Domino Reactions

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Exploiting the Divergent Reactivity of Aryl–Palladium Intermediates for the Rapid Assembly of Fluorene and Phenanthrene Derivatives**

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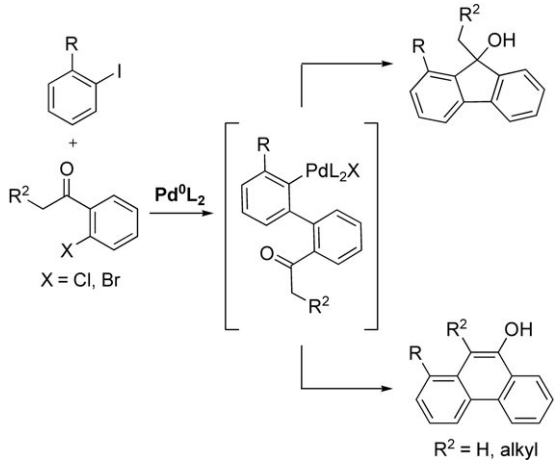
Domino reactions have attracted significant attention in the synthetic community because of their ability to create complex and diverse scaffolds in an efficient manner.[1] The value of domino processes can be greatly enhanced when divergence from a common intermediate is possible. In order for this strategy to be of synthetic utility, the reactivity of the intermediate must be controlled to provide one of two products selectively.

Palladium intermediates provide an avenue by which this strategy can be realized. It has been well established that palladium intermediates possess electrophilic character; however, it has recently been demonstrated that nucleophilic behavior is also possible.[2–4] Herein we report our preliminary studies on a strategy in which the dual reactivity of aryl–palladium intermediates is exploited (Scheme 1). After a sequence of norbornene mediated C–H activation and subsequent *ortho*-arylation the resulting aryl–palladium intermediate can go on to provide the product of α-arylation or addition onto the carbonyl functionality.[3–6] Subtle variation of the reaction conditions could alter the reactivity of this intermediate to favor either product selectively, demonstrating the balance that exists between the dual character of aryl–palladium intermediates.[7] By employing this strategy, a diverse array of fluorene and phenanthrene derivatives were synthesized. These compounds are known for their biological activity and applications in materials chemistry.[8] Thus, the development of efficient, diversity-oriented strategies for their synthesis is a useful endeavor.

The sequence of domino *ortho*-arylation and subsequent addition to a carbonyl group was discovered serendipitously during our investigation into a sequence of domino *ortho*-functionalization and subsequent cyanation.[9] The reaction of 2′-chloroacteophenone and 1-iodonaphthalene under the optimized conditions for cyanation afforded **1** as the major product (Table 1, entry 1).



Scheme 1. The synthetic strategy.

Encouraged by this result, an optimization was undertaken and it was found that the presence of water was critical to obtaining high yields of the desired product. In the absence of water a mixture of products arising from both the carbonyl addition and α-arylation was always obtained. A variety of aryl chlorides can be used in the reaction, affording the 9*H*-fluoren-9-ol derivatives in moderate to good yields, and aryl bromides afford similar results (Table 1).

The observation of α-arylated products prompted us to explore this alternate mode of reactivity for the aryl–palladium intermediate. In acetonitrile, under anhydrous conditions, it was possible to obtain the phenanthren-9-ol products in moderate to good yield (Table 2). These subtle variations of the reaction conditions had a profound influence on the outcome of the reaction.[7]

Our success with the addition of aryl–palladium intermediates to ketones encouraged us to explore addition to other carbonyl-containing functionalities including esters, which are generally considered to be unreactive in the presence of palladium. Recently, Solé and Serrano reported the intramolecular addition of a Pd^{II} species to aliphatic esters.[7] They found that an *ortho*-nitrogen atom was needed to activate the metal center and facilitate addition to the ester functionality via an azapalladacycle intermediate.

Initial attempts to add the aryl–palladium intermediates to the ester functionality were unsuccessful, presumably because of reduced reactivity. However, by modifying the catalyst system and heating the reaction mixture to 150 °C in a microwave reactor, it was possible to achieve the desired

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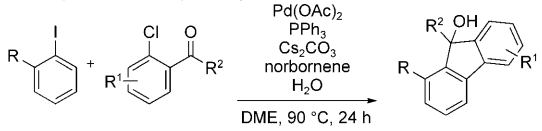
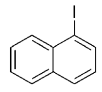
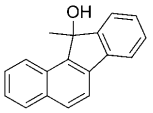
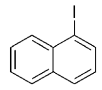
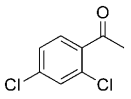
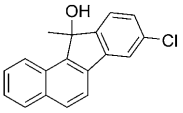
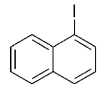
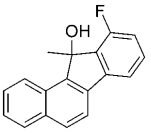
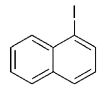
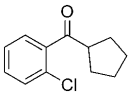
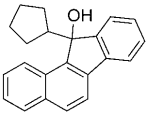
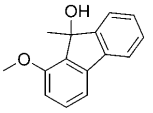
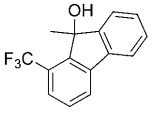
Table 1: Scope of *ortho*-arylation/ketone addition.[a]



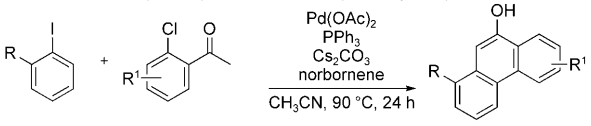
No.	Aryl iodide	Ketone	Product		Yield [%][b]
1				**1**	82 80[c]
2				**2**	81
3				**3**	86
4				**4**	64
5				**5**	71
6				**6**	65

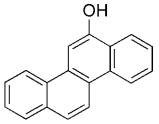
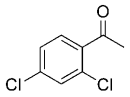
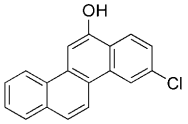
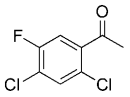
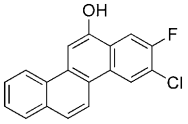
[a] All reactions were run under the following conditions: Aryl iodide (1.0 equiv), aryl chloride (1.5 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), Cs_2CO_3 (3.0 equiv), norbornene (3.0 equiv), and H_2O (48 equiv) in DME (0.05 M) were heated in a sealed tube at 90°C for 24 h using an oil bath. [b] Yield of the isolated product. [c] 2′-Bromoacteophenone was used.

transformation (Table 3). A lower ligand to palladium ratio was beneficial for this transformation, suggesting that a coordinatively unsaturated palladium species is needed. Furthermore, coordination of the ester functionality may also play a role in the catalytic cycle.[4,7] Under the optimized conditions a number of 9*H*-fluoren-9-one derivatives could be prepared in moderate to good yield. Unfortunately, a limitation of this protocol is that aryl chlorides failed to provide the desired product in good yield (Table 3, entry 1).

Preliminary investigations have also been carried out into the addition of aryl–palladium intermediates to aldehydes. Subjecting 2-bromobenzaldehyde to the reaction conditions produced a mixture of 9*H*-fluoren-9-one and 9*H*-fluoren-9-ol products. By omitting water it was possible to obtain an excellent yield of the 9*H*-fluoren-9-one (Table 4, entry 1). The mixture is likely to result from rapid protonation of the palladium alkoxide formed after the addition process rather than β-hydride elimination.[3] Several aldehydes were subjected to the reaction conditions affording the 9*H*-fluoren-9-one products in good yields (Table 4).

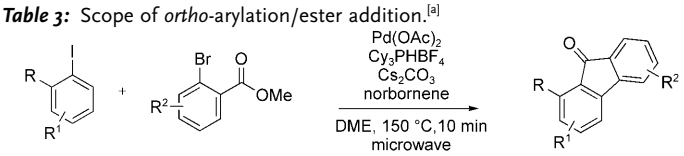
Table 2: Preliminary study of the *ortho*-arylation/α-arylation.[a]

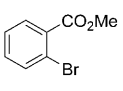
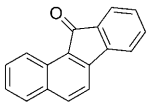
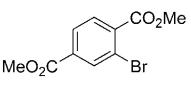
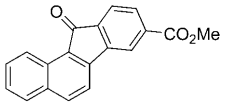
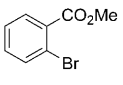
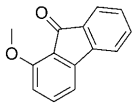
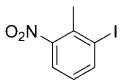


No.	Aryl iodide	Ketone	Product		Yield [%][b]
1				**7**	70
2				**8**	47
3				**9**	52

[a] All reactions were run under the following conditions: Aryl iodide (1.0 equiv), aryl chloride (1.5 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), Cs_2CO_3 (3.0 equiv), and norbornene (3.0 equiv) in CH_3CN (0.05 M) were heated in a sealed tube at 90°C for 24 h using an oil bath. [b] Yield of isolated product.

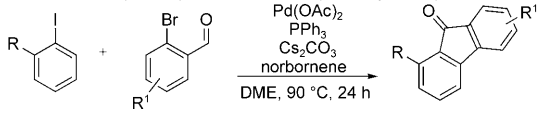
Table 3: Scope of *ortho*-arylation/ester addition.[a]

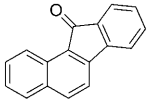
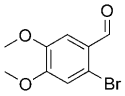
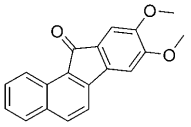
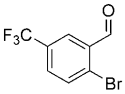
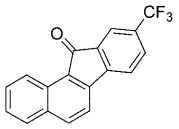


No.	Aryl iodide	Ester	Product		Yield [%][b]
1				**10**	72 15[c]
2				**11**	88
3				**12**	83
4				**13**	46
5				**14**	59

[a] All reactions were run under the following conditions: Aryl iodide (1.0 equiv), aryl bromide (1.0 equiv), $Pd(OAc)_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Cs_2CO_3 (1.5 equiv), and norbornene (1.0 equiv) in DME (0.05 M) were heated in a sealed tube at 150°C for 10 min under microwave irradiation. [b] Yield of isolated product. [c] Methyl-2-chlorobenzoate was used.

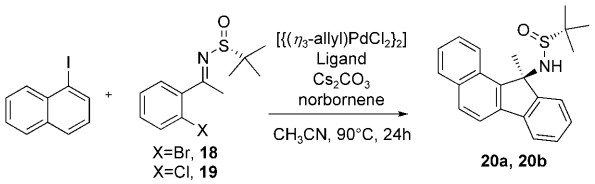
Table 4: Preliminary study of the *ortho*-arylation/aldehyde addition.[a]



No.	Aryl iodide	Aldehyde	Product		Yield [%][b]
1				**10**	93
2				**15**	93
3				**16**	60

[a] All reactions were run under the following conditions: Aryl iodide (1.0 equiv), aryl bromide (1.5 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), Cs_2CO_3 (3.0 equiv), and norbornene (3.0 equiv) in DME (0.05 M) were heated in a sealed tube at 90 °C for 24 h using an oil bath. [b] Yield of isolated product.

Recently, Dai and Lu reported the palladium-catalyzed diastereoselective addition of arylboronic acids to *N*-sulfinyl iminoacetates yielding arylglycine derivatives in good yields and high diastereoselectivity.[10a] Intrigued by these results, an attempt was made to react aryl–palladium intermediates with *N*-sulfinyl imines [Eq. (1)]. The results demonstrate a proof of principle and the potential for this transformation to be a highly selective, synthetically viable process.



(1)

Ligand = PPh_3: X = Br, 85%, d.r. = 2:1; X = Cl, 62%, d.r. = 1.1:1
Ligand = 2-(di-*tert*-butylphosphino)biphenyl: X = Br, 15%, d.r. = 10:1; X = Cl, 20%, d.r. = 14:1

In conclusion, the methodology reported allows the rapid assembly of a number of diverse fluorene and phenanthrene derivatives. Furthermore, it demonstrates the dual character of organopalladium complexes and the manner in which this character can be manipulated by a subtle variation in the reaction conditions. The exploitation of this dual reactivity has been demonstrated to be a powerful synthetic tool. Studies are ongoing to expand the scope and application of the present methodology, as well as to elucidate the mechanistic details of these catalytic processes.

Experimental Section

Typical procedure for additions to ketones: Palladium acetate (0.1 equiv), triphenylphosphine (0.22 equiv), norbornene (3.0 equiv), and cesium carbonate (3.0 equiv) were added to a 5 mL microwave vial (previously dried overnight in an oven at 120 °C) containing a magnetic stir bar. The vial was then sealed and flushed with argon for 1 min by venting through a needle, after which dry dimethoxyethane (4 mL) was added and stirring was begun. Argon was then bubbled through the solvent for 5 min as the remaining reagents were added. The aryl iodide (1.0 equiv, 0.2 mmol scale), aryl chloride (1.5 equiv), and water (48 equiv) were added by syringe (if the aryl iodide or chloride is a solid it was weighed out along with the other solids prior to sealing the vessel). The resulting mixture was then stirred at room temperature for 5 min and then placed in a preheated oil bath at 90 °C for 24 h. The reaction mixture was then cooled to room temperature and then diluted with dichloromethane (5 mL). The mixture was washed with brine (1 × 10 mL), and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The organic extracts were dried over sodium sulfate and filtered. Concentration of the solution by rotary evaporation under reduced pressure gave a residue which was purified by using flash column chromatography.

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Keywords: annulation · C–H activation · domino reactions · homogeneous catalysis · palladium

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[2] a) E. Negishi, A. de Meijere, *Handbook of Organopalldium Chemistry for Organic Synthesis I and II*, Wiley-VCH, New York, **2002**; b) J. Tsuji, *Palladium Reagents and Catalysts—New Perspectives for the 21st Century*, Wiley, Chichester, **2004**.
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