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Palladium-Catalyzed Coupling of Vinylogous Amides with Aryl Halides: Applications to the Synthesis of Heterocycles

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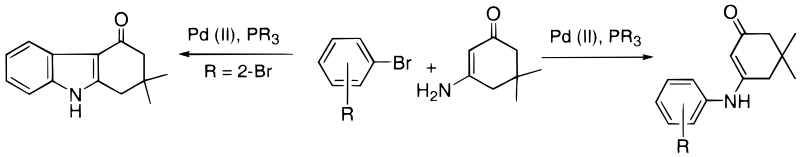
ABSTRACT



Described herein is the first example of the palladium-catalyzed coupling of vinylogous amides with aryl bromides and chlorides. The scope of this reaction with respect to the aryl component is investigated. Additionally, a tandem reaction sequence in which the above coupling is followed by an intramolecular Heck reaction is presented. These reactions can be applied to high-yielding, one-pot syntheses of nitrogen-containing heterocycles.

The palladium-catalyzed C−N bond formation using aryl halides has been an area of intense research in recent literature.[1] Elegant work by the groups of Buchwald and Hartwig has detailed the palladium-catalyzed formation of nitrogen−aryl bonds using primary and secondary amines, hydrazines, anilines, imines, and nitrogen-containing heterocycles.[1,2] To date, the coupling of less nucleophilic nitrogen sources has received comparably little attention, being restricted to a few examples of simple carbamates, lactams, sulfoximines, and the intramolecular coupling of amides and carbamates.[2d,3]

Over the course of our search for novel therapeutics, we needed convenient access to *N*-aryl vinylogous amides (enaminones). Current methods for the formation of these moieties vary depending on the electronic state of the starting aniline derivative. Moreover, moderate yields using these methods are often obtained.[4] We sought a mild, universal, and high-yielding process for the synthesis of these versatile synthetic intermediates that did not rely upon aniline derivatives as starting materials. A palladium-catalyzed coupling of primary vinylogous amides to aryl halides would not only constitute an extension of known methodology in the field but also provide a novel entry to *N*-aryl enaminones. We were pleased to discover that this process proved to be an efficient and widely applicable synthesis of *N*-aryl enaminones (Table 1).[5]

(1) For recent reviews, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(2) (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (c) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (d) Hartwig, J. F.; Kawatsure, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (f) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(3) (a) Yang, B. Y.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (b) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035. (c) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169.

(4) (a) Jirkovsky, I. *Can. J. Chem.* **1974**, *52*, 55. (b) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277. (c) Tamura, Y.; Chen, L. C.; Fujita, M.; Kiyokawa, H.; Kita, Y. *Chem. Ind. (London)* **1979**, 668. (d) Chen, L. C.; Yang, S. C.; Wang, H. M. *Synthesis* **1995**, 385.

(5) A related palladium-catalyzed transformation has been reported in moderate yield using a titanium isocyanate complex. The scope and exact mechanism of this process, however, is unclear. See: Mori, M.; Uozumi, Y.; Shibasaki, M. *Heterocycles* **1992**, *33*, 819.

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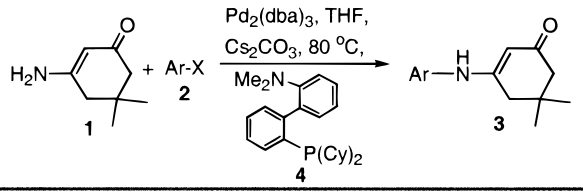
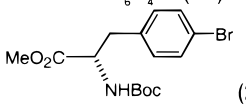
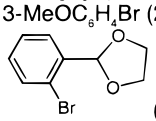
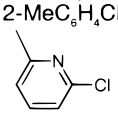
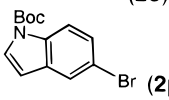
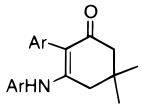
Table 1. Palladium-Catalyzed Coupling of **1** with Aryl Halides



entry	Ar-X	time (h)	yield of **3** (%)
1	4-$NO_2C_6H_4Br$ (**2a**)	4	38, **3a**
2	4-NCC_6H_4Br (**2b**)	14	69, **3b**
3	PhBr (**2c**)	24	68, **3c**
4	4-MeC_6H_4Br (**2d**)	24	77, **3d**
5	 (**2e**)	20	96, **3e**
6	4-$MeOC_6H_4Br$ (**2f**)	20	87, **3f**
7	3-$CF_3C_6H_4Br$ (**2g**)	8	82, **3g**
8	3-$MeOC_6H_4Br$ (**2h**)	14	89, **3h**
9	 (**2i**)	24	97, **3i**
10	4-$NO_2C_6H_4Cl$ (**2j**)	2.5	92, **3a**
11	4-$MeO_2CC_6H_4Cl$ (**2k**)	5	96, **3j**
12	PhCl (**2l**)	14	93, **3c**
13	3-$MeOC_6H_4Cl$ (**2m**)	8	98, **3h**
14	2-MeC_6H_4Cl (**2n**)	20	90,**3k**
15	 (**2o**)	12	98, **3l**
16	 (**2p**)	24	65, **3m**

In order to investigate the conditions for this process, the reaction of commercially available enaminone **1** with 4-bromobenzonitrile (**2b**) was initially studied (entry 2, Table 1).[6] A quick survey of reaction conditions revealed that moderate yields (20−50%) of **3b** could be obtained by heating **1** and **2b** in DME with cesium carbonate, ligand **4** (10 mol %),[7] and a palladium source such as $Pd_2(dba)_3$ (5 mol %). Although substitution of ligand **4** with 2-(dicyclohexylphosphino)biphenyl was tolerated, other ligands proved to be inferior.[8] While we discovered that THF could replace DME as solvent, toluene could not be used due to the insolubility of the enaminone. Optimal yields (60−70%) were obtained when an excess of bromide **2b** (1.5 equiv relative to enaminone **1**) was used. The use of equivalent amounts of bromide and enaminone resulted in slightly diminished yields of products.[9]

In the case of *para*- and *meta*-substituted bromides, 2-substituted enaminones such as **5** were sometimes encountered as side products. Since no 2-aryl derivatives of **1** itself were detected, these products presumably arise from a Heck reaction which occurs after initial C−N bond formation. Up to 15% of enaminones **5f** and **5h** could be isolated when



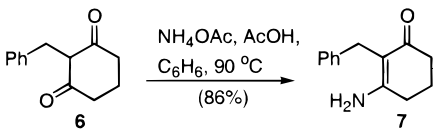
5a, Ar = 4-$NO_2C_6H_4$
5f, Ar = 4-$MeOC_6H_4$
5h, Ar = 3-$MeOC_6H_4$

more than 1.5 equiv of the bromides was used for extended reaction times (>24 h). Fortunately, this side reaction can usually be suppressed using shorter reaction times and less of the bromide coupling partner. Because of the facility of the Heck reaction with highly reactive bromide **2a**, only a moderate yield of **3a** could be attained. The problem could be circumvented, however, with the use of 1.1 equiv of chloride **2j**, which afforded product **3a** in a much improved 92% yield. Not surprisingly, this side reaction was not encountered with aryl chlorides or with sterically crowded substrates such as 2-substituted enaminones (vide infra) and *ortho*-substituted aryl bromides.

The coupling reaction typically affords high yields of the desired *N*-aryl enaminones regardless of substitution pattern or electronic state of the aryl halide. As expected on the basis of literature precedent, ligand **4** induces the coupling of aryl chlorides as efficiently as aryl bromides.[2f] A direct comparison of aryl bromides with chlorides reveals that higher yields are often obtained with chlorides in the case of enaminone **1**. Heterocycles **2o** and **2p** also undergo efficient coupling with **1** under the described reaction conditions.[10] Although the presence of a carbamate (**2e**) did not affect the reaction, some epimerization of phenylalanine derivative **3e** was observed.[11]

To examine the sensitivity of this coupling reaction to steric effects, we sought a sterically demanding 2-substituted enaminone. Since 1,3-cyclohexanedione affords good yields of C-alkylation products with reactive electrophiles such as benzyl bromide,[12] we decided to investigate the 2-benzyl derivative. The corresponding enaminone **7** was easily synthesized in 86% yield by treatment of β-diketone **6** with ammonium acetate under Dean−Stark conditions (Scheme 1).[13]

Scheme 1



Enaminone **7** was then coupled to halides **2a**−**o** using the optimized conditions (Table 2). The additional steric demand

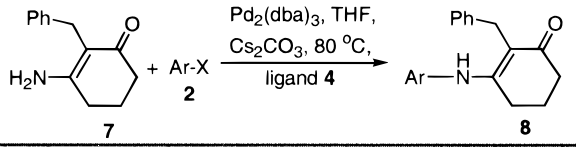
(6) All reactions were performed using Radley's Carousel Reaction Station (see http//radleys.co.uk). All products were characterized by ^1H and ^{13}C NMR and LC-MS.

(7) Recently made commercially available by Strem Chemical Co.

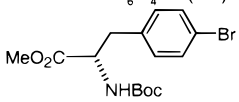
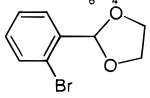
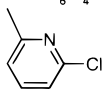
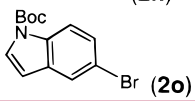
(8) With some electron deficient aryl bromides, DPPF could be used as the ligand, but the reaction was slower and less efficient than with **4**. The replacement of **4** with other ligands such as PPh_3, BINAP, P(*t*-Bu)$_3$, or 1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine was not well tolerated and produced little or no product under the above conditions after 48 h. $Pd(OAc)_2$ could be used as a Pd source in the reaction while $Pd(PPh_3)_4$ was ineffective as a catalyst.

(9) Control experiments in which the optimized conditions were applied to the reaction of **1** with **2b** in the absence of either palladium or ligand **4** failed to produce **3b**. Reactions in Tables 1 and 2 were not optimized with respect to reaction times.

Table 2. Palladium-Catalyzed Coupling of **7** with Aryl Halides



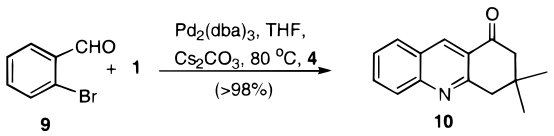
7 8

entry	Ar-X	time (h)	yield of **8** (%)
1	4-$NO_2C_6H_4Br$ (**2a**)	17	98, **8a**
2	4-CN C_6H_4Br (**2b**)	21	91, **8b**
3	PhBr (**2c**)	24	90, **8c**
4	4-Me C_6H_4Br (**2d**)	48	97, **8d**
5	 (**2e**)	20	94, **8e**
6	4-MeO C_6H_4Br (**2f**)	48	90, **8f**
7	3-CF_3 C_6H_4Br (**2g**)	24	82, **8g**
8	3-MeO C_6H_4Br (**2h**)	17	92, **8h**
9	 (**2i**)	17	90, **8i**
10	4-MeO_2C C_6H_4Cl (**2j**)	48	82, **8j**
11	PhCl (**2k**)	48	88, **8c**
12	3-MeO C_6H_4Cl (**2l**)	48	84, **8h**
13	2-MeC_6H_4Cl (**2m**)	48	96, **8k**
14	 (**2n**)	24	88, **8l**
15	 (**2o**)	36	84, **8m**

of the benzyl group is apparent by the decrease in reaction rates of aryl halides with **8** relative to unsubstituted enaminone **1**. Although the rates were slower, the coupling yields of enaminone **7** with aryl bromides were almost uniformly superior to those of enaminone **1**, most likely due to the absence of the aforementioned side reaction. Aryl chlorides on the other hand appear to be more sensitive to the additional steric crowding and thus typically require longer reaction times and afford products in slightly diminished yields.[14]

In addition to the formation of *N*-aryl enaminones, the above reaction can be applied in a tandem fashion to form heterocycles. For example, quinoline **10** can be synthesized in a single step from bromoaldehyde **9** in quantitative yield under these reaction conditions (Scheme 2). By comparison,

Scheme 2

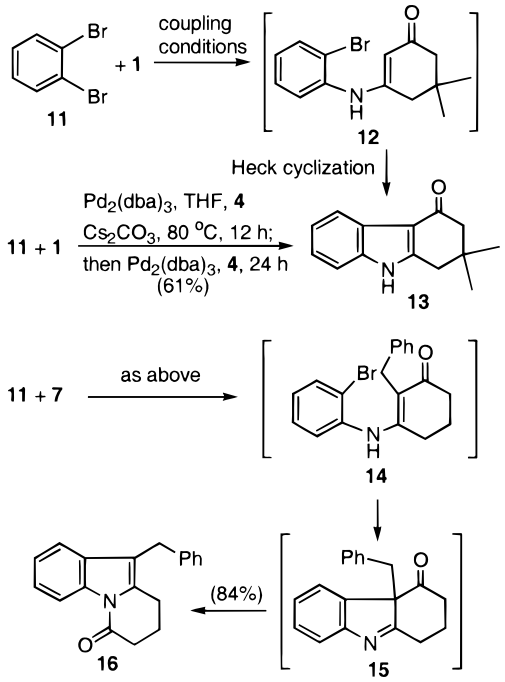


9 10

the reported synthesis of **10** was accomplished in four steps and 18% overall yield.[15]

Another application of this methodology lies with the synthesis of 2,3-disubstituted indoles (Scheme 3).[4d,16] We

Scheme 3



hoped to take advantage of this palladium-catalyzed reaction by combining C−N bond formation with an intramolecular Heck reaction to achieve a one-pot indole synthesis. Indeed, we were encouraged by the facility with which side products **5** were produced from the corresponding intermolecular Heck reactions from Table 1 above. Consequently, exposure of 1,2-dibromobenzene (**11**) to the standard coupling conditions for 24 h afforded a 1.4:1 mixture of addition product **12** and indole **13** (Scheme 3).[17] After some experimentation,[18] we

(10) It should be noted that the deprotected version of **2p** (without the Boc) did not undergo a coupling reaction with **1**.

(11) Chiral HPLC failed to separate enantiomers, so deprotection of **3e** (TFA/CH_2Cl_2) followed by Mosher amide analysis of the resulting amine indicated 33% ee of product.

(12) Rajamannar, T.; Palani, N.; Balasubramanian, K. K. *Synth. Commun.* **1993**, *23*, 3095.

(13) For a convenient, high-yielding method for the synthesis of primary vinylogous amides, see: Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902.

(14) As before, a 33% ee was observed in **8e** by chiral HPLC (ChiralPak AS column, 1:3 alcohol/hexanes). Also, no coupling was observed with the deprotected version of **2o**.

(15) Tominaga, Y.; Okuda, H.; Kohra, S.; Mazume, H. *J. Hetereocycl. Chem.* **1991**, *28*, 1245.

(16) For other examples of palladium-catalyzed formation of indoles, see: (a) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938. (b) Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4282. (c) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215. (d) Koerber-Ple, K.; Massiot, G. *Synlett* **1994**, 759. (e) Akermark, B.; Oslob, J. D.; Heuschert, U. *Tetrahedron Lett.* **1995**, *36*, 1325. (f) Chen, C. Y.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676.

(17) Suzuki, H.; Thiruvikraman, S. V.; Osuka, A. *Synthesis* **1984**, 616.

(18) Extended reaction times, higher reaction temperatures (refluxing DME), and an increase in the starting amounts of cesium carbonate and/or ligand **4** failed to induce complete conversion of **12** to **13**.

discovered that addition of a second portion of palladium catalyst and ligand **4** to the reaction mixture after 12 h induced conversion of enaminone **1** to indole **13** in 61% yield. Interestingly, exposure of enaminone **7** to the same conditions produced cyclized product **16**.[19] Although the precise mechanism of this transformation is uncertain, intermediate **14** was isolated as the major product when the second portion of catalyst and ligand was omitted. Most likely **14** gives way to Heck cyclization product **15** which then leads to **16** in high yield (84%) after acyl migration.

In conclusion, the first application of Hartwig−Buchwald couplings to the synthesis of *N*-aryl enaminones has been accomplished in high yields under palladium catalysis with commercially available ligand **4**. The reaction is widely applicable to a variety of electron rich, electron poor, and neutral aromatic bromides or chlorides as well as heterocyclic halides. Excellent yields were obtained regardless of the substitution pattern on the aromatic halide. Additionally, the first tandem Hartwig−Buchwald−Heck cyclization has been reported and applied to the synthesis of 2,3-disubstituted indole derivatives. This extension of the current methodology should be a valuable addition to natural product total synthesis as well as the synthesis of molecules of medicinal interest. Moreover, these coupling reactions should also be amenable to applications involving solid-phase synthesis.[20] Further investigations into the scope of these reactions and their application to heterocycle synthesis are currently underway.[21]

Acknowledgment. We gratefully acknowledge Drs. Steven L. Colletti and Jean-Francois Marcoux and Mr. Richard Berger for helpful discussions.

Supporting Information Available: Full experimental details and $^{1}H/^{13}C$ NMR spectroscopic data for heretofore unreported compounds **3**, **5**, **7**, **8**, **12**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For **16**: IR ($CDCl_3$) 3068, 3026, 2954, 2910, 2839, 1703, 1617, 1494, 1458 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, $J = 7.9$ Hz, 1 H), 7.40 (d, $J = 7.9$ Hz, 1 H), 7.34−7.22 (m, 7 H), 4.06 (s, 2 H), 2.94 (t, $J = 6.3$ Hz, 2 H), 2.81 (t, $J = 6.3$ Hz, 2 H), 2.11 (quin, $J = 6.3$ Hz, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.5, 140.0, 135.0, 134.7, 130.6, 128.8 (2C), 128.5 (2C), 126.5, 124.5, 124.1, 118.6, 116.7, 115.6, 34.7, 30.2, 22.2, 21.5; LC-MS (*m*/*z*) 276.19 ($M^{+}+1$). Not surprisingly **16** is inert to $NaBH_4$ reduction.

(20) For examples of Hartwig−Buchwald couplings on solid phase, see: (a) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993. (b) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181. For a lead reference involving solid-phase indole synthesis, see: Zhang, H. C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89.

(21) **Representative procedure:** $Pd_2(dba)_3$ (23 mg, 0.025 mmol) was added to a mixture of bromide **2d** (128 mg, 0.75 mmol), enaminone **1** (70 mg, 0.5 mmol), ligand **4** (20 mg, 0.05 mmol), and Cs_2CO_3 (260 mg, 0.8 mmol) in 5 mL of THF. Next, the mixture was stirred at 80 °C under nitrogen until TLC showed complete reaction (24 h). The reaction mixture was then diluted with 120 mL of EtOAc, washed with saturated NH_4Cl (20 mL) and brine (20 mL), dried over Mg_2SO_4, filtered, and concentrated. The crude orange oil was then purified by preparative TLC (SiO_2, 80% EtOAc/hexanes) to afford **3d** (88 mg, 77%) as a waxy yellow solid.