Letter

Silver-Promoted Domino Pd-Catalyzed Amination/Direct Arylation: Access to Polycyclic Heteroaromatics

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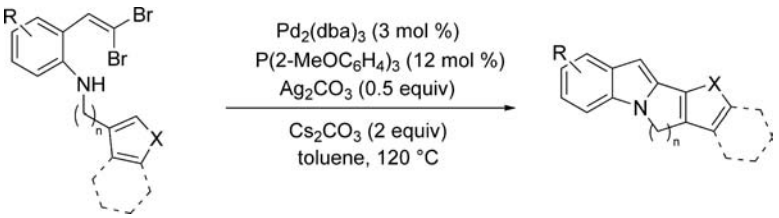

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Silver-Promoted Domino Pd-Catalyzed Amination/Direct Arylation: Access to Polycyclic Heteroaromatics

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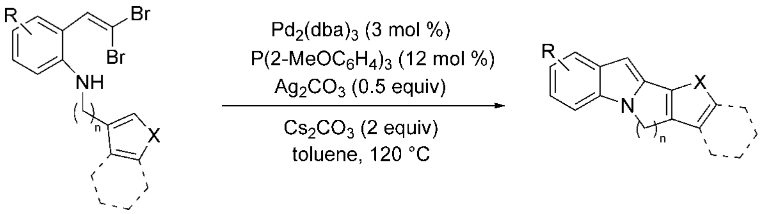
ABSTRACT



Novel tetracyclic and pentacyclic indole derivatives can be prepared from readily available *gem*-dibromovinyl substrates in a single step by means of an efficient Pd-catalyzed domino Buchwald−Hartwig amination/direct arylation reaction. Enhanced reactivity and selectivity are obtained by the addition of silver salts.

The use of direct arylation (or “C−H activation”) as a means of forming aryl−aryl bonds is a rapidly expanding area of chemical research.[1] These methods offer significant advantages over traditional cross-coupling reactions, namely, a reduction in the amount of waste produced and shorter synthetic sequences. Although the scope of possible transformations has greatly expanded in recent times,[2] the number of tandem and domino processes, where a direct arylation is combined with a second orthogonal coupling process, is significantly smaller. In particular, the union of a direct arylation with a catalytic amination has received far less attention.[3] In this report, we describe a domino Pd-catalyzed amination/direct arylation and show the effects of added silver salts in promoting this reaction.

We have previously described the use of *ortho-gem*-dihalovinyl anilines in the synthesis of various 2-substituted indoles by pairing intramolecular C−N bond formation with inter- or intramolecular Suzuki−Miyaura,[4] Heck−Mizoroki,[5]

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(1) For recent reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (e) *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vols *1 and 2*. (f) Schnürch, M.; Flasik, R.; Farooq Khan, A.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283. (g) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (h) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (i) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173, and references cited therein.

(2) For selected examples of tandem/domino processes involving direct arylation, see: (a) Wegner, H. A.; Scott, L. T.; de Meijere, A. *J. Org. Chem.* **2003**, *68*, 883. (b) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (c) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (d) Tietze, L. F.; Lotz, F. *Eur. J. Org. Chem.* **2006**, 4676. (e) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827. (g) Leclerc, J.-P.; André, M.; Fagnou, K. *J. Org. Chem.* **2006**, *71*, 1711.

(3) (a) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109. (b) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310. (c) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403. (d) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (e) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. (f) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S; Fujii, N.; Ohno, H. *Chem. Commun.* **2007**, 4516. (g) Meyers, C.; Rombouts, G.; Loones, K. T. J.; Coelho, A.; Maes, B. U. W. *Adv. Synth. Catal.* **2008**, *350*, 465. (h) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888.

(4) (a) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (b) Fang, Y.-Q.; Karisch, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341. (c) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538.

(5) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203.

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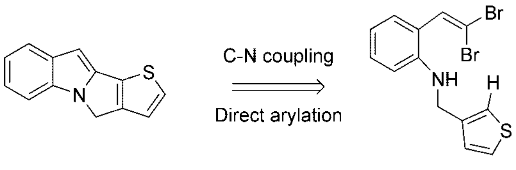
Sonogashira,[6] and amidation[7] reactions. We wish to extend this concept to incorporate a direct arylation as the second step in the cascade (Scheme 1). This method could be used to create novel polycyclic heteroaromatic molecules, which can serve as templates for drug discovery[8] or show utility in organic electronic devices.[9] These targets are inaccessible by our previous methods.

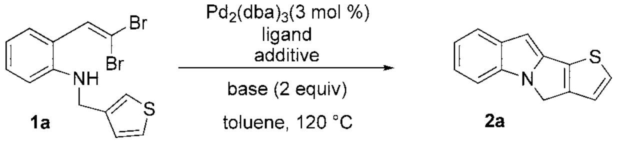
Scheme 1. Strategy for the Synthesis of Fused Indole Derivatives



The reaction was initially screened using the parent substrate **1a** to investigate the effects of different Pd sources, ligands, bases, solvents, and temperatures. We found that $Pd_2(dba)_3/P(2\text{-}MeOC_6H_4)_3$ in toluene with 2 equiv of Cs_2CO_3 as base at 120 °C (Table 1, entry 8) were optimal conditions. However, when we attempted to expand the substrate scope, the reactions became messy and yields decreased. We noted that increasing the ratio of ligand to palladium partially alleviated this problem (entry 9), and we postulated that liberated halide may act as a catalyst poison.[10] The fact that no product was detected when the reaction was run in the presence of 1 equiv of exogenous bromide in the form of Bu_4NBr (entry 10) supports this hypothesis. Gratifyingly, we found that the addition of 1 equiv of cationic silver (in the form of Ag_2CO_3) led to cleaner reactions and allowed us to reduce the ligand/Pd ratio to 2:1 (entry 11).[11,12] We confirmed that this effect is not just that of adding an extra equivalent of base by perfoming the reaction in the presence of 3.0 equiv of Cs_2CO_3 (entry 12).

With these optimized conditions in hand, we set out to investigate the scope of the domino process. We began by altering the substitution of the aryl ring (Table 2). It was found that tetracycles bearing a wide variety of functional groups could be synthesized. Halide (entries 1 and 6), electron-donating (entries 2, 3, and 5), and electron-withdrawing (entries 4, 7, and 8) moieties were all well tolerated. It was also possible to add a substituent at the methylene group with no adverse effects (entry 9). Unfortunately, replacement of the vinyl hydrogen with an aryl group completely shuts down the reactivity (entry 10).

Table 1. Optimization of the Domino C−N Coupling/Direct Arylation Conditions[a]



entry	ligand	ligand/Pd ratio	base (2 equiv)	yield (%)[b]
1	PPh_3	10:1	Cs_2CO_3	36
2[c]	PPh_3	10:1	Cs_2CO_3	30
3	BINAP	4:1	Cs_2CO_3	57
4	BINAP	4:1	K_2CO_3	36
5	BINAP	4:1	Et_3N	–
6[d]	BINAP	4:1	Cs_2CO_3	41
7[e]	BINAP	4:1	Cs_2CO_3	–
8	$P(2\text{-}MeOC_6H_4)_3$	2:1	Cs_2CO_3	70
9	$P(2\text{-}MeOC_6H_4)_3$	10:1	Cs_2CO_3	80
10[f]	$P(2\text{-}MeOC_6H_4)_3$	10:1	Cs_2CO_3	–
11[g]	$P(2\text{-}MeOC_6H_4)_3$	2:1	Cs_2CO_3	90[h]
12[i]	$P(2\text{-}MeOC_6H_4)_3$	2:1	Cs_2CO_3	69

[a] All entries were performed with 3 mol % of $Pd_2(dba)_3$, ligand, and 2 equiv of base in toluene at 120 °C unless otherwise noted. [b] Yields determined by NMR spectroscopy. [c] 6 mol % of $Pd(OAc)_2$ was used as catalyst. [d] Dioxane was used as solvent. [e] DMA was used as solvent. [f] 1 equiv of Bu_4NBr was added [g] 0.5 equiv of Ag_2CO_3 was added. [h] Isolated yield. [i] 3.0 equiv of Cs_2CO_3 was used.

We anticipated that a more difficult modification would be to change the heterocycle since this could have a profound change on the reactivity of the site of direct arylation (Table 3). The reaction proceeded smoothly when benzothiophene was used as the heterocycle instead of thiophene. Use of nitro-substituted thiophene (entry 3) led to a sluggish reaction, which did not reach full conversion even after several days at 120 °C; still, compound **4b** could be obtained in 50% yield. The slower rate of this substrate may give some insight as to the mechanism of the arylation step: if a Heck-type pathway was operative for the arylation step,[13] this reaction should proceed faster than the unsubstituted thiophene (Table 1, entry 7). The retarded reactivity of this substrate suggests that the reaction proceeds via a different arylation pathway, possibly an electrophilic aromatic substitution. Furan and pyrrole derivatives (entries 4 and 5, Table 3) were also successful, albeit in lower yields.

We next modified the linker between the nitrogen atom and the thiophene to examine the effect of ring size (Scheme 2). Synthesis of the six-membered ring **6a** proceeded smoothly, while the phenyl-fused seven-membered ring **6b** proved more difficult to form, yielding only 54% under our standard conditions. However, the yield could be increased to 71% by raising the catalyst loading to 10 mol %.

One limitation of this method is that substrates bearing an amide functional group, rather than an amine, fail to

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(6) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955.

(7) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.

(8) See: Ohno, H.; Iuchi, M.; Fujii, N.; Tanaka, T. *Org. Lett.* **2007**, *9*, 4813. and references cited therein.

(9) For a review on acene- and heteroacene-based OED's, see: Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028.

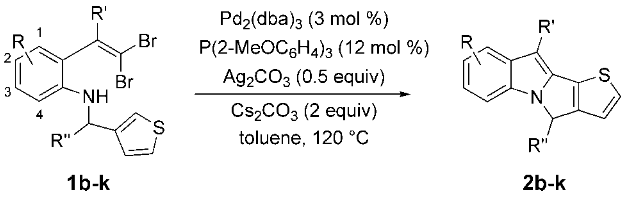
(10) For a review of halide effects in transition metal chemistry, see: Fagnou, K.; Lautens, M. *Angew. Chem, Int. Ed.* **2002**, *41*, 26.

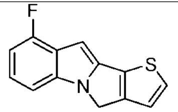
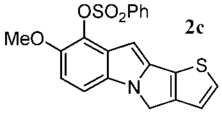
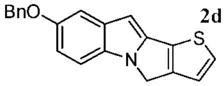
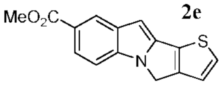
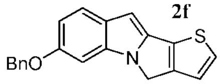
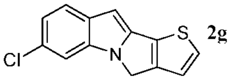
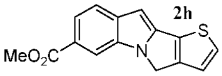
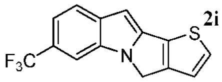
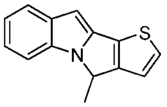
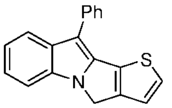
(11) For the use of silver salts to sequester iodide in direct arylation reactions, see: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879, and references therein.

(12) The use of Ag_2CO_3 as a base in Rh-catalyzed direct arylation has also been described. See: Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.

(13) (a) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. (b) Gozzi, C; Lavenot, L.; Ilg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 8867.

Table 2. Effect of Phenyl Substitution on the Tandem Process[a]

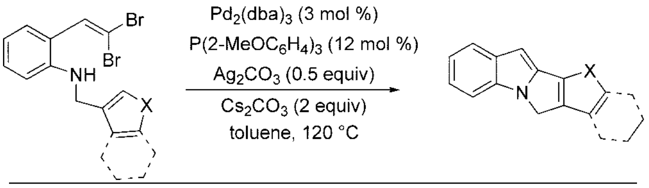


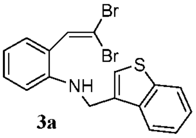
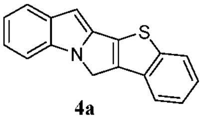
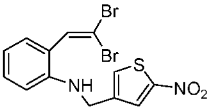
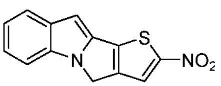
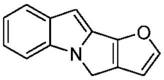
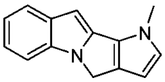
entry	substrate	product	yield (%)
1	**1b** R = 1-F, R'=R''=H	 **2b**	87
2	**1c** R = 1-OSO$_2$Ph, 2-OMe, R'=R''=H	 **2c**	91
3	**1d** R = 2-OBn, R'=R''=H	 **2d**	80
4	**1e** R = 2-CO$_2$Me, R'=R''=H	 **2e**	73
5	**1f** R = 3-OBn, R'=R''=H	 **2f**	81
6	**1g** R = 3-Cl, R'=R''=H	 **2g**	92
7	**1h** R = 3-CO$_2$Me, R'=R''=H	 **2h**	88
8	**1i** R = 3-CF$_3$, R'=R''=H	 **2i**	84
9	**1j** R = R'=H, R'' = Me	 **2j**	83
10[b]	**1k** R = H, R' = Ph, R'' = H	 **2k**	Traces

[a] All reactions were performed on a 0.13 mmol scale using 3 mol % of Pd$_2$(dba)$_3$, 12 mol % of P(2-MeOC$_6$H$_4$)$_3$, 0.5 equiv of Ag$_2$CO$_3$, and 2.0 equiv of Cs$_2$CO$_3$ in toluene at 120 °C unless otherwise noted. [b] 10 mol % of Pd$_2$(dba)$_3$ and 40 mol % of P(2-MeOC$_6$H$_4$)$_3$.

cyclize. To overcome this problem, we sought to oxidize the methylene group of product **1a** (Scheme 3). To our surprise, this transformation could be performed with 2−3 equiv of mCPBA. There is limited precedent for the oxidation of methylene groups α- to nitrogen atoms using this extremely mild oxidant.[14] The sulfur atom is untouched under these conditions.

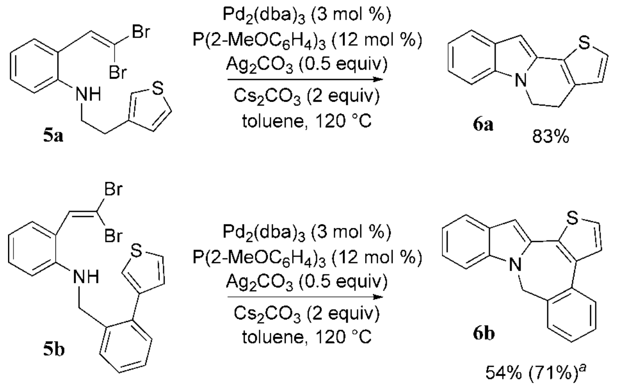
Table 3. Variation of the Heterocycle[a]



entry	substrate	product	yield (%)
1	 **3a**	 **4a**	78
2[b]	 **3b**	 **4b**	50
3	**3c** X = O	 **4c**	72
4	**3d** X = NMe	 **4d**	55

[a] All reactions were performed on a 0.13 mmol scale using 3 mol % of Pd$_2$(dba)$_3$, 12 mol % of P(2-MeOC$_6$H$_4$)$_3$, 0.5 equiv of Ag$_2$CO$_3$, and 2.0 equiv of Cs$_2$CO$_3$ in toluene at 110 °C unless otherwise noted. [b] 10 mol % of Pd$_2$(dba)$_3$ and 40 mol % of P(2-MeOC$_6$H$_4$)$_3$.

Scheme 2. Formation of Different Ring Sizes



[a]Performed with 10 mol % of Pd$_2$(dba)$_3$ and 40 mol % of P(2-MeOC$_6$H$_4$)$_3$

In conclusion, we have demonstrated a domino process comprising the union of palladium-catalyzed direct arylation and C−N bond formation using *gem*-dibromoaniline substrates to form a series of polycyclic indole derivatives in good yields. We have also demonstrated the use of added

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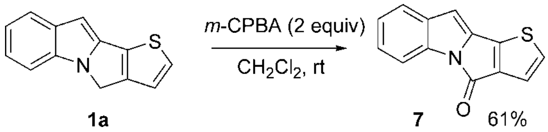
[14] Yokoshima, S.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Chem. Lett.* **2002**, 122.

Scheme 3. *m*-CPBA-Mediated Oxidation of a Methylene Group



silver salts to sequester bromide, thereby improving the reaction rate and selectivity. The method is notable for its broad functional group tolerance and efficiency.

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

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