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Palladium-catalyzed mono-γ-arylation of 7-methoxy-4-methylcoumarin

Mary E. Sexton, Ami Okazaki, Zhuowen Yu, Alexis van Venrooy, Jason R. Schmink [1], William P. Malachowski *

Department of Chemistry, Bryn Mawr College, 101 North Merion Avenue, Bryn Mawr, PA 19010-2899, United States

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ABSTRACT

Herein, we report the selective mono-γ-arylation of 7-methoxy-4-methylcoumarin under palladium-catalyzed conditions. The Buchwald G3 pre-catalyst in conjunction with either the Xantphos or *N*-Xantphos ligand proves to be highly reactive, engaging aryl iodides, bromides, chlorides, and triflates to effect the desired transformation. A wide range of functionality is tolerated, including the ability to activate heteroaryl halides in the transformation. The initial scope of aryl halides and limitations of this methodology are presented.

Coumarins are of particular interest due to their wide variety of therapeutic applications, such as their antibiotic and antifungal [1], anti-inflammatory [2], and antiviral activities [3]. In addition, coumarin's strong fluorescence under UV light leads to their frequent use in different laser dyes and optical brighteners (410–470 nm) [4]. Indeed, the range of applications for coumarin derivatives makes them valuable to the chemistry community.

Over the past two decades, enolate α-arylation chemistry has been studied extensively and comprehensively [5–7]. γ-Arylation, a related phenomenon in conjugated enolates, has received considerable recent attention due to the challenges of regioselectively arylating the γ-position, selectively monoarylating, and avoiding potential condensation side products [8]. α,β-Unsaturated ketones and esters are difficult to selectively mono-γ-arylate due to the dienolate intermediate that forms in the reaction, which can produce multiple unwanted products, including α-arylation, β-arylation *via* Heck reaction, and polyarylation. In the past, alkylation was utilized successfully to functionalize the γ-position; however, the methods were limited in scope [9–11].

Despite these challenges, the alkylation of α,β-unsaturated ketones and esters has been widely studied. Regioselectivity in the alkylation of α,β-unsaturated ketones and esters has been controlled by direct alkylation at the γ-position using various metals such as copper [9] and tin [10]. Yamamoto and co-workers cross-coupled tin dienolates at the γ-position with aryl bromides in the presence of $Pd(PPh_3)_4$ with high selectivity [11]. Unfortunately, using stoichiometric amounts of tin compounds make this method less attractive due to the toxicity of tin and the limited availability of tin dienolates.

Fortunately in 1998, Miura and co-workers demonstrated that α,β-unsaturated ketones and aldehydes react with aryl bromides under basic conditions to selectively produce the γ-arylated product using palladium acetate with triphenylphosphine as the catalyst [12]. (Fig. 1, Panel A) This method eliminated the need for toxic metals and expanded the scope of reagents that could be utilized at the γ-position due to the wide variety of aryl bromides available. Importantly, they were able to avoid Heck reactions of the C—C double bond and alkene isomerization *via* β-hydride elimination. By varying the amounts of aryl bromide, they were also able to synthesize the diphenylated derivative.

In 2005, Varseev and Maier described the synthesis of 7-aryltetralones (Fig. 1, Panel B) [13]. They initially desired to mono-γ-arylate 3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one; however, they were only able to isolate tetralone derivatives. Their sequence included a sequential palladium catalyzed γ-arylation and dehydrogenation for the synthesis of substituted tetralones.

In 2008, Buchwald and Hyde described among the first examples of palladium catalyzed γ-arylation of β,γ-unsaturated ketones to create quaternary centers, which previously had not been explored due to the difficulty of this process [14]. Among the reasons this process is considered more difficult are: dienolates are less nucleophilic than enolates, dienolates are more prone to self-condensation through Michael reactions, and there exists the potential for the generation of regioisomeric products. Buchwald

* Corresponding author.
E-mail address: wmalacho@brynmawr.edu (W.P. Malachowski).
[1] Current address: Pennsylvania College of Health Sciences, 850 Greenfield Road, Lancaster, PA 17601, United States.

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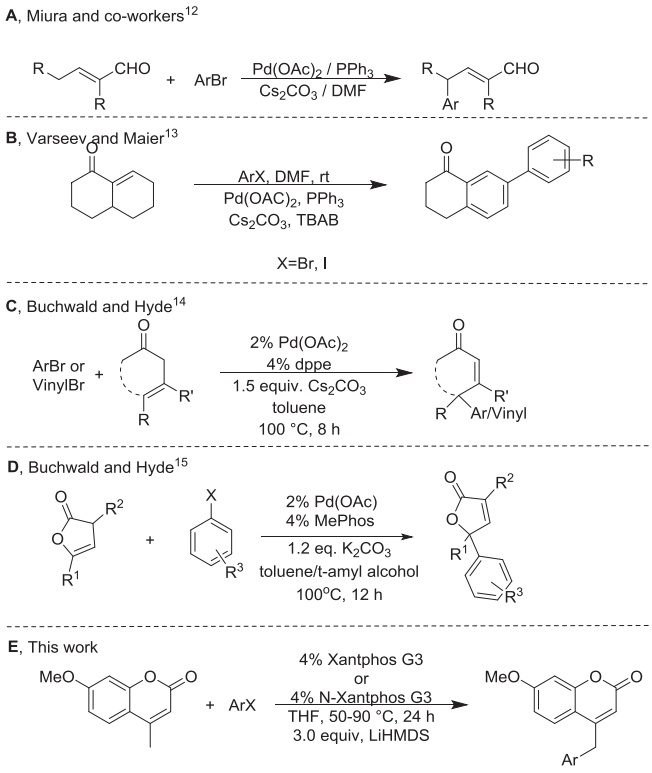


Fig. 1. Survey of approaches toward γ-arylation.

and Hyde found that there was subsequent isomerization to the α, β-product when β,γ-unsaturated ketones were utilized. Nevertheless, they were able to produce the desired product with a sterically congested quaternary center under basic conditions (Fig. 1, Panel C). They were also able to apply their results to a one-pot ketoinoline synthesis (Fig. 1, Panel D). In 2009, Buchwald and Hyde constructed 5,5-disubstituted butenolides, which provided another example of a quaternary center being made from γ-arylation [15].

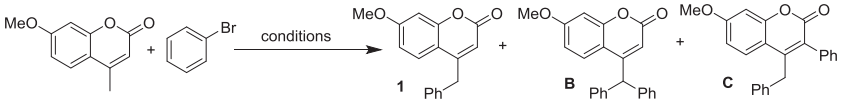
In 2015, Skrydstrup and co-workers reported the carbonylation of vinylogous esters at the γ-position [16]. They successfully produced the gamma product with no trace of α-arylation present for 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one. These publications, in addition to the others reported above, represent the few examples of γ-arylation of ketones and esters.

Expanding on the work of Miura, Maier, Buchwald, and Skrydstrup, we began our study to mono-γ-arylate 7-methoxy-4-methylcoumarin (Fig. 1, Panel E). This compound was considered to be electronically and sterically favorable to form the γ-arylated product due to the proton in the γ-position being most acidic. Breaking aromaticity or conjugation is highly unfavorable. This leaves strictly the α- and γ-positions being available for cross coupling. Although there have been several Pd-catalyzed approaches to γ-arylated coumarins [17–20], these utilized Suzuki-Miyaura and Negishi cross-coupling approaches, therefore, to the best of our knowledge, this is the first report of an enolate arylation approach to γ-aryl coumarins.

With our desired substrate in hand, the reaction was optimized using the reaction conditions in Table 1. Utilizing similar conditions to previous studies on α-arylation chemistry [5–7], we were able to produce the desired monoarylated product. Initially, cesium carbonate, potassium-*tert*-butoxide, and lithium hexamethyldisilazide were screened for reactivity. Both cesium carbonate (Table 1, Entry 1) and potassium-*tert*-butoxide (Table 1, Entry 2) reactions showed trace amounts of product with mainly starting material *via* GC analysis; however, lithium hexamethyldisilazide produced the desired mono-γ-arylated product (Table 1, Entry 3).

Utilizing the third generation (G3) Buchwald precatalyst scaffold [21] (Table S1, structures available in the ESI) and a variety of readily available ligands, the catalyst was screened for optimization (Table 1). All third generation Buchwald precatalysts listed were prepared using the general procedure described by Bruno, Tudge, and Buchwald. *N*-Xantphos G3 (Entry 5) [22] as well as DPEPhos G3 (Entry 6) were promising due to their high yield of product and minimal starting material remaining. DPPF G3 (Entry 7) [23] was incomplete and produced more of **B** than **1**. MorDalPhos G3 (Entry 8), and PA-PPh G2 (Entry 9) provided incomplete reactions with production of the undesired polyarylated products **B** and **C**. Xantphos as the ligand produced 100% of product with no

Table 1
Optimization of the reaction conditions.



Entry	Base	Solvent	Temp (°C)	Catalyst (loading)[c]	**1**[a]	**B**[a]	**C**[a]	s.m.
1[b]	Cs_2CO_3	CPME	90	Xantphos G3 (4%)	trace	0	0	100
2[b]	KOtBu	CPME	90	Xantphos G3 (4%)	trace	0	0	100
3[b]	LiHMDS	CPME	r.t.	Xantphos G3 (4%)	(TLC)	nd	nd	(TLC)
4	LiHMDS	MeTHF	85	Xantphos G3 (4%)	99	0	0	Trace
5	LiHMDS	MeTHF	85	NiXantphos G3 (4%)	92	0	0	8
6	LiHMDS	MeTHF	85	DPEPhos G3 (4%)	90	0	0	10
7	LiHMDS	MeTHF	85	DPPF G3 (4%)	33	40	0	27
8	LiHMDS	MeTHF	85	MorDalPhos G3 (4%)	64	trace	0	36
9	LiHMDS	MeTHF	85	PA-PPh G2 (4%)	52	30	10	6
10	LiHMDS	MeTHF	70	Xantphos G3 (4%)	98	0	0	2
11	LiHMDS	THF	70	Xantphos G3 (4%)	100	0	0	0
12	LiHMDS	Toluene	70	Xantphos G3 (4%)	62	4	0	34
13	LiHMDS	CPME	70	Xantphos G3 (4%)	76	2	0	22
14	LiHMDS	THF	70	Xantphos G3 (2%)	100	0	0	0

[a] Values reported are GC yields using biphenyl as an internal standard.
[b] Used 4-bromoanisole instead of bromobenzene.
[c] Ligands are listed in the Supporting Information (S3).

remaining starting materials at 70 °C (Entry 11). Reduction of the precatalyst to 2% (Entry 14) did not hinder the amount of product being produced. Ultimately, THF was found to be the best solvent for the reaction in all of the trials completed. Toluene, a non-polar solvent, provided an incomplete reaction with small amounts of diarylated product formed (Entry 12).

After initial optimization, we explored our substrate scope with a variety of aryl bromides, aryl chlorides, aryl iodides, and an aryl triflate as shown in Table 2. γ-Arylation worked very well for a range of electronically and sterically diverse aryl bromides (Table 2, Entries 1–11). The electron deficient aryl bromide, 4-bromobenzotrifluoride (Entry 12), only afforded 22% yield of trifluoromethyl derivative **12**; and the significantly less electron withdrawing cyano analog (Entry 13**)** was obtained in 95% yield. A heteroaryl bromide (Entry 14) provided excellent results with a yield of 92%. However, the pyridine derivatives in entries 15 and 16 provided low yields of 57% and 32% respectively. It is likely that the pyridine nitrogen was binding to palladium and attenuating catalysis as both reactions were incomplete due to remaining 7-methoxy-4-methyl coumarin in the GCMS.

The aryl iodide, aryl chloride, and aryl triflate examples shown in entries 18–25 also provided the desired products. Aryl iodides reacted at lower temperature (50 °C) than the aryl bromides (70 °C). The aryl chlorides required higher temperatures (90 °C) and *N*-Xantphos G3 rather than the less expensive variant, Xantphos G3, which was the optimal palladium precatalyst for the aryl bromides, iodides and triflates. Entries 26–28 illustrate several substrates that proved unreactive in our studies. For β-bromostyrene and 4-chloroanisole, the starting materials failed to react at all; while for 3-bromobenzothiophene we obtained a complex reaction mixture. The lack of reactivity in the aryl bromides is difficult to explain, but the electron rich aryl chloride likely made it a poor substrate for oxidative addition.

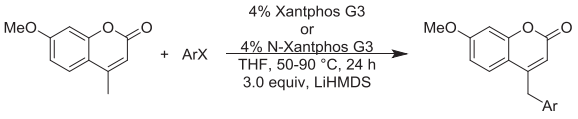
It is already known that oxidative addition of aryl chlorides using bidentate phosphine ligands, such as *N*-Xantphos, proceeds through a higher energy Pd-L_2 pathway than if a bulky monodentate phosphine were utilized [24]. Consequently, higher temperatures are typically necessary for palladium catalyzed reactions with aryl chlorides. *N*-Xantphos is favored over Xantphos for aryl chlorides because it can help lower the activation energy for oxidative addition.

N-Xantphos has been reported [24] by Mao and Walsh and co-workers to have an acidic phenoxazine N—H ($pK_a \sim 21$ in DMSO [25]), which under basic reaction conditions, deprotonates and associates with a main group metal, in our case lithium, and the ligand pi-system [22]. Walsh and co-workers had proposed that the main group metal cooperates with the palladium center to help lower the barrier for the oxidative addition of aryl chlorides, which they propose *N*-Xantphos is superior to Xantphos for aryl chlorides. Our results are consistent with this proposal.

Mechanistically, the desired cross coupling likely proceeds through a traditional Pd^0/Pd^{II} catalytic cycle. The desired aryl halide should oxidatively add into the catalytic cycle. Next, the base deprotonates the substrate and substitutes for the bromide associated with the palladium. Finally, reductive elimination occurs to produce the desired gamma-arylated product.

In conclusion, we have reported a method to synthesize γ-arylated 7-methoxy-4-methylcoumarin using a variety of aryl halides. We were able to utilize the less expensive Xantphos Pd G3 over the more expensive *N*-Xantphos Pd G3 precatalyst for most of the aryl halides, except the aryl chlorides. We were able to do so using lower temperatures as well as only reacting for 24 h. These compounds were UV active and could be easily observed *via* TLC analysis due to their highly fluorescent blue property. These fluorescent compounds may have applications in transistors, laser dyes, or even for medicinal purposes. Future studies could explore utilizing these compounds in a variety of ways as well as studying the diarylated product for their fluorescent capabilities. Ultimately this method provides a simple way of functionalizing 7-methoxy-4-methylcoumarin at the γ-position and creating new coumarin derivatives.

Table 2
Substrate scope and limitations.



Entry	Ar–X	Product	Yield (%)[a]
Aryl bromides[b]			
1	Bromobenzene	**1**	90
2	4-Bromoanisole	**2**	88
3	3-Bromoanisole	**3**	93
4	2-Bromoanisole	**4**	98
5	4-Bromo-*tert*-butylbenzene	**5**	75
6	3-Bromotoluene	**6**	70
7	4-Bromotoluene	**7**	65
8	2-Bromomesitylene	**8**	81
9	2-Bromonaphthalene	**9**	74
10	2-Bromo-4-*tert*-butyltoluene	**10**	68
11	4-Bromo-*N*,*N*-dimethylaniline	**11**	70
12	4-Bromobenzotrifluoride	**12**	22
13	4-Bromobenzonitrile	**13**	95
14	5-Bromobenzofuran	**14**	92
15	2-Bromopyridine[e]	**15**	57
16	3-Bromopyridine[e]	**16**	32
17	4-Chlorobromobenzene	**17**	70
Aryl iodides[c]			
18	4-Iodoanisole	**2**	42
19	1-Iodonaphthalene	**18**	53
20	4-Bromoiodobenzene	**19**	70
21	2-Iodotoluene	**20**	84
Aryl chlorides[d]			
22	Chlorobenzene	**1**	70
23	1-Chloronapthalene	**18**	58
24	4-Chlorobenzophenone	**21**	23
Aryl triflate[b]			
25	4-Methoxyphenyl-trifluoromethanesulfonate	**2**	84
Unsuccessful substrates			
26	Beta-bromostyrene		
27	3-Bromobenzothiophene		
28	4-Chloroanisole		

[a] Isolated yield after column chromatography.
[b] 70 °C, Xantphos G3.
[c] 50 °C, Xantphos G3.
[d] 90 °C, *N*-Xantphos G3.
[e] Incomplete reaction.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151057.

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