ORGANIC
LETTERS

2009
Vol. 11, No. 20
4588−4591

Highly Efficient and Versatile Synthesis of Polyarylfluorenes via Pd-Catalyzed C−H Bond Activation

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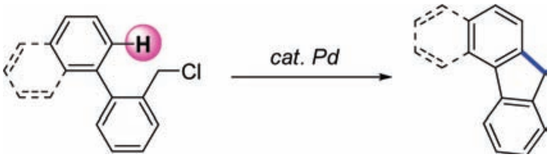
Received August 10, 2009

ABSTRACT

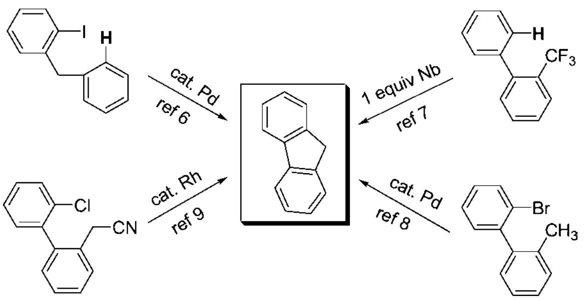


A facile protocol for the Pd-catalyzed preparative synthesis of fluorene derivatives has been developed. While a wide range of fluorenes were easily obtained with high efficiency and selectivity under mild conditions, excellent functional group tolerance was also demonstrated. On the basis of Hammett and KIE studies, the present reaction is proposed to proceed via a base-assisted deprotonative metalation pathway.

Polycyclic aromatic hydrocarbons (PAHs) have been of great interest especially in materials science because of their utilities in organic electronics, such as light-emitting diodes, field-effect transistors, and solar cells.[1] For this reason, development of an efficient and preparative method for simple or functionalized PAHs is considered to be highly important. In particular, fluorene derivatives are a notable structural motif for the diverse PAH derivatives having various applications as dyes or optical brightening agents.[2] In addition, while some types of fluorene-bearing compounds exhibit interesting bioactivities,[3] they are also frequently utilized as effective ligands in organometallic chemistry.[4]

Although conventional multistep procedures were reported for the synthesis of fluorenes,[5] transition-metal-mediated cyclizations have been extensively investigated in recent years as a promising route utilizing a C−H bond activation strategy (Scheme 1).[6−9] Intermolecular catalytic reactions were also developed for the synthesis of methylene-disubstituted fluorene derivatives.[10]

Scheme 1. Precedent Metal-Mediated Routes to a Fluorene Skeleton



Described herein are our most recent studies on the Pd-catalyzed intramolecular cyclization of *o*-aryl-substituted benzyl chlorides to obtain polyarylfluorene derivatives.[11] Its

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(1) (a) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891. (b) Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028. (c) Murphy, A. R.; Frechet, J. M. J. *Chem. Rev.* **2007**, *107*, 1066.

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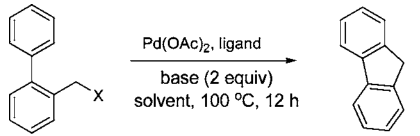
10.1021/ol901854f CCC: $40.75

mechanistic pathway is also proposed on the basis of kinetic isotope and Hammett studies.

Recently, we have reported a Pd-catalyzed cyclization of *N*-(2-halobenzyl)pyrroles to give pyrroloindoles.[12] While the scope and synthetic applicability were quite versatile, the reaction has a notable mechanistic aspect in that it utilizes metal-catalyzed activation of benzylic halides which had been much less studied when compared to aryl or vinyl (pseudo)-halides.[13] Although one preliminary result of the synthesis of a parent skeleton of 9*H*-fluorene was briefly shown in the report using 2-phenylbenzyl bromide,[12] its comprehensive scope, mechanistic details, and synthetic applications were not further investigated. This led us to initiate our efforts on the detailed optimization of reaction conditions using 2-phenylbenzyl (pseudo)halides as model substrates (Table 1).[14]

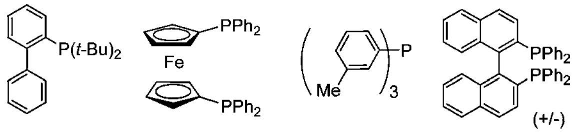
Table 1. Cyclization of 2-Phenylbenzyl (Pseudo)halides[a]



1 **2a**

entry	X	Pd (mol %)	ligand	base	solvent	yield[b] (%)
1	Br	5		$NaHCO_3$	benzene	<1
2	Br	5	**L1**	$NaHCO_3$	benzene	8
3	Br	5	**L2**	$NaHCO_3$	benzene	<1
4	Br	5	**L3**	$NaHCO_3$	benzene	16
5	Br	5	**L3**	$NaHCO_3$	DME	19
6	Cl	5	**L3**	$NaHCO_3$	DME	90
7	Cl	5	**L3**	Cs_2CO_3	DME	96
8	Cl	2	**L4**	Cs_2CO_3	DME	92
9	OAc	2	**L4**	Cs_2CO_3	DME	<1
10	I	2	**L4**	Cs_2CO_3	DME	5

[a] Conditions: substrate (**1**, 0.2 mmol), $Pd(OAc)_2$ (indicated mol %), ligand (2 equiv to Pd), base (2 equiv to **1**) in solvent (0.3 mL). [b] ^1H NMR yield (internal standard: 1,1,2,2-tetrachloroethane).



L1 **L2** **L3** **L4**

When 2-phenylbenzyl bromide (**1a**, X = Br) was subjected to our previous reaction conditions,[12] the reaction was sluggish in the absence of external ligands (entry 1).[15] Whereas the use of biphenyl (**L1**) or ferrocene (**L2**) ligands resulted in no improvement, $(m\text{-Tol})_3P$ (**L3**) gave a moderate increase of product yield (entries 4−5).

It was revealed that the employment of 2-phenylbenzyl chloride (**1b**, X = Cl) offered a dramatic improvement, presumably due to the reluctance to the reductive dehalogenation when compared to the bromo- and iodo counterparts, with the use of **L3** and $NaHCO_3$ or Cs_2CO_3 in 1,2-dimethoxyethane (entries 6−7). It was later found that the reaction could be best run with *rac*-BINAP **L4** as a ligand and Cs_2CO_3 as a base, thereby allowing the use of only 2 mol % of $Pd(OAc)_2$ to afford satisfactory yield of **2a** (entry 8). In contrast, whereas 2-phenylbenzyl acetate (**1c**, X = OAc) was inert to the conditions (entry 9), reaction of an iodo analogue (**1d**, X = I) gave poor product yield due to reductive elimination leading to 2-phenyltoluene (entry 10). On the other hand, in our previous study,[12] the highest yield of **2a** was 55% when **1a** (X = Br) was used in the presence of 5 mol % of $Pd(OAc)_2$, ligand **L1** (10 mol %), and Et_3N (2 equiv to **1a**) in toluene (100 °C, 12 h).

The present synthetic route to a fluorene motif was quite general, thus allowing the cyclization of a wide range of 2-arylbenzyl chlorides to take place smoothly to furnish the corresponding fluorene derivatives (Table 2). While substrates having electron-rich substituents underwent the cyclization more efficiently (entries 2 and 3), those bearing certain electron-withdrawing groups gave products in moderate yields (entries 4 and 5), although this trend of the electronic effects could not be generalized in some cases (e.g., entry 6). Disubstituted fluorene compounds were also easily obtained in high yields (entries 7 and 8). Functional group tolerance to the reaction conditions turned out to be quite high, thus producing fluorene derivatives having chloro, acetyl, or fluoro substituents (entries 4, 5, and 9, respectively).

When 2-(1-naphthyl)benzyl chloride was employed, the annulation took place readily to afford 7*H*-benzo[*c*]fluorene (**3**) in excellent yield (entry 10). 4*H*-Indeno[1,2-*b*]thiophene (**4**) was also obtained from 3-(chloromethyl)-2-phenylthiophene (entry 11). The present procedure was readily operative even with a multigram scale (10 mmol) without difficulty.[15]

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(5) For selected recent examples, see: (a) Reisch, H.; Wiester, U.; Scherf, U.; Tuytuylkov, N. *Macromolecules* **1996**, *29*, 8240. (b) Merlet, S.; Birau, M.; Wang, Z. Y. *Org. Lett.* **2002**, *4*, 2157. (c) Wong, K.; Chi, L.; Huang, S.; Liao, Y.; Wang, L. Y. *Org. Lett.* **2006**, *8*, 5029. (d) Clive, D. L. J.; Sunasee, R. *Org. Lett.* **2007**, *9*, 2677.

(6) (a) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Shimizu, M.; Mochida, K.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9760.

(7) Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 1434.

(8) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289.

(9) Tobisu, M.; Kita, Y.; Ano, Y.; Chatani, N. *J. Am. Chem. Soc.* **2008**, *130*, 15982.

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(11) For recent reviews on the direct C−H functionalization, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2007**, 3382. (g) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727. (h) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949.

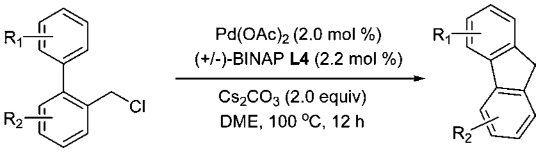
(12) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158.

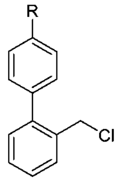
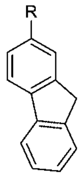
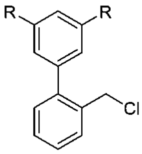
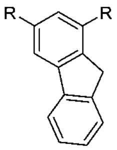
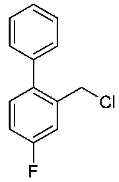
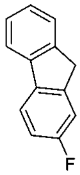
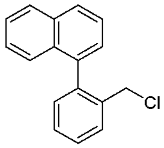
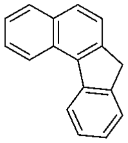
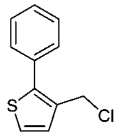
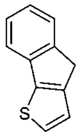
(13) (a) Liégault, B.; Renaud, J.-L.; Bruneau, C. *Chem. Soc. Rev* **2008**, *37*, 290. (b) Kuwano, R. *Synthesis* **2009**, 1049.

(14) For relevant examples from this laboratory, see: (a) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750. (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (c) Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455. (d) Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824. (e) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254.

(15) For details, see the Supporting Information.

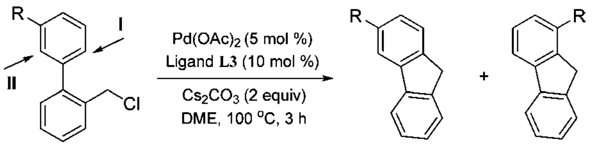
Table 2. Pd-Catalyzed Synthesis of Fluorene Derivatives[a]



entry	substrate	product			yield (%)[b]
1			R = H	(2a)	89
2			OCH$_3$	(2b)	99
3			CH$_3$	(2c)	80
4			Cl	(2d)	52
5			Ac	(2e)	48
6			CF$_3$	(2f)	98
7			R = OCH$_3$	(2g)	99
8			CH$_3$	(2h)	70
9				(2i)	74
10[c]				(3)	99
11[c]				(4)	70

[a] Conditions: substrate (0.2 mmol), Pd(OAc)$_2$ (2 mol %), ligand (±)-BINAP (**L4**, 2.2 mol %), Cs$_2$CO$_3$ (2 equiv) in DME (0.3 mL) at 100 °C. [b] Isolated yield. [c] Pd(OAc)$_2$ (5 mol %) and **L3** (10 mol %) at 100 °C.

Table 3. Pd-Catalyzed Synthesis of Fluorene Derivatives[a]



I **II**

entry	R	yield[b] (%)	ratio of **I**/**II**[c]
1	Cl	90	1.2:1
2	Ac	72	>30:1
3	CF$_3$	72	>30:1
4	CH$_3$	99	2.8:1
5	*i*-Pr	91	10:1
6	N(CH$_3$)$_2$	69	20:1

[a] Conditions: substrate (0.2 mmol) and indicated amounts of Pd(OAc)$_2$, **L3**, and Cs$_2$CO$_3$ in DME (0.3 mL) at 100 °C. [b] Combined isolated yield. [c] Determined by ^{1}H NMR integration of crude reaction mixture.

We next examined the effects of electronic and/or steric influence of substrates on the regioselectivity (Table 3). In this case, a less expensive ligand of **L3** was employed instead of **L4** which shows a similar catalytic activity when compared to **L3**. It was found that the reaction proceeded selectively to offer one type (**I**) of fluorenes among two possible regioisomers, and the ratio varied depending on the *meta* substituents.

In general, steric factors seemed to be more dominant for the regiocontrol than electronic effects. For instance, whereas the reaction of a substrate bearing a *m*-chloro group afforded two isomeric products nonselectively (entry 1), those of acetyl or trifluoromethyl-containing substrates were highly selective (entries 2 and 3). In addition, while a *m*-methyl group provided a moderate ratio (entry 4), change of the substituent to bulkier isopropyl moiety significantly favored the type **I** product (entry 5). A high degree of selectivity was also observed in the cyclization of an amino group-substituted compound.[6]

Measurement of relative reaction rates between *para*-substituted 2-phenylbenzyl chlorides was next performed to elucidate electronic influence on the reaction progress (Figure 1). Hammett plotting of log(k_{rel}) versus σ_{m} revealed a positive ρ value of 0.42 ($r = 0.98$), implying that there is a buildup of partial negative charge in the rate-limiting transition state.

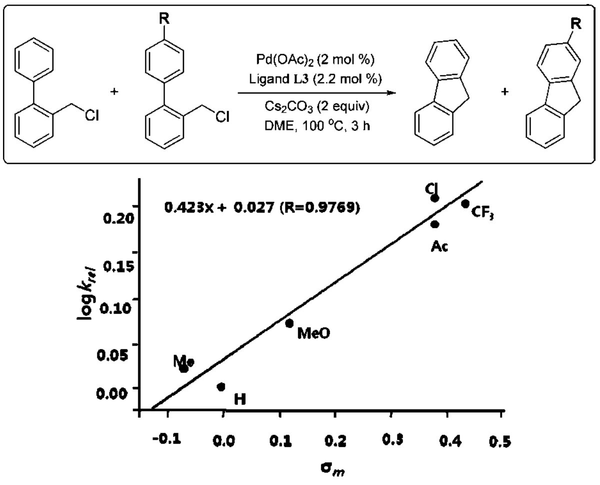


Figure 1. Hammett plot in the Pd-catalyzed cyclization.

In addition to Hammett studies, the presence of kinetic isotope effects (KIE) can provide intuitive mechanistic clues.[16] Experiments revealed that the cyclization proceeds

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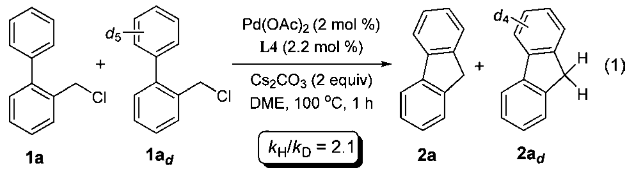
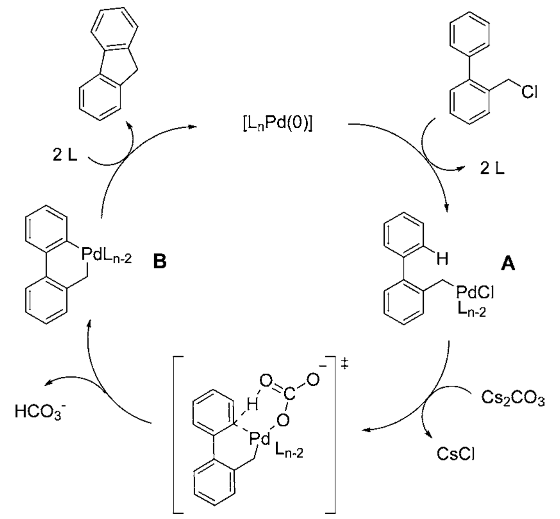
(16) (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (b) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

with intermolecular KIE of $k_H/k_D = 2.1$ without *d*-incorporation at the C-9 methylene position (eq 1).



Based on the above mechanistic data and precedent information,[17] it is presumed that the reaction is initiated by an oxidative addition of benzylic halide into the Pd(0) center to generate a Pd(benzyl) intermediate **A** (Scheme 2). While a Tsuji−Trost type allylpalladium species or Heck-type carbopalladation pathway[18] can be envisioned to occur subsequently, they are unlikely mainly due to the observed kinetic isotope effects and the absence of deuterium scrambling during the reaction course.

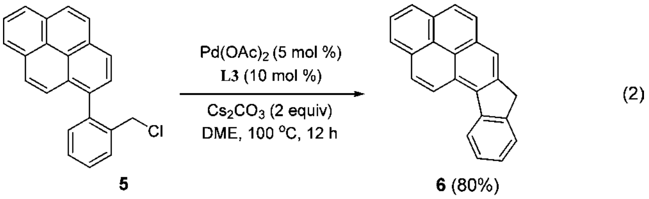
Scheme 2. Plausible Mechanistic Pathway

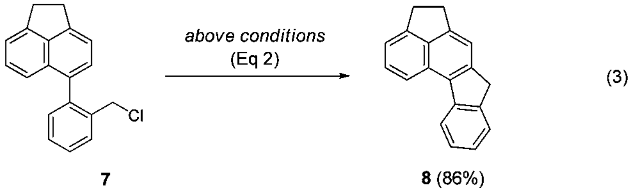


Alternatively, other mechanistic possibilities need to be considered for the generation of a key palladacycle species **B** from **A**. Electrophilic aromatic attack of the 2-phenyl moiety onto the Pd(II) center of **A** followed by deprotonation is a plausibe pathway as was proposed in the numerous reported reactions of electron-rich aromatic compounds.[19] However, the mechanistic observations of this study do not support the electrophilic palladation pathway, in which a negative slope of Hammett plot and KIE values close to 1 would be expected.

Consequently, we propose that the palladacycle-forming step proceeds via a base-assisted deprotonative metalation path as depicted in Scheme 2 considering that base additive effects are significant in the reaction (Table 1).[19] Finally, a reductive elimination of the palladacyclic intermediate **B** will lead to fluorene and Pd(0) species which enters into the next catalytic cycle.

The synthetic utility of the present protocol was next demonstrated in the facile synthesis of 7*H*-indenopyrene (**6**) and 5,7-dihydro-4*H*-indenofluorene (**8**) under the optimized conditions except that (*m*-Tol)$_3$P (**L3**) was employed as a phosphine ligand (eq 2 and 3, respectively). The starting materials (**5** and **7**) were easily prepared by a two-step procedure of Suzuki coupling of 2-bromobenzyl alcohols with arylboronic acids followed by halogenation of the resultant 2-(polyaryl)benzyl alcohols.[15] Therefore, the present procedure offers an elegant and practical synthetic route to polyaryl fluorenes.





In summary, a preparative protocol is developed for the synthesis of polyarylfluorenes via the Pd-catalyzed cyclization of 2-(aryl)benzyl chlorides. A wide range of fluorene derivatives were readily obtained with excellent efficiency, selectivity, and functional group tolerance. The reaction is proposed to proceed via a base-assisted C−H bond activation based on the mechanistic studies.

Acknowledgment. This research was supported by the Korea Research Foundation (KRF-2008-C00024, Star Faculty Program).

Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For an example of stoichiometric palladium insertion into a benzylic carbon−halogen bond, see: Fitton, P.; Mckeon, J. E.; Ream, B. C. *J. Chem. Soc. D* **1969**, 370.

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(19) (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.