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Synthesis of Fused Polycycles by 1,4-Palladium Migration Chemistry

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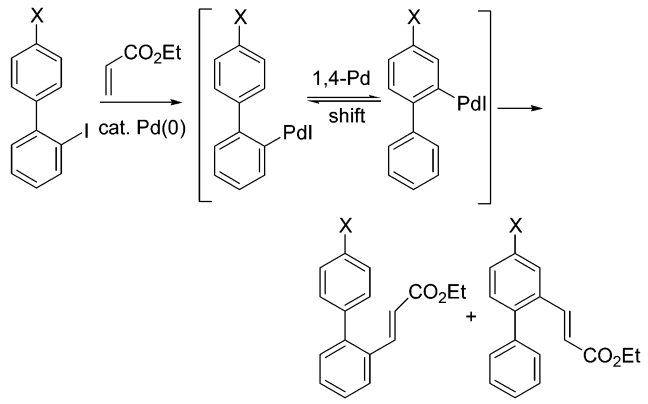
Novel palladium migration/arylation methodology for the synthesis of complex fused polycycles has been developed, in which one or more sequential Pd-catalyzed intramolecular migration processes involving C−H activation are employed. The chemistry works best with electron-rich aromatics, which is in agreement with the idea that these palladium-catalyzed C−H activation reactions parallel electrophilic aromatic substitution.

Introduction

The ability of palladium to activate C−H bonds has been used extensively in organic synthesis in recent years due to the wide variety of reactions this metal will catalyze.[1] For instance, catalytic amounts of Pd salts have been used to effect the addition of C−H bonds of electron-rich arenes to alkenes and alkynes and to effect carbonylation.[1a,2−4] We have previously reported the synthesis of 9-benzylidene-9*H*-fluorenes by Pd-catalyzed intramolecular C−H activation involving the rearrangement of organopalladium intermediates derived from aryl halides and internal alkynes.[3b] Similarly, intramolecular C−H activation in organopalladium intermediates derived from *o*-halobiaryls leads to a 1,4-palladium migration (Scheme 1).[3a,5] We have already shown that such arylpalladium intermediates can be trapped by Heck and alkyne annulation reactions.[5] We have recently reported that this aryl-to-aryl palladium migration process, followed by arylation, provides a novel, new route to a wide variety of carbocycles and heterocycles.[6] Herein, we wish to report further details on this aryl−aryl migration and also vinylic−aryl migration chemistry, followed by intramolecular arylation.

SCHEME 1



Our strategy involves palladium C−H activation and 1,4-palladium migration within a biaryl, which generates key arylpalladium intermediates which subsequently undergo C−C bond formation by intramolecular arylation producing fused polycycles (Scheme 2). This process represents a very powerful new tool for the preparation of complex molecules, which might be difficult to prepare by any other present methodology.

Results and Discussion

To obtain an optimum set of reaction conditions for palladium migration, we have reinvestigated the palladium-catalyzed transformation of 1-iodo-1,2,2-triphenylethene (**1**) to 9-benzylidene-9*H*-fluorene (**2**) as our model system[3b] (Table 1). While this system may not be the most obvious for a study of aryl-to-aryl Pd migrations, we had previously accumulated substantial data on this system. To begin with, we carried out this reaction using our previously reported conditions[3b] and obtained the desired compound **2** in a 73% yield, along with triphenylethene (**3**) in a 15% yield (entry 1).

(1) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731. (b) Li, C.-J. *Acc. Chem. Res*. **2002**, *35*, 533. (c) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem*. **1983**, *250*, 509. (d) Oyamada, J.; Jia, C.; Fujiwara, Y. *Chem. Lett*. **2002**, 2. (e) Oyamada, J.; Jia, C.; Fujiwara, Y. *Chem. Lett.* **2002**, 380. (f) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem*. **2000**, *65*, 7516.

(2) For reviews, see: (a) Fujiwara, Y.; Jia, C. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons; New York, 2002; Vol. *2*, p 2859. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633. (c) Catellani, M. *Synlett* **2003**, 298. (d) Dyker, G. *Chem. Ber. Recl.* **1997**, *130*, 1567.

(3) For palladium migration, see: (a) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (b) Tian, Q.; Larock, R. C. *Org. Lett*. **2000**, *2*, 3329. (c) Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147. (d) Markies, B. A.; Wijkens, P.; Kooijman, H.; Spek, A. L.; Boersma, J.; van Koten, G. *J. Chem. Soc., Chem. Commun*. **1992**, 1420. (e) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *279*, 225. (f) Huang, Q.; Fazio A.; Dai G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460.

(4) For rhodium migration, see: Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464.

(5) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc*. **2002**, *124*, 14326.

(6) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506.

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SCHEME 2

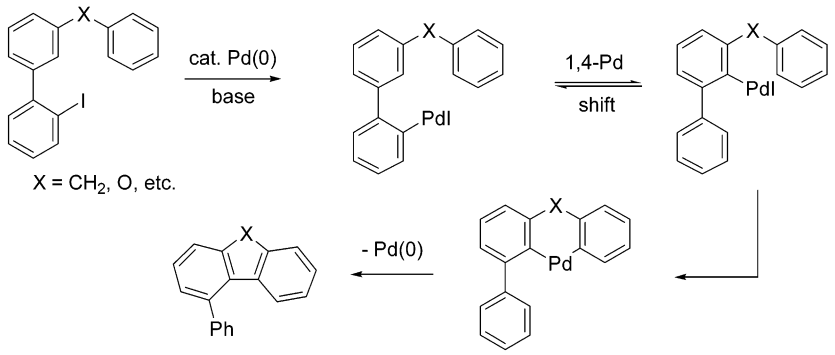
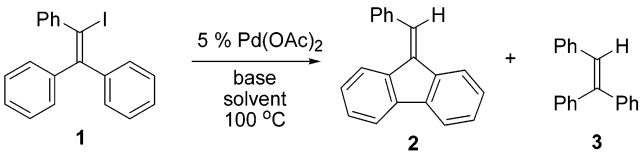


TABLE 1. Palladium-Catalyzed Cyclization of 1-Iodo-1,2,2-triphenylethene (1) to 9-Benzylidenefluorene (2)[a]



1 2 3

entry	ligand (mol %)	base	chloride source	solvent	time (d)	% yield of **2**	% yield of **3**
1	PPh_3 (10)	NaOAc	TBAC[b]	DMF	3	73	15
2	P(*o*-tol)$_3$ (10)	NaOAc	TBAC	DMF	3	75	20
3	dppm[c](5)	NaOAc	TBAC	DMF	3	79	15
4	dppm (5)	NaOAc		DMF	1	47	47
5	dppm (5)	NaOAc		DMA	1.5	52	48
6	dppm (5)	NaOAc		NMP	1	46	46
7	dppm (5)	NaOAc		DMSO	1		
8	dppm (5)	pyridine		DMF	1		
9	dppm (5)	*i*-Pr_2NEt		DMF	1		
10	dppm (5)	Na_2CO_3		DMF	1	70	26
11	dppm (5)	$NaHCO_3$		DMF	1	65	23
12	dppm (5)	Na_2CO_3[d]		DMF	1		47
13	dppm (5)	Cs_2CO_3		DMF	1	74	22
14	dppm (5)	CsOAc		DMF	2	90	4
15	dppm (5)	CsO_2CCMe_3		DMF	1	96	4
16	dppm (5)	CsO_2CCMe_3		DMA	1	59	17[e]
17	dppe[f](5)	CsO_2CCMe_3		DMF	1	90	10
18	dppm (5)	*n*-Bu_4NOAc		DMF	1	<10	

[a] The reaction was run with 0.25 mmol of 1-iodo-1,2,2-triphenylethene (**1**), 5 mol % of $Pd(OAc)_2$ and 4 mL of solvent at 100 °C. [b] TBAC = *n*-Bu_4NCl. [c] Dppm = 1,1-bis(diphenylphosphino)methane. [d] 1 equiv of NaI was added. [e] 24% of **1** was recovered. [f] Dppe = 1,2-bis(diphenylphosphino)ethane.

The first variable to be examined was the ligand on palladium. We examined phosphines other than PPh_3. Entries 2 and 3 indicate that P(*o*-tol)$_3$ and $CH_2(PPh_2)_2$ (dppm) are superior to PPh_3 in affording higher yields of the fluorene **2**. However, the reactions with all of these phosphine ligands required 3 d to reach completion. To shorten this relatively lengthy reaction time, we eliminated *n*-Bu_4NCl (TBAC) and found that the reaction was complete after only 1 d (entry 4). It is likely that coordination of chloride to palladium increases the stability and electronic density of the palladium intermediate, and thus lowers its reactivity toward the C−H bond, which subsequently slows the Pd migration. Unfortunately, this led to a much lower yield of the desired compound **2** (47%), and the yield of reduced product **3** increased to 47%. To investigate whether DMF was the hydride source for the reduction of **1** to **3**, we carried out this reaction using other solvents, such as DMA, NMP, and DMSO (entries 5−7). DMSO gave none of the desired fluorene **2** or any reduction product **3**. The amount of reduction was more or less the same in the other solvents. Thus, we continued our investigation using DMF as the reaction solvent.

We also examined the effect of various bases on the yields of **2** and **3**, including organic bases, such as pyridine and diisopropylethylamine (entries 8 and 9). These bases were ineffective in promoting the reaction and TLC analysis of the reaction mixtures indicated only the presence of the starting vinylic halide **1**. The use of Na_2CO_3 as the base provided **2** in a 70% yield, but we also obtained reduced product **3** in a 26% yield (entry 10). The base $NaHCO_3$ provided a 65% yield of **2** and a 23% yield of **3** (entry 11). We believe that the solubility of these bases in the reaction mixture may be playing a critical role in determining the outcome. Thus, once again we used Na_2CO_3 as the base, but this time we added 1 equiv of NaI, which is completely soluble in DMF, as an additive to promote a sodium common ion effect intended to make Na_2CO_3 less soluble in the reaction mixture. Indeed, this experiment revealed that under such reaction conditions only the reduced product **3** was produced in a 47% yield (entry 12). None of the desired product **2** was observed (compare entries 10 and 12). Although there may be a number of other effects going on under these reaction conditions, it seemed logical to assume that the yield of the reaction would improve by using more soluble inorganic bases. Thus, the use of Cs_2CO_3, which presumably has better solubility than other alkali carbonates in DMF,[7] provided a slightly higher 74% yield of compound **2**, along with a 22% yield of the reduced product **3** (entry 13). Similarly, the use of very soluble CsOAc as the base provided a 90% yield of the desired product **2**, along with 4% of the reduced product **3** after 2 d (entry 14). We subsequently found that cesium pivalate (CsO_2CCMe_3), unlike any other previously studied base, was completely soluble in DMF at 100 °C. In this case, we obtained the desired compound **2** in an impressive 96% yield, along with only a small amount of the reduced product **3** (4%) after only 1 d (entry 15). Clearly, cesium pivalate is far superior as a base in this reaction, and its high solubility in DMF seems to be one of the reasons to explain this phenomena. To illustrate, we carried out the reaction of **1** under conditions identical with those described in entry 15, but we used DMA

(7) Satoh, T.; Inoch, J.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.

instead of DMF as the solvent, in which cesium pivalate is not completely soluble. Under these conditions, we obtained the desired compound **2** in a relatively low 59% yield, along with the reduced product **3** in a 17% yield (entry 16). Twenty four percent of the starting vinylic iodide **1** was also obtained. Finally, to test whether dppm was indeed critical to this reaction, we carried out the transformation using another chelating phosphine ligand, namely 1,2-bis(diphenylphosphino)ethane (dppe), and we obtained compound **2** in a 90% yield, along with reduced product **3** in a 10% yield (entry 17).

As a result of this optimization work, our optimal set of reaction conditions for this transformation are those listed in entry 15 of Table 1. Notice that the newly developed reaction conditions catalyze the transformation of **1** to **2** in high yield and much shorter reaction time than our earlier reported procedure (entry 1).[3b] The variable most critical to the success of this process appears to be the highly soluble cesium pivalate base. Surprisingly, the use of *n*-Bu_4NOAc as the base, which is also completely soluble in DMF under reaction conditions identical with those described in entry 15, failed to promote this reaction, affording only trace amounts of the desired product **2** after 1 d (entry 18). Thus, not only the solubility, but also the exact nature of the base appears critical in determining the yield of fluorene. It is interesting to note that the work of Buchwald, Hartwig, and Fu has demonstrated that steric congestion imposed on palladium by bulky, electron-rich ligands facilitates both the oxidative addition and reductive elimination steps involving palladium, and gives rise to more effective catalyst systems.[8] However, nothing is apparently known about the effects of using a sterically hindered base, such as pivalate, in palladium chemistry, and whether it may give similar results to those obtained with bulky ligands.

With an apparently "optimal" set of reaction conditions for palladium migration chemistry at our disposal, we proceeded to study the sequential Pd-catalyzed migration/arylation of various 3′-substituted 2-iodobiphenyls (Table 2). We began by allowing 3′-benzyl-2-iodobiphenyl (**4**) to react under our standard reaction conditions at 100 °C, but after 2 d this substrate failed to react. However, by simply increasing the reaction temperature to 110 °C, we were able to obtain the desired compound **5** in a 40% yield (entry 1). The disappointingly low yield obtained with this substrate might be explained by the poor reactivity of the benzyl moiety as an intramolecular trap. To test this idea, we carried out the reaction with the more electron-rich 2-iodo-3′-phenoxybiphenyl (**6**) and obtained the desired 4-phenyldibenzofuran (**7**) in an impressive 89% yield (entry 2). Clearly, these results indicate that the electron-rich oxygen-substituted phenyl ring is superior as an arene trap. Our finding that electron-rich arenes are superior to electron−neutral arene traps is consistent with literature reports indicating that the ease of C−H activation by palladium parallels electrophilic aromatic substitution.[9] Similarly, we have been able to selectively obtain 3-chloro-5-phenyldibenzofuran (**9**) in an 82% yield from 3-(*p*-chlorophenoxy)-2-iodobiphenyl (**8**) under our standard conditions, while leaving the chloro functionality intact (entry 3).

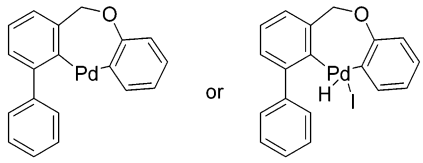


FIGURE 1. Unfavorable seven-membered-ring palladacycle intermediates.

Motivated by the ease of preparation of the following starting materials and by the knowledge that electron-rich arenes are apparently superior as intramolecular traps for our arylpalladium intermediates, we synthesized the indole derivatives **10** and **12**. To our great satisfaction, compound **10** smoothly underwent the desired reaction, producing the relatively strained isoindoloindole **11** in a 70% yield (entry 4). Surprisingly, compound **12** produced the strained and sterically congested 2-methylisoindoloindole **13** in a comparable 71% yield (entry 5).

We next examined the possibility of using an intramolecular arylation to form six-membered rings. Unfortunately, 3-(2-iodophenyl)benzyl phenyl ether (**14**) failed to react under our standard reaction conditions. Even at 110 °C, the reaction was sluggish, so the temperature was increased to 120 °C, in which case the reaction was complete after 2 d. Unfortunately, an inseparable 60:40 mixture of the desired compound **15** and the reduced product **16** was obtained in a 75% overall yield (entry 6). Clearly, the formation of a six-membered ring is not as favorable as five-membered ring formation (compare entries 2 and 6). This might be due to the difficulty in forming a seven-membered-ring palladacycle (Figure 1).

We proceeded to investigate the sequential migration/arylation reaction of more complex polyaromatic compounds. In theory, 2-iodo-1-phenylnaphthalene (**17**) should afford fluoranthene (**18**) using our methodology. Mechanistically, the palladium must first undergo a 1,4-palladium migration from the 2-position of the naphthalene to the ortho position of the phenyl substituent, followed by arylation at the 8-position of the naphthalene (Scheme 3). Although the reaction did not proceed at 100 °C, at 110 °C compound **17** produced the desired compound **18** in an 81% yield (entry 7). Similarly, 2-bromo-1-phenylnaphthalene (**19**) produced the desired fluoranthene (**18**) in a 70% yield, indicating that this aryl bromide also undergoes the desired transformation, but in a somewhat lower yield and a longer reaction time.

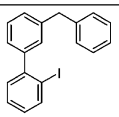
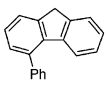
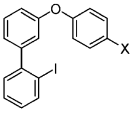
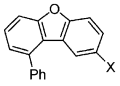
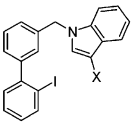
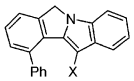
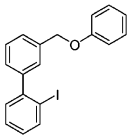
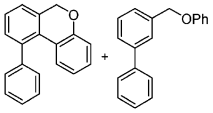
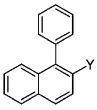
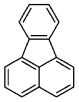
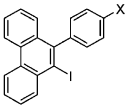
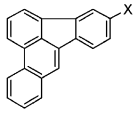
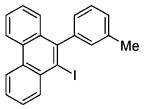
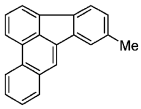
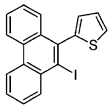
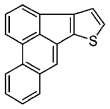
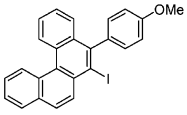
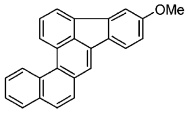
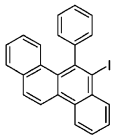
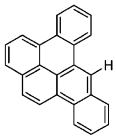
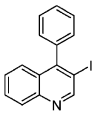
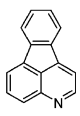
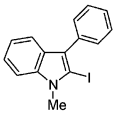
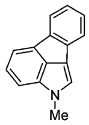
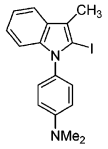
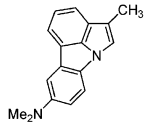
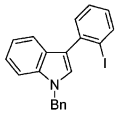
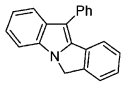
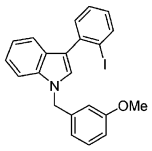
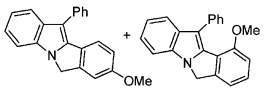
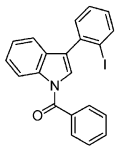
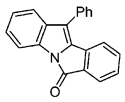
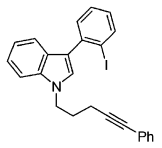
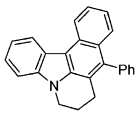
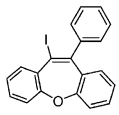
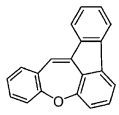
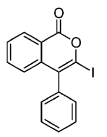
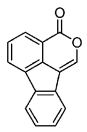
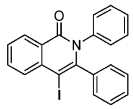
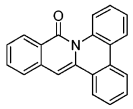
Another interesting example of this migration/arylation chemistry involves the rearrangement of easily prepared 9-iodo-10-arylphenanthrenes[10] to benz[*e*]acephenanthrylenes (entries 9−12). In this case, the palladium migrates from the 9-position of the phenanthrene to the ortho position of the aryl substituent, followed by cy-

(8) (a) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (c) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

(9) For mechanistic studies suggesting electrophilic species in intramolecular C−H activation processes employing palladium, see: (a) Martin-Matute, B.; Mateo, C.; Cardenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2001**, *7*, 2341 and references therein. (b) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *425*, 151 and references therein.

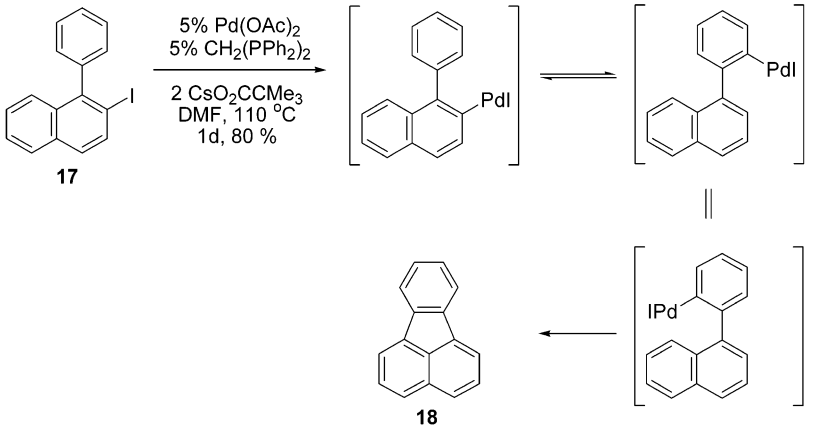
(10) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677.

TABLE 2. Sequential 1,4-Palladium Migration, Followed by Intramolecular Arylation[a]

entry	substrate		product(s)		time (d)	% yield[b]
1		**4**		**5**	3[c]	40
2	 X = H	**6**		**7**	1[c]	89
3	X = Cl	**8**		**9**	1[c]	82
4	 X = H	**10**		**11**	1	70
5	X = Me	**12**		**13**	1	71
6		**14**	 **15** **16**		2[d]	75 (60 : 40)
7	 Y = I	**17**		**18**	1[c]	81
8	Y = Br	**19**			3[c]	70
9	 X = H	**20**		**21**	2[c]	78 (18)
10	X = OMe	**22**		**23**	2[c]	71 (22)
11	X = CO_2Et	**24**		**25**	2[c]	50 (20)
12		**26**		**27**	2[c]	56 (37)
13		**28**		**29**	2[c]	0
14		**30**		**31**	2[c]	65
15		**32**		**33**	2[c]	0 (80)
16		**34**		**35**	2.5[c]	54
17		**36**		**37**	2[c]	0
18		**38**		**39**	2[c]	0
19		**40**		**41**	1	92[e]
20		**42**	 **43** **44**		0.5	78 + 12
21		**45**		**46**	1	33
22		**47**		**48**	0.5	65
23		**49**		**50**	2[c]	80
24		**51**		**52**	2	0
25		**53**		**54**	5[c]	0 (12)
26		**55**		**4**	1	88 (<5)
27		**56**		**57**	14	0 (62)[e]

[a] The reaction was carried out under the following standard conditions employing 0.25 mmol of the aryl halide, 5 mol % of $Pd(OAc)_2$, 5 mol % of dppm, and 2 equiv of CsO_2CCMe_3 in DMF (4 mL) at 100 °C unless otherwise noted. [b] The yield in parentheses corresponds to the GC yield of product in which the C−I bond has been reduced to a C−H. [c] The reaction was run at 110 °C. [d] The reaction temperature was increased to 120 °C. [e] The yield was determined by ^1H NMR spectroscopy.

SCHEME 3



clization onto the 1-position of the phenanthrene. Indeed, the reaction of 9-iodo-10-phenylphenanthrene (**20**) under our standard reaction conditions at 110 °C produced the desired benz[*e*]acephenanthrylene (**21**) in a 78% yield (entry 9). We proceeded to investigate electronic effects in this phenanthrene reaction by looking at different substituents on the phenyl moiety. As expected, the use of an electron-donating methoxy group in compound **22** gave a good yield (71%) of the corresponding benz[*e*]-acephenanthrylene **23**, although the yield was slightly lower than that of the parent system (entry 10). As expected, the introduction of an electron-withdrawing CO_2Et group in the para position of the phenyl substituent was detrimental to the reaction, producing compound **25** in only a 50% yield. All of these phenanthrene reactions gave approximately a 20% yield of the corresponding reduction product.

We have also studied the regioselectivity of the migration by using an *m*-tolyl moiety in the 10-position of the 9-iodophenanthrene (entry 12). Compound **26** has two available positions for palladium migration, the more sterically congested neighboring 2-position or the remote 6-position of the phenyl ring. The palladium-catalyzed cyclization of compound **26** generated compound **27** exclusively in a 56% yield, alongside a significant amount of reduction product (37%). This result indicates that palladium migration occurs exclusively onto the less sterically congested 6-position of the phenyl moiety and that the presence of a methyl group apparently completely inhibited migration to the more hindered 2-position or at least cyclization of that intermediate to the corresponding polycyclic product.

We next tried to prepare the more strained fused thiophene **29** from phenanthrene **28**. Unfortunately, this reaction led to a very complex mixture, which produced none of the desired compound **29**. Besides the unfavorable ring strain associated with the final product **29**, intramolecular sulfur chelation of the intermediate 10-(thiophen-2-yl)phenanthren-9-ylpalladium iodide might be inhibiting the palladium migration step (Figure 2).

The relatively electron-rich benzo[*e*]phenanthrene **30** also underwent the migration/arylation reaction, producing the highly conjugated hexacyclic compound **31** in a 65% yield (entry 14). Unfortunately, compound **32** failed to generate the desired hexacycle **33** under our reaction conditions at 110 °C (entry 15). Only reduction product was isolated in an 80% yield. This example once again

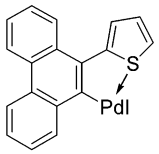


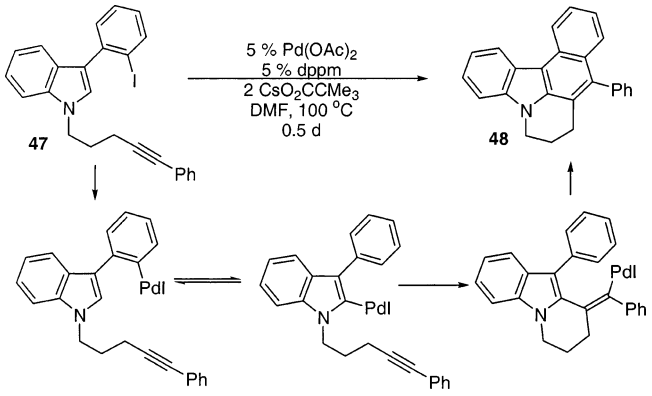
FIGURE 2. Intramolecular palladium chelation by sulfur.

indicates that intramolecular cyclization to form a six-membered ring is apparently unfavorable.

Having studied the palladium-catalyzed transformation of a variety of polycyclic aromatic halides, we switched our attention to heterocyclic aromatic compounds. To begin with, we carried out the reaction of 3-iodo-4-phenylquinoline (**34**) under our standard reaction conditions at 100 °C, but after 2 d this substrate failed to react. By simply increasing the reaction temperature to 110 °C, we obtained the desired indeno[1,2,3-*de*]quinoline (**35**) in a 54% yield. Again the modest yield obtained with this electron-deficient substrate is consistent with our previous observations that electron-deficient substrates do not perform as well as more electron-rich substrates (compare entries 7 and 16). We also allowed 2-iodo-1-methyl-3-phenylindole (**36**) to react under our standard reaction conditions at 110 °C, but failed to obtain the desired tricyclic compound **37** (entry 17). A similar negative result was obtained with iodoindole **38** (entry 18). The poor results obtained with substrates **36** and **38** can be explained in terms of the unfavorable ring strain of the corresponding products **37** and **39**. In addition, we have previously established, using Heck trapping experiments, that palladium prefers to reside on the indole moiety in such substrates.[5]

To confirm our suspicion that the palladium prefers to migrate to a more electron-rich position, because of the relatively easy activation of an electron-rich C−H bond,[5,9] compound **40** was allowed to react under our migration conditions and indole **41** was produced in a 92% yield in 1 d at 100 °C (entry 19). From the results of entries 1 and 19, it appears that the high efficiency of palladium migration to a relatively electron-rich ring allows the sequential migration/arylation to proceed smoothly at a lower temperature and in a shorter reaction time, although the benzyl group does not appear to be a particularly good arylating agent. When a methoxy group was introduced into the meta position of the benzyl group, this migration/arylation reaction af-

SCHEME 4

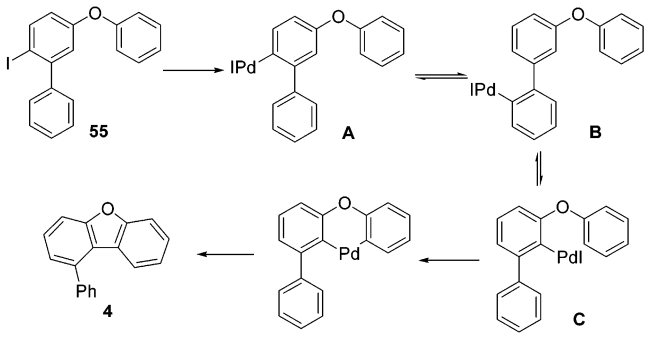


forded a mixture of indoles **43** and **44** in 78% and 12% yields, respectively (entry 20). This result is consistent with our previous observation (see entry 12) that the palladium intermediate is more likely to form the final carbon−carbon bond at the less hindered position of the aryl terminus. When compound **45**, which has an electron-deficient aryl terminus, was allowed to react under the standard migration conditions, product **46** was isolated in 33% yield (entry 21). This is consistent with electron-deficient termini giving lower yields.

We have also examined the possibility of trapping palladium migration species by alkynes. Thus, we have carried out the palladium-catalyzed sequential migration/alkyne insertion/arylation of aryl halide **47** in the hope that the arylpalladium intermediate generated by a 1,4-Pd shift via through-space C−H activation could be trapped by alkyne insertion−annulation chemistry described earlier by us (Scheme 4).[11] The reaction was carried out under our standard migration conditions and carbazole **48** was isolated in a 65% yield (entry 22). Importantly, this reaction was complete in 0.5 d at 100 °C, consistent with the particularly facile migration of Pd to the electron-rich indole ring system. Although we cannot rule out the possibility that this reaction is proceeding by direct endocyclic addition of the initial arylpalladium species to the alkyne triple bond and subsequent ring closure onto the indole to give product **48**, this seems unlikely since exocyclic addition is more common. This successful alkyne insertion chemistry suggests that there is the exciting possibility of trapping aryl- and other organopalladium intermediates generated by a 1,4-Pd shift by many other synthetically useful palladium methodologies, such as amination and annulation. We are presently examining such possibilities.

While our efforts have focused on synthesizing polycyclic compounds in which the key 1,4-palladium shift occurs from an aryl to another aryl position, we wanted to establish that our methodology could also make use of a vinylic to aryl palladium migration to generate the key intermediate for the intramolecular arylation step. We have already shown one example of such a transformation in converting compound **1** to **2** (Table 1). Another illustration of this process involves the use of 9-iodo-10-phenyldibenz[*b,f*]oxepine (**49**). The reaction of this relatively electron-rich substrate produced the desired pentacyclic compound **50** in an 80% yield (entry 23). On the other hand, treating the electron-deficient 3-iodo-4-phenylisocoumarin (**51**) under our standard reaction conditions gave a complex mixture, and we failed to isolate any of the desired tricyclic compound **52** (entry 24). This disappointing result was not unexpected, since our previous experience with compound **51** has indicated that palladium easily catalyzes its decomposition. Our last attempt to generate polycycles from vinylic iodides involved the use of isoquinolone **53** (entry 25). This substrate suffers the disadvantage that the intramolecular arylation step requires the formation of a six-membered ring. As expected, the reaction of substrate **53** under our standard reaction conditions at 110 °C failed to produce the desired pentacyclic product **54**. After 5 d of reaction, we were only able to isolate the reduction product *N*-phenyl-3-phenylisoquinolone[12] in a 12% yield.

SCHEME 5



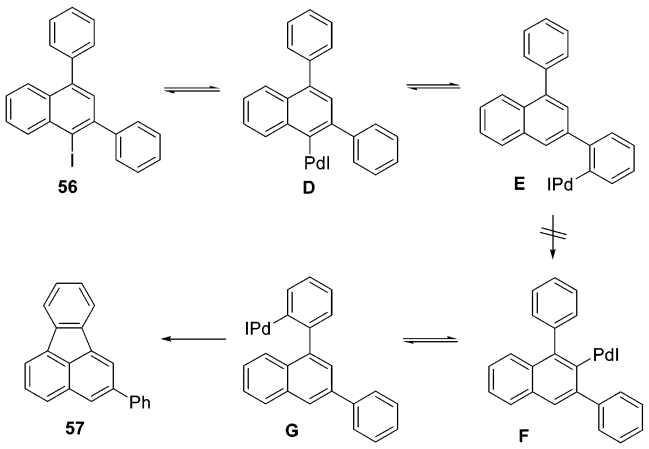
A mechanistically interesting question is whether the arylpalladium intermediate can migrate more than once and still effect synthetically useful chemistry. To examine this possibility, 2-iodo-5-phenoxybiphenyl (**55**) was allowed to react under our migration conditions and double migration product **4** was isolated in an 88% yield (entry 26 and Scheme 5). Mechanistically, the palladium first inserts into the aryl iodide bond to form intermediate **A**, which migrates to the phenyl unit by through-space C−H activation. The metal moiety in the first migration intermediate **B** can either return to the original aromatic ring in the position from which it originally migrated (**A**) or migrate to the position ortho to the phenoxy group (**C**), where it can be trapped by arylation. Note that the yield for this double migration chemistry is very similar to that from the single migration chemistry (entry 2) and the success of this double palladium migration indicates that multiple migration processes are entirely feasible.

One attempt to extend this chemistry to a triple migration process has been unsuccessful. The reaction of iodonaphthalene **56** under our standard migration conditions afforded none of the desired triple migration product **57**, producing instead the reduction product in 62% yield (entry 27). The reason for this failure to afford compound **57** is indicated in Scheme 6. While we would anticipate that intermediates **D** and **E** should be easily formed, we believe that the problem lies in getting the relatively unhindered species **E** to migrate the palladium to the more hindered position present in **F**. Instead the

(11) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536.

(12) The spectral properties for this compound were identical with those previously reported: Hellwinkel, D.; Goeke, K. *Synthesis* **1995**, 1135.

SCHEME 6



palladium presumably migrates back to the less hindered position present in intermediate **D**. This is consistent with our previous observation in entries 12 and 20 that palladium is more likely to migrate to or form a new C−C bond at a less hindered position. Therefore, the palladium intermediates only equilibrate between **D** and **E**, and eventually produce the reduced 1,3-diphenylnaphthalene.

Conclusions

In conclusion, we have developed novel methodology for the synthesis of complex fused polycycles employing two or more sequential Pd-catalyzed intramolecular processes involving C−H activation. This methodology exploits relatively facile aryl-to-aryl and vinylic-to-aryl palladium migrations, followed by intramolecular arylation to prepare a wide variety of carbocycles and heterocycles. This chemistry works best with electron-rich aromatics, which is in agreement with the idea that these palladium-catalyzed C−H activation reactions parallel electrophilic aromatic substitution. The success of our double palladium migration for the conversion of biphenyl **55** to dibenzofuran **4** indicates that multiple migration processes can be employed to produce novel new routes to a variety of polycycles. Finally, our demonstration that this chemistry is applicable to alkyne insertion processes as well opens up still further unique routes to polycylic products.

Experimental Section

Compounds **19**,[14] **20**,[14] **36**,[14] and **49**[14] were prepared according to previous literature procedures.

Representative Procedure for the Palladium-Catalyzed Migration Reactions. The appropriate aryl iodide (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), 1,1-bis(diphenylphosphino)methane (dppm) (4.8 mg, 0.0125 mmol), and CsO_2CCMe_3 (CsPiv) (0.117 g, 0.5 mmol) in DMF (4 mL) were stirred under Ar at 100 °C for the specified period of time. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (35 mL), and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel.

1-Phenyldibenzofuran (7). Compound **6** (93.0 mg, 0.25 mmol) or compound **55** (93.0 mg, 0.25 mmol) was allowed to react under our standard reaction conditions for 1 d. The reaction mixtures were chromatographed with 30:1 hexane/EtOAc to afford 54.4 mg (89%) (entry 2, Table 2) or 54.0 mg (88%) (entry 8, Table 2) of the indicated compound **7**, respectively, as a white solid: mp 62−63 °C (lit.[13] mp 63−64 °C); ^{1}H NMR ($CDCl_3$) δ 7.10−7.14 (m, 1H), 7.24−7.26 (m, 1H), 7.37−7.42 (m, 1H), 7.46−7.64 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 110.5, 111.6, 121.8, 122.3, 122.5, 123.9, 124.0, 127.1, 127.1, 127.9, 128.6, 129.0, 138.0, 140.0, 156.4, 156.5. The other spectral properties were identical with those previously reported.[13]

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Supporting Information Available: The preparation and characterization of the starting materials **4**, **6**, **8**, **10**, **12**, **14**, **17**, **22**, **24**, **26**, **28**, **30**, **32**, **34**, **36**, **38**, **40**, **42**, **45**, **47**, **51**, **53**, **55**, and **56**; the characterization data for compounds **5**, **7**, **9**, **11**, **13**, **15**, **16**, **18**, **21**, **23**, **25**, **27**, **31**, **35**, **41**, **43**, **44**, **46**, **48**, and **50**; and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **4**−**18**, **21**−**28**, **30**−**32**, **34**−**36**, **38**, **40**−**48**, **50**−**51**, **53**, **55**, and **56** are available in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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