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Palladium-Catalyzed Annulation of Aryl Heterocycles with Strained Alkenes

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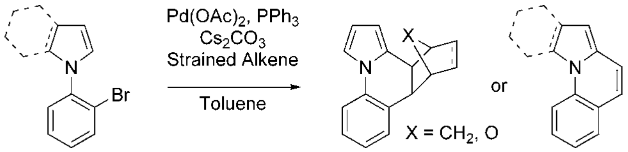
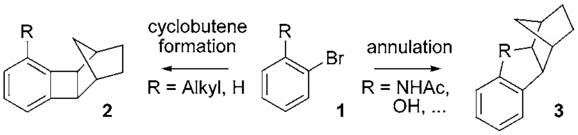
ABSTRACT



An annulation reaction proceeding by the intermolecular addition of an arylpalladium(II) halide across a strained alkene, followed by an intramolecular C–H functionalization of a pendant heterocycle is described. A variety of polycyclic heterocycles have been prepared from readily accessible haloaryl heterocycles by annulation with a range of strained alkene partners.

The catalytic activation of aromatic C−H bonds and direct arylation processes are emerging as effective methods for C−C bond formation.[1] These methods do not require stoichiometric organometallic reagents and as such can shorten synthetic sequences and minimize waste. It has been shown that the treatment of aryl halides **1** with norbornene in the presence of catalytic amounts of palladium(0) can produce cyclobutene products **2** via ortho C−H functionalization.[2] Alternatively, annulation products **3** may arise if a suitable functional group **R** is in place adjacent to the halide (Scheme 1).[3]

Scheme 1. Reaction of Aryl Halides with Norbornene



The synthesis and elaboration of nitrogen-containing heterocycles is an active area of organic chemistry, among which pyrrole occupies a prominent role. This is due in part to its presence in a wide variety of biologically active natural products and drug molecules.[4] Our group has previously demonstrated that the norbornene-mediated palladium-catalyzed domino ortho-alkylation reactions of aryl iodides can be terminated by the direct arylation of a number of different heterocyclic systems.[5] We therefore began to explore the idea that aryl halides substituted by N-containing heterocycles would react with strained alkenes to provide interesting annulation rather than cyclobutene products. The annulation of biologically active heterocycles with norbornene can provide new active compounds with improved

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(1) For a recent review, see: Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238.

(2) (a) Catellani, M. *Top. Organomet. Chem.* **2005**, 21−53. (b) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769−772.

(3) For annulation onto an alkene, see: (a) Grigg, R.; Kennewell, P.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 153−156. For annulation onto a nitrile, see: (b) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276−9287. For annulation onto phenols and anilines, see: (d) Catellani, M.; Del Rio, A. *Russ. Chem. Bull.* **1998**, *47*, 928−931. Saito, K.; Katsuhiko, O.; Sano, M.; Kiso, S.; Takeda, T. *Heterocycles* **2002**, *57*, 1781−1786. Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlma, M. *J. Org. Chem.* **2001**, *66*, 8217−8134.

(4) See: (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katrizsky, A. R., Rees, C. W., Scriven, E. S. V., Eds.; Pergamon Press: New York, 1996; Vol. 2, pp 207−257. (b) Le Quesne, P. W.; Dong, Y.; Blythe, T. A. *Alkaloids: Chem. Biol. Perspect.* **1999**, *13*, 237−287. (c) Janosik, T.; Bergman, J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Amsterdam, 2003; Vol. 15, pp 140−166.

(5) (a) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148−13149. (b) Blaszykowski, C.; Aktoudianakis, V.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043−2045. (c) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827−4829.

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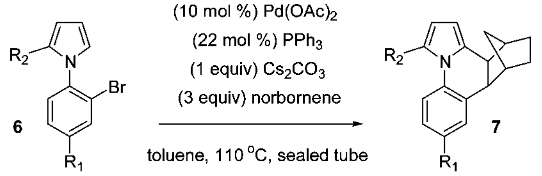
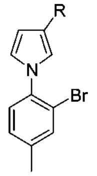
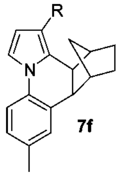
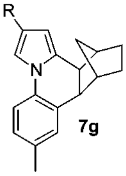
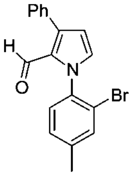
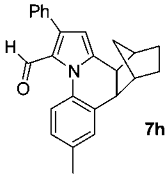
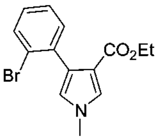
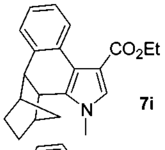
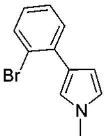
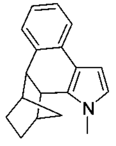
druglike properties such as lipophilicity.[6] We initially investigated the reaction of the pyrrole **6a** with strained alkenes based on a norbornene skeleton. Gratifyingly, treatment of **6a** with norbornene, in the presence of a Pd(OAc)$_2$/PPh$_3$ catalyst system and using Cs$_2$CO$_3$ as a base, provided the annulated product **7a** (Table 1, entry 1) in quantitative yield. We next explored the effect of different functional groups on both the pyrrole and the aryl rings (Table 1). The annulation reaction was found to be tolerant of a variety of functionalities, including aldehyde (entries 5 and 7), ester (entry 8), and chloride (entry 4) moieties, which allow further elaboration of the products. The aldehyde-containing substrates **6e** and **6g** show excellent regioselectivity, providing solely annulation products. However, upon substitution of the C-3 of the pyrrole, regioselectivity became problematic, as the annulation products were isolated as an inseparable, nonstatistical mixture of compounds showing annulation at the C-2 and C-5 positions (entry 6). Annulation of the 3,4-disubstituted pyrrole **6h** proceeded with excellent yield and regioselectivity to deliver the annulation product **7i** (entry 8). Annulation of the 3-substituted pyrrole **6i** proceeded in good yield onto the C-2 position of the pyrrole ring to provide **7j**, and only trace amounts of the C-4 annulated product were detected (entry 9). Interestingly, a reverse in regioselectivity was observed when the biaryl bromide **4** was treated under similar reaction conditions, with norbornadiene as the strained alkene, providing solely the cyclobutene product **5** in quantitative yield (Scheme 2).[7]

Table 1. Annulation of Pyrroles with Norbornene



entry	substrate	product	yield (%)
1	**6a** R$_1$ = Me, R$_2$ = H	**7a**	100
2	**6b** R$_1$ = H, R$_2$ = H	**7b**	83
3	**6c** R$_1$ = F, R$_2$ = H	**7c**	81
4	**6d** R$_1$ = Cl, R$_2$ = H	**7d**	89
5	**6e** R$_1$ = Me, R$_2$ = CHO	**7e**	89
6	 **6f**	 **7f**  **7g**	R = Me[a] 95 (1.47:1) R = Ph[a] 84 (1.67:1)
7	 **6g**	 **7h**	90
8	 **6h**	 **7i**	92
9	 **6i**	 **7j**	85

[a] Isolated as an inseparable mixture.

Scheme 2. Annulation of Biaryl Bromide **4**

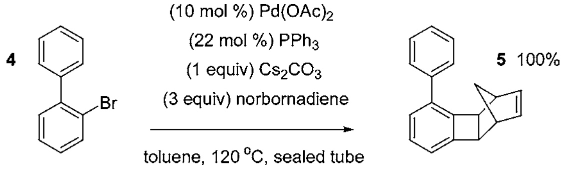
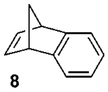
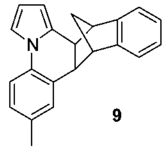
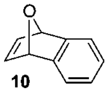
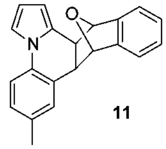
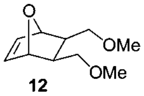
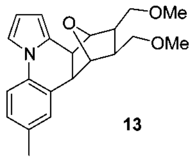
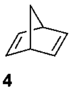
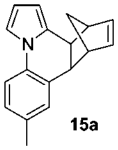
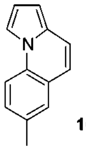
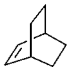


Table 2. Annulation of **6a** with Other Strained Alkenes[a]

entry	alkene	product	yield (%)
1	 **8**	 **9**	100
2	 **10**	 **11**	79
3	 **12**	 **13**	91
4	 **14**	 **15a**  **16a**	87 (1:2)
5	 **17**	-	-

[a] Reaction conditions: Pd(OAc)$_2$ (10 mol %), PPh$_3$ (22 mol %), Cs$_2$CO$_3$ (1 equiv), the alkene (3 equiv), and **6a** (1 equiv) were heated in toluene at 110 °C in a sealed tube overnight.

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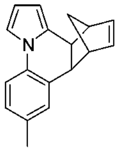
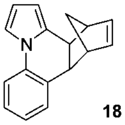
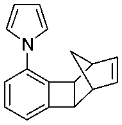
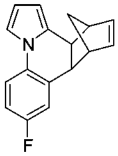
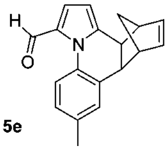
[6] Leysk, R.; Zimenkovsky, B.; Atamanyuk, D.; Jensen, F.; Kiec-Kononowicz, K.; Gzella, A. *Bioorg. Med. Chem.* **2006**, *14*, 5230−5240.

To extend the scope of this process, we next examined the reaction of **6a** with a range of strained alkene partners (Table 2). Benzonorbornene **8** (entry 1) and the oxabicycles **10** (entry 2) and **12** (entry 3) reacted smoothly to generate the corresponding annulated products in good to excellent yields. No ring-opened products were detected with the oxabicyclic substrates. The use of norbornadiene **14** (entry 4) provided an interesting result as both the annulated species **15a** and the aromatic compound **16a** were isolated.[8] The pyrroloquinoline **16a** arises via an in situ retro-Diels−Alder reaction and loss of cyclopentadiene from **15a**.[8] The use of the less strained [2.2.2]-bridged bicycle **17** led only to recovery of starting material (entry 5).

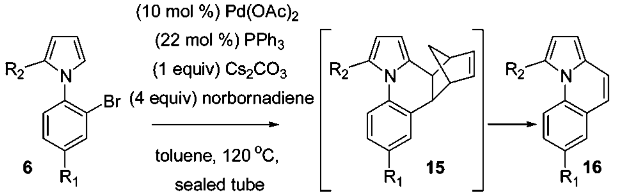
We were able to selectively obtain either the norbornadiene-annulated product or the annulation/retro Diels−Alder product through careful control of the reaction temperature. At a lower temperature, good yields of the annulated alkene products were generated with a range of functional groups on the aryl ring (Table 3). The regioselectivity in this case seems dependent on the substitution pattern of the benzene ring, as treatment of the unsubstituted substrate **6b** provides a 1:1 ratio of the isomeric products **15b** and **18** (entry 2), whereas the alkyl- or fluoro-substituted aryl substrates were more selective (entries 1, 3, and 4).

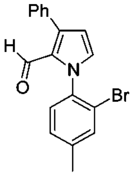
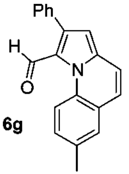
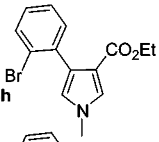
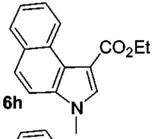
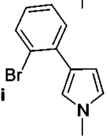
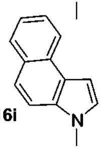
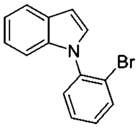
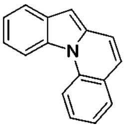
Table 3. Annulation of Pyrroles with Norbornadiene[a]

entry	substrate	product	yield (%)
1	**6a**	 **15a**	94
2	**6b**	 **15b**  **18**	80 (1:1)
3	**6c**	 **15c**	77
4	**6e**	 **15e**	64

[a] Reaction conditions: Pd(OAc)$_2$ (10 mol %), PPh$_3$ (22 mol %), Cs$_2$CO$_3$ (1 equiv), norbornadiene (4 equiv), and the substrate (1 equiv) were heated in toluene at 80 °C in a sealed tube overnight.

Table 4. Synthesis of Retro-Diels−Alder Products



entry	substrate	product	yield (%)
1	**6a** R$_1$ = Me, R$_2$ = H	**16a**	98
2	**6b** R$_1$ = H, R$_2$ = H	**16b**	92
3	**6c** R$_1$ = F, R$_2$ = H	**16c**	86
4	**6d** R$_1$ = Cl, R$_2$ = H	**16d**	93
5	**6e** R$_1$ = Me, R$_2$ = CHO	**16e**	81
6	 **6g**	 **16g**	84
7	 **6h**	 **16h**	100
8	 **6i**	 **16i**	86
9	 **6j**	 **16j**	70

At a higher reaction temperature, we were able to synthesize a range of pyrroloquinoline and related heterocyclic compounds. Bridgehead nitrogen heterocycles such as these are an important class of natural products; many exhibit interesting biological activity.[9,10] For example, substituted pyrroloquinolines have been found to be activators of caspases and inducers of apoptosis, while it has also been shown that Birch reduction of these compounds can provide dihydroquinolines, showing activity against P388 leukemia.[11−13] Pyrroloquinolines have also found utility in

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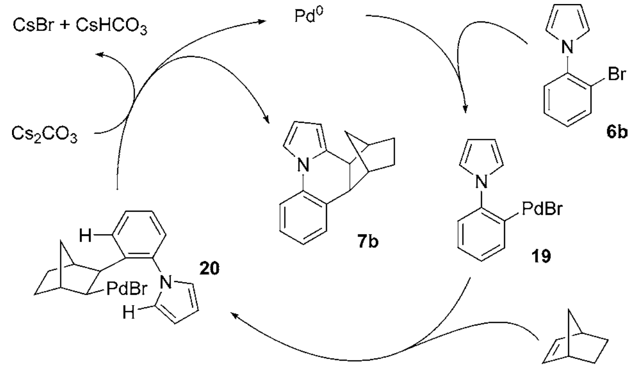
(7) For synthesis of biaryl analogues, see: (a) Albrecht, K.; Reiser, O.; Weber, M.; Knieriem, B.; de Meijere, A. *Tetrahedron* **1994**, *50*, 383−401. (b) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C. *Org. Lett.* **2006**, *8*, 5581−5584.

(8) (a) For an example of an analogous Pd-catalyzed transformation in the synthesis of coumarin, see: An, Z.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1989**, *371*, C51−C52. (b) For an analogous Pd-catalyzed synthesis of *cis*-olefins, see: Masanori, K.; Kumara, T.; Oda, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3522−3524.

(9) Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. *Adv. Heterocycl. Chem.* **1987**, *23*, 103.

(10) Hermecz, I.; Vasvari-Debreczy, L.; Matyus, P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: London, 1996; Vol. 8, Chapter 23, pp 563−595.

Scheme 3. Proposed Mechanism



organic electroluminescent devices.[14] At the higher temperature, the reaction is tolerant of a range of functionalities (Table 4), although some loss of the formyl group was observed with substrates **6e** (entry 5) and **6g** (entry 6).

Under these conditions, we found that annulation of the indole substrate **6j** (entry 9) occurred in good yield and regioselectivity, in contrast to the use of norbornene with this substrate under similar conditions.

Mechanistically, we propose that oxidative insertion of palladium(0) into the aryl−bromine bond and subsequent carbopalladation of the reactive alkene provides intermediate **20**. Reaction of this intermediate with the aryl ring would provide the known cyclobutene products;[4] however, under our conditions, the heterocycle reacts in preference to form the annulated products such as **7b** (Scheme 3). Functionalization of the pyrrole ring could be envisaged to occur by a Heck process, electrophilic aromatic substitution by attack of the pyrrole onto the palladium(II) species, or by direct C−H insertion.

In summary, we have developed a straightforward method for the assembly of a variety of heterocyclic scaffolds. These reactions are tolerant of a wide range of functional groups and allow the rapid assembly of interesting structures amenable to further elaboration. Studies toward the synthesis of other heterocyclic species with interesting biological activities and physical properties are underway and will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the National Sciences and Engineering Research Council (NSERC) of Canada, the Merck Frosst Centre for Therapeutic Research for an Industrial Research Chair, and the University of Toronto. D.G.H. thanks the Leverhulme Trust for a postdoctoral fellowship.

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

OL070475W

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(11) Cai, S. X.; Drewe, J. A.; Jiang, S.; Kasibhatla, S.; Kuemmerle, J. D.; Sirisoma, N. S.; Zhang, H. Z. WO2004055163, 2004.

(12) Kim, J. T.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 2054−2059.

(13) (a) Anderson, W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. *J. Med. Chem.* **1998**, *31*, 2097−2102. (b) Anderson, W. K.; De Ruiter, J.; Heider, A. R. *J. Org. Chem.* **1985**, *50*, 722−724.

(14) Nakatsuka, M.; Shimamura, T. JP2000277263, 2000.