

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2. Liu, P.; Lanza, T.; Jewell, J. P.; Jones, C. P.; Hagmann, W. K.; Lin, L. S. *Tetrahedron Lett.* **2003**, *44*, 8869.
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9. For an analogous cyclization, see: Lewis, C. N.; Spargo, P. L.; Staunton, J. *Synthesis* **1986**, *11*, 944.
10. Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725.
11. *General experimental conditions. Microwave*: **1** (200 mg, 0.96 mmol), $Pd_2(dba)_3$ (70.0 mg, 0.07 mmol), S-Phos (80.0 mg, 0.20 mmol), ZnF_2 (119 mg, 1.10 mmol) and 2-trimethylsilyloxypropene (188 mg, 1.40 mmol) were mixed in 4.5 mL of DMF in a 5 mL microwave vial. The vial was capped and heated in the microwave reactor for 15 min at 150 °C. Once complete, the reaction mixture was diluted with 1 N HCl (20 mL) and EtOAc (20 mL). The EtOAc layer was removed, dried over $MgSO_4$, filtered and concentrated giving rise to an oil. The oil was chromatographed on silica gel (40–70% EtOAc–hexanes) and concentrated under reduced pressure to yield 178 mg (86%) of **2** as an orange oil: ^1H NMR (500 MHz, CD_3OD) δ 9.02, (s, 1H), 8.24 (s, 1H), 7.90 (d, $J = 8$ Hz, 1H), 7.76 (s, 1H), 7.63 (dd, $J = 8.5$, 14 Hz, 1H), 7.51 (dd, $J = 7.0$, 14.5 Hz, 1H), 4.11 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (500 MHz, CD_3OD) δ 206.4, 151.7, 142.9, 135.3, 131.2, 128.6, 126.2, 123.3, 44.3, 28.6. LC–MS: *m/z* 186.24 $(M+H)^+$.

Thermal: **1** (490 mg, 2.3 mmol), $Pd_2(dba)_3$ (173 mg, 0.20 mmol), S-Phos (193 mg, 0.40 mmol), ZnF_2 (292 mg, 2.80 mmol) and 2-trimethylsilyloxypropene (460 mg, 3.50 mmol) were mixed in 20 mL of DMF in an Ace-Glass heavy walled pressure tube with a Teflon cap. The vial was capped and heated in an oil bath for 10 h at 120 °C. Once complete, the reaction mixture was diluted with 1 N HCl (20 mL) and EtOAc (40 mL). The EtOAc layer was removed, dried over $MgSO_4$, filtered and concentrated giving rise to an oil. The oil was chromatographed on silica gel (40–70% EtOAc–hexanes) and concentrated under reduced pressure to yield 371 mg (85%) of **2** as an orange oil.