ORGANIC LETTERS

2013
Vol. 15, No. 11
2742–2745

Novel Syntheses of Fluorenones via Nitrile-Directed Palladium-Catalyzed C–H and Dual C–H Bond Activation

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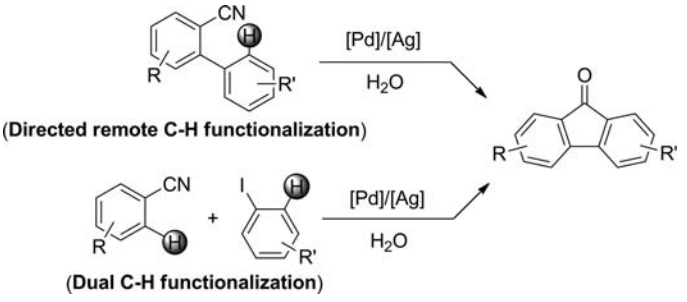
Received April 18, 2013

ABSTRACT



Novel procedures for the [Pd]/[Ag]/TFA system catalyzed cascade reactions of nitrile directed remote C–H and dual C–H bond activation with insertion of nitrile were developed, which afforded variously polysubstituted fluorenones in moderate to good yields with tolerance of a wide variety of substrates.

The fluorenone scaffold is important for organic synthesis because of its wide applications in bioactive compounds[1] as well as electronic and optical materials.[2] Most of them were prepared by Friedel–Crafts acylation,[3] remote metalation,[4] and oxidation of fluorenes[5] or fluorenols.[6] Other strategies for the synthesis of fluorenones include radical cyclization,[7] coupling reactions of arylpalladium,[8] and intramolecular dehydro Diels–Alder reactions.[9]

In recent years, the Pd-catalyzed C–H functionalization has been well developed and grown as a powerful method for constructing carbon–carbon[10] and carbon–heteroatom[11] bonds. Although there are numerous reports related to the Pd-catalyzed activation of C–H bonds, only a few of them involve the construction of fluorenones. In 2000, Larock first realized the synthesis of fluorenones

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10.1021/ol401063w
Published on Web 05/14/2013

via C−H bond activation.[12] Later, he also developed a palladium migration process involving C−H bond activation to provide the same subunit.[13] Recently, Cheng carried out the Pd-catalyzed cascade reaction of oxime directed dual C−H activation and Heck cyclization to furnish fluorenones.[14] Shi at a similar time also addressed the same issue by a different protocol.[15] In this context, the independent reports by Cheng[16] and Shi[17] have disclosed dual C−H activation of diarylketones to provide fluorenones.

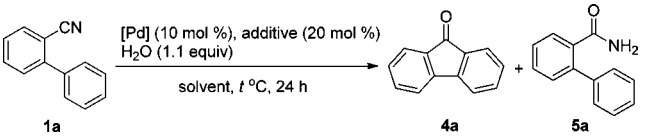
For those reactions involving C−H activation, directing groups are often required to assist in activating the C−H bond. Various functional groups were reported as directing groups; however, there are only two examples regarding the Pd-catalyzed nitrile directed C−H functionalization.[18] Our experience in the catalytic coupling reactions involving nitriles[19] encouraged us to explore the possibility for the combination of C−H bond activation with 1,2-insertion of nitriles. Herein, we wish to report the first example of an efficient and convenient Pd-catalyzed synthetic pathway for the CN directed remote C−H and dual C−H bond activation with intramolecular 1,2-insertion of nitriles.

We initiated our studies by using 2-phenylbenzonitrile (**1a**) as a model substrate (Table 1, entry 1), which was treated with 10 mol % of $Pd(OAc)_2$ in TFA at 120 °C for 24 h. However, only 12% NMR yield of desired product (**4a**) was observed. Some of the substrate was maintained, but most of them underwent hydrolysis to form corresponding amide (**5a**).

To understand the nature of present Pd-catalyzed nitrile directed remote C−H bond activation with nitrile insertion, the effect of solvents, additives, reaction temperatures, and palladium sources were investigated (Table 1). It was found that the use of other organic acids as solvents could not improve the catalytic reaction (entries 2 and 3). In addition, we further investigated the additives and found that AgTFA significantly reduced the rate of hydrolysis. Other additives performed as Lewis acids, facilitating the hydrolysis but not improving the cyclization.[20] We then reduced the amount of TFA and employed other cosolvents (entries 6−10). It was observed that the highly polar solvents such as DMF, DMA, and DMSO successfully suppressed the formation of amide (**5a**), and DMA was found to be superior to other solvents. Increasing the reaction temperature and reaction time led to higher conversion of desired product (entries 11−13). The presence of palladium sources were also surveyed for the Pd catalysis (entries 14−16); among the various palladium complexes employed, $Pd(MeCN)_2Cl_2$ was found to be the most effective for this transformation, increasing the yield of **4a** to 91% NMR yield (entry 15). Moreover, the desired product was not obtained in the absence of palladium complex (entry 17).

The Pd-catalyzed C−H activation with nitrile insertion was successfully extended to various substrates (**1**), and the results are listed in Scheme 1. The reactions required at least 72 h to fully consume the substrates (**1**). As indicated, reactions worked well for various substrates and electron density of the terminal aryl ring dramatically affects the cyclization (Scheme 1). Thus, substrates with an

Table 1. Optimization of Reaction Conditions[a]



					yield[b] (%)		
entry	[Pd]	additive	solvent	temp (°C)	**1a**	**4a**	**5a**
1	$Pd(OAc)_2$	none	TFA	120	15	12	54
2	$Pd(OAc)_2$	none	PivOH	120	92	0	0
3	$Pd(OAc)_2$	none	AcOH	120	60	3	26
4	$Pd(OAc)_2$	none	TFA	140	0	27	52
5	$Pd(OAc)_2$	AgTFA	TFA	120	43	28	16
6[c]	$Pd(OAc)_2$	AgTFA	Benzene/TFA	120	0	27	68
7[c]	$Pd(OAc)_2$	AgTFA	DMF/TFA	120	96	0	0
8[c]	$Pd(OAc)_2$	AgTFA	DME/TFA	120	62	0	31
9[c]	$Pd(OAc)_2$	AgTFA	DMA/TFA	120	85	8	0
10[c]	$Pd(OAc)_2$	AgTFA	DMSO/TFA	120	97	0	0
11[c]	$Pd(OAc)_2$	AgTFA	DMA/TFA	140	67	26	0
12[c,d]	$Pd(OAc)_2$	AgTFA	DMA/TFA	140	0	84	0
13[c]	$Pd(OAc)_2$	AgTFA	DMA/TFA	160	3	74	6
14[c,d]	$Pd(TFA)_2$	AgTFA	DMA/TFA	140	0	79	0
15[c,d]	$Pd(MeCN)_2Cl_2$	AgTFA	DMA/TFA	140	0	91	0
16[c,d]	$Pd(PPh_3)_2Cl_2$	AgTFA	DMA/TFA	140	0	62	0
17[c,d]	none	AgTFA	DMA/TFA	140	94	0	0

[a] Reactions were carried out using 0.2 mmol (1.0 equiv) of **1a** with 10 mol % of [Pd], 20 mol % of additive and H_2O (1.1 equiv) in 0.45 mL of solvent at the indicated temperature for 24 h. [b] ^1H NMR yields based on internal standard mesitylene. [c] TFA (0.3 mL), cosolvent (0.15 mL). [d] 72 h.

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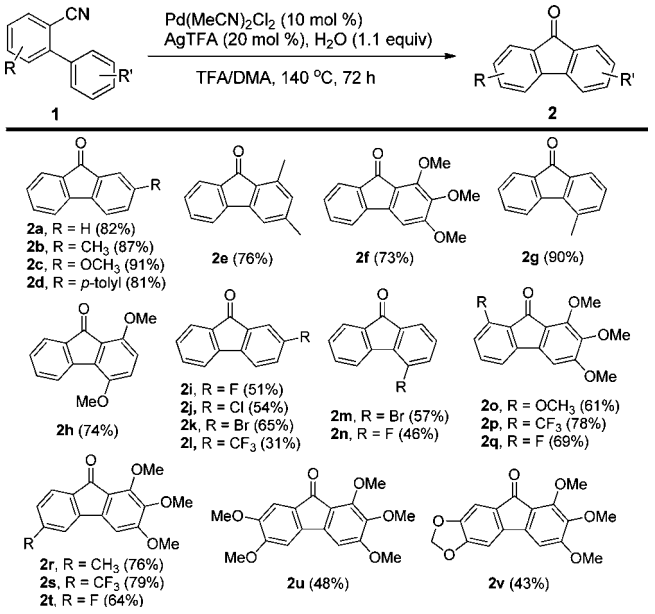
(20) See the Supporting Information for detailed studies.

Scheme 1. Pd-Catalyzed Synthesis of Fluorenones via Nitrile Directed Remote C−H Bond Activation[a,b]

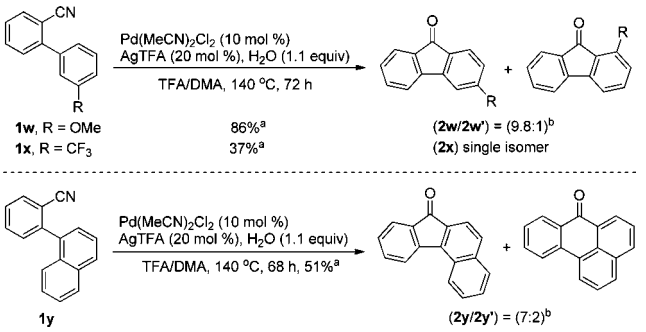


[a] Reactions were carried out using 0.5 mmol (1.0 equiv) **1** with 10 mol % of $Pd(MeCN)_2Cl_2$, 20 mol % of AgTFA, and 1.1 equiv of H_2O in 0.75 mL of DMA and 1.5 mL of TFA at 140 °C for 72 h. [b] Isolated yields.

electron-donating group provided higher yields of the corresponding products (**2b**−**h**) than substrates with an electron-withdrawing group (**2i**−**n**). Notably, the strong electron-withdrawing group CF_3 on the terminal aryl ring (**2l**) could be tolerated as well, which can not be performed by an electrophilic aromatic substitution. Products with a bromo substituent (**2k** and **2m**) can be reserved after the Pd catalysis, and this offers other application via a further coupling reaction. Substituents on the moiety of benzonitrile were also tolerated, and we observed the opposite reactivity to that when the substituents were equipped on the terminal aryl ring. Thus, reactions for the substrates with high electron density on the moiety of benzonitrile hardly completed and gave the corresponding products (**2o**, **2r**, **2u**, and **2v**) in low yields even with longer reaction time. On the contrary, reactions for the substrates with lower electron density on the same moiety processed well and afforded the corresponding products (**2p**, **2q**, **2s**, and **2t**) in good yields.

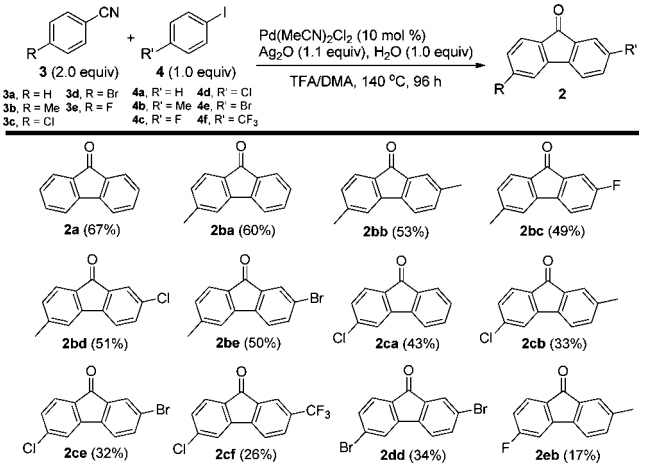
The regioselectivity for the cyclization of 7-substituted biphenyl nitriles (Scheme 2, **1w** and **1x**) was investigated, and the high selectivity was consistent in both electron-donating and electron-withdrawing groups. Thus, reaction for the substrate bearing a methoxy group (**1w**) proceeded smoothly and gave 3- and 1-methoxyfluorenone in 86% isolated yield with 9.8:1 NMR ratio. Furthermore, a single isomer of 3-substituted fluorenone (**2x**) was observed when the substrate bearing a CF_3 group. These results strongly suggest that the Pd-catalytic C−H activation is dominated by the steric effect of intermediates. In addition, selectivity for the ring size was investigated as well. It was found that the formation of five- and six-membered compounds

Scheme 2. Selectivity of the Cyclization



[a] Isolated yield. [b] Ratio was determined by ^1H NMR.

Scheme 3. Pd-Catalyzed Cascade Reaction of Dual C−H Bond Activation To Form Fluorenones



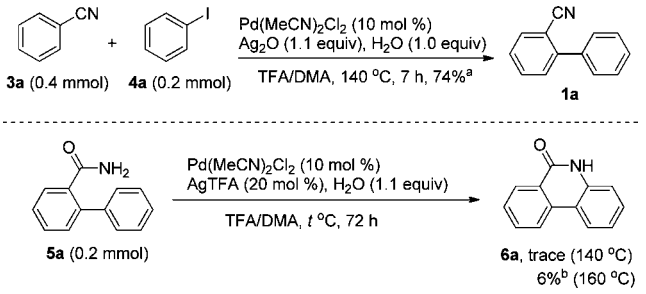
[a] Reactions were carried out with 1.0 mmol (2.0 equiv) of **3**, 0.5 mmol (1.0 equiv) of **4**, 10 mol % of $Pd(MeCN)_2Cl_2$, 1.1 equiv of Ag_2O, and 1.0 equiv of H_2O in 5 mL of TFA and 0.25 mL of DMA at 140 °C for 96 h. [b] Isolated yields were calculated on the basis of **4**.

(**2y** and **2y′**) from 2-(naphthalen-1-yl)benzonitrile (**1y**) was feasible and gave 51% yield with a 7:2 NMR ratio.

The cascade reaction for dual C−H bond activation to form fluorenones was also able to be carried out by using a similar protocol with modification of the silver source and the ratio of reagents (Scheme 3). Thus, benzonitrile (**3a**) and 4-methylbenzonitrile (**3b**) smoothly reacted with aryl iodide (**4**) to provide the corresponding products (**2a**−**be**) in moderate yields. However, when the electron-deficient aryl nitriles (**3c**, **3,d** and **3e**) were employed as substrates, we got the corresponding products (**2ca**−**eb**) in poor yields and observed a lot of the corresponding aryl acids.

To study the mechanism, some control experiments were conducted to understand the reaction (Scheme 4). Thus, we proceeded the reaction with short reaction time and found that the coupling reaction of **3a** with **4a** was occurred to form compound **1a**. The phenyl iodide (**4a**) was completely consumed within 7 h; however, we did not observe

Scheme 4. Control Experiments



[a] Isolated yield. [b] Determined by GC−MS.

any fluorenone at such reaction time. In addition, cyclization of the biphenyl amide (**5a**) did not furnish any desired product, but a small amount of unexpected phenanthridinone (**6a**) was detected by GC−MS.

Although a more detailed study might be required to fully understand the mechanism of this Pd-catalyzed C−H and dual C−H bond activation, a tentative pathway can be proposed according to the above results and the previous report (Scheme 5).[18] Thus, the catalytic reaction is likely to be initiated by the C−H bond activation of in situ generated $Pd(TFA)_2$ to afford complex **A**, followed by the oxidative addition of phenyl iodide to form Pd(IV) species (complex **B**).[21] Reductive elimination provides compound **1**, and the nitrile directed remote C−H bond activation by $Pd(TFA)_2$ is then occurred to form complex **C**; coordination of silver might prevent the hydrolysis of **C**.

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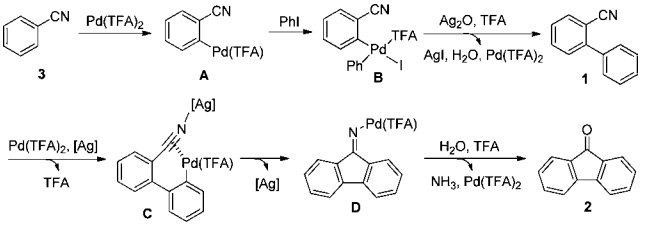
Scheme 5. Proposed Mechanism



1,2-Insertion of nitrile produces the intermediate **D**, which is then hydrolyzed by H_2O and TFA to provide desired product **2** and regenerate Pd(II) species.

In conclusion, we have developed a novel method for the cascade reactions of nitrile directed remote C−H and dual C−H bond activation with insertion of nitrile catalyzed by a palladium complex. This method efficiently provides poly substituted fluorenones in moderate to good yields with tolerance of a wide variety of substrates. Further studies to explore the possibility for synthesizing natural alkaloids as well as extending the applications of this catalytic system are currently underway.

Acknowledgment. We thank the National Science Council of the Republic of China (NSC-101-2113-M-032-004-MY2) for the support of this research.

Supporting Information Available. Experimental procedures, characterization, spectral data, and copies of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.