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Biaryl Synthesis via Direct Arylation: Establishment of an Efficient Catalyst for Intramolecular Processes

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Recognizing the need for efficient routes to biaryl compounds, chemists have developed an arsenal of catalytic methods including the Suzuki−Miyaura, Stille, Negishi, Kumada−Corriu, and Hiyama couplings.[1] Recently, the direct arylation of electron-rich, heteroaromatic rings has begun to replace these more traditional techniques in specific cases.[2] In contrast to these advances, the direct arylation of simple aromatic rings remains a significant challenge.[3] Intramolecular variants involving simple aromatic rings are an important subset of these processes, yet have found limited use in organic synthesis due to narrow substrate scope and high[4] (even stoichiometric)[5] catalyst loadings under optimized conditions.[6] Overcoming these hurdles will necessarily require the discovery and development of novel catalysts. Success in this pursuit would allow for a conceptually different approach to molecules such as **1** (Scheme 1, path C) to be generally applied, thereby obviating the need to work with organometallic reagents (paths A and B). Herein we describe arylation reactions with greatly improved scope and catalyst activity. The enhanced catalytic activity not only extends these transformations to include previously unreactive and poorly reactive substrates, but also allows for very low catalyst loadings to be employed—as little as 0.1 mol %. We also disclose a new ligand that permits such processes to be efficiently extended to larger ring sizes in excellent yield, which should find wider use in this class of transformation.

Phenolates have been shown to exhibit enhanced reactivity in intramolecular arylation reactions.[7] On the other hand, ethers such as **3** that lack a phenolate activating group react poorly and have not previously been shown to undergo selective ring closure.[8] Consequently, we opted to use aryl bromide **3**, lacking such activation, as our model substrate in initial screens.[9] Poor reactivity and significant dehalogenation were obtained under previously reported conditions.[8] In contrast, excellent results were obtained with 5 mol % $Pd(OAc)_2$ and 10 mol % 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl **6**,[10] which generates **4** in 96% yield along with 4% of debrominated ether **5** (Table 1, entry 1).

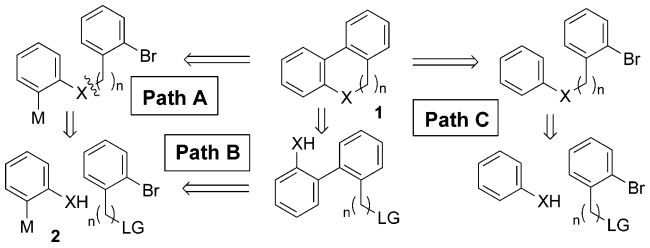
A base screen revealed that substituting Cs_2CO_3 with inexpensive K_2CO_3 not only resulted in faster reaction, generating **4** in 95% yield after 4 h with 5 mol % catalyst at 95 °C, but also increased the ratio of **4**:**5** to greater than 160:1. Further investigation of the reaction conditions revealed that the reaction could be run with greatly reduced catalyst loadings. At 125 °C, the reaction gives 100% conversion with as little as 0.5 mol % catalyst within 4 h (TON 200; TOF 50 h^{-1}). At 145 °C, 0.1 mol % palladium is sufficient to reach 100% conversion and give **4** in 96% isolated yield (TON 1000). This is a rare example in this type of transformation where such low catalyst loadings have been employed[4] and constitutes, to our knowledge, a new benchmark in the formation of biaryls via this approach.

A variety of ethers were reacted with varying amounts of catalyst as outlined in Table 2. Ortho, meta, and para substituents are compatible, including electron-donating and -withdrawing groups. Interestingly, chloro substituents remain intact under the reaction conditions, as illustrated by reaction with **15** (entries 9 and 10). Furthermore, the oxygen atom in the tether can be replaced by a carbon or nitrogen atom, as illustrated by reactions with **19** and **21** (entries 12−14). An increase in catalyst loading was required in these cases to ensure complete conversion.[11]

Formation of larger ring sizes required further development. For example, reaction of **23** with 2.5 mol % of a catalyst generated from $Pd(OAc)_2$ and ligand **6** gave **24** in only 35% yield after 6 h (Scheme 2). Ligand **26**, lacking the dimethylamino moiety, gave slightly better reactivity. Efforts aimed at increasing the reactivity of the catalyst toward electrophilic palladation led to the preparation of electron-deficient ligand **27**. Gratifyingly, with ligand **27**, only 1 mol % catalyst is sufficient to induce complete reaction and give **24** in 90% yield. Since most ligand development efforts are directed at the preparation of bulky electron-rich systems,[12] our observations that the use of bulky electron-deficient ligands can lead to excellent results should prompt their investigation in other challenging direct arylation reactions.

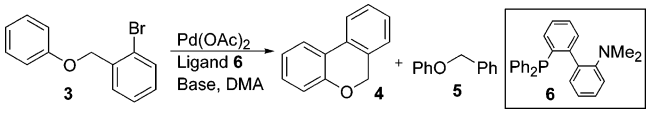
These reactions most likely proceed via initial insertion into the aryl bromide bond, followed by electrophilic attack of the arylpalladium(II) intermediate on the adjacent aromatic ring.[13] It is

Scheme 1. Routes to Tricyclic Biaryl Compounds[a]



[a] M = $B(OR)_2$, SnR_3, SiR_3; X = O, NR, CR_2; LG = leaving group.

Table 1. Reaction Optimization[a]

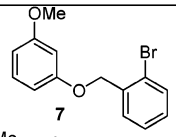
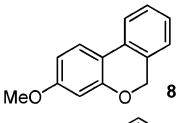
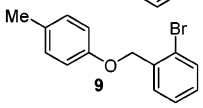
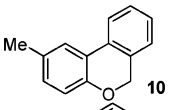
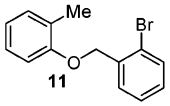
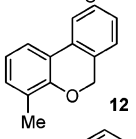
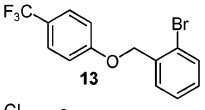
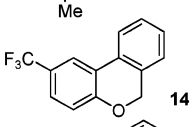
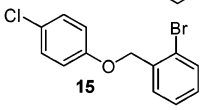
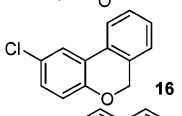
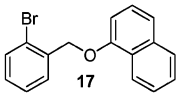
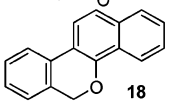
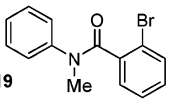
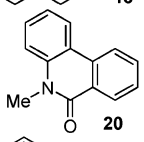
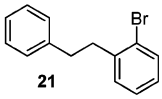
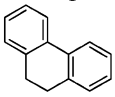


entry	mol % Pd	base	temp (°C)	time (h)	yield **4** (%)[b]	**4**:**5**[b]
1	5	Cs_2CO_3	95	10	94	24:1
2	5	Cs_2CO_3	80	20	44[c]	7.5:1
3	5	K_2CO_3	95	4	95	160:1
4	2	K_2CO_3	125	2	98	160:1
5	0.5	K_2CO_3	125	4	94[d]	165:1
6	0.1	K_2CO_3	145	14	96[d]	165:1

[a] Conditions: biaryl **3**, $Pd(OAc)_2$, ligand **6** (2 equiv per [Pd]), and base (2 equiv) dissolved in DMA and heated to the indicated temperature until judged complete as determined by GCMS. [b] Yield determined by GCMS analysis. [c] Remainder is unreacted **3**. [d] Isolated yield.

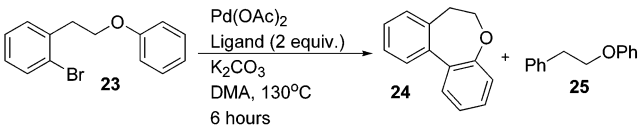
10.1021/ja049017y CCC: $27.50

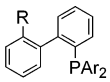
Table 2. Scope of Biaryl Formation[a]

Entry	Substrate	Product	Mol % Pd	*T* (°C)	Yield (%)[b]
1	 **7**	 **8**	1	125	91[c]
2			0.2	145	94[c]
3	 **9**	 **10**	1	125	90
4			0.5	145	92
5	 **11**	 **12**	1	125	93
6			0.5	145	94
7	 **13**	 **14**	1	135	97
8			0.2	145	98
9	 **15**	 **16**	1	125	93
10			0.1	145	97
11	 **17**	 **18**	0.5	125	91
12	 **19**	 **20**	2	135	83
13	 **21**	 **22**	5	135	79

[a] Conditions: under a nitrogen atmosphere, the substrate, $Pd(OAc)_2$, ligand **6**, and K_2CO_3 (2 equiv) were dissolved in DMA (0.2 M) and heated to the indicated temperature for 10 to 14 h. [b] Isolated yield. [c] Para/ortho 21:1.

Scheme 2. Ligand Effect on Seven-Membered Ring Formation





Ligand	mol% [Pd]	Yield (%)	24:25[a]
none	2.5	<5[a]	2:1
6	2.5	35[a]	10:1
26	2.5	45[a]	10:1
27	2.5	92[a]	14:1
27	1	90[b]	14:1

Ar = Ph; R = NMe_2: Ligand **6**
Ar = Ph; R = H: Ligand **26**
Ar = 4-$CF_3C_6H_4$; R = H: Ligand **27**

[a] Determined by GCMS, average of 3 runs. [b] Isolated yield, overnight reaction.

noteworthy that we observe an intramolecular k_H/k_D value of 3.5,[14] which is atypical of most electrophilic additions to arenes[15] but is not unprecedented with palladium.[16] This can be rationalized by invoking either a fast and reversible electrophlic palladation followed by a slow deprotonation (S_E2), or a concerted electrophilic palladation−deprotonation process (S_E3).[17]

In conclusion, we have shown that a catalyst generated from $Pd(OAc)_2$ and ligand **6** efficiently catalyzes the intramolecular formation of biaryl compounds with previously incompatible substrates and with very low catalyst loadings. These results led to the design and application of electron-deficient ligand **27**, which permits this methodology to be efficiently applied in the formation of more challenging seven-membered rings. We are currently exploring the application of this methodology in the context of total synthesis and working to fully establish the reaction mechanism.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Initial catalyst screens were carried out with **3** in DMA (0.1 M), $Pd(OAc)_2$ (5 mol %), ligand (10−15 mol %), and Cs_2CO_3 (2 equiv) at 95 °C in a Labmate heater shaker.

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