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Synthesis of Novel Tetracycles via an Intramolecular Heck Reaction with *anti*-Hydride Elimination

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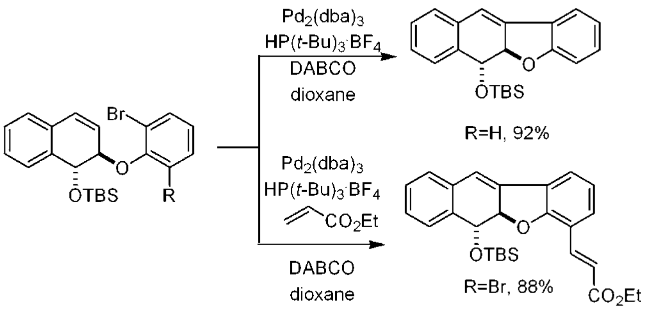
ABSTRACT

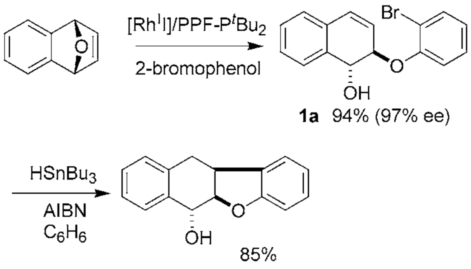


The catalytic combination of $Pd_2(dba)_3$/$HP(t\text{-}Bu)_3 \cdot BF_4$ and DABCO gives an unusual intramolecular Heck reaction with dihydronaphthalene substrates, yielding formal *anti*-hydride elimination products in good to excellent yields under mild conditions. For dibromo substrates, multiple Heck reactions are possible when an external acceptor is added to afford more highly functionalized products.

Rhodium- and palladium-catalyzed asymmetric ring-opening (ARO) reactions of oxabenzonorbornadiene with various nucleophiles give enantiomerically enriched dihydronaphthalene derivatives in good to excellent yields (Scheme 1).[1] As part of our investigation to demonstrate the utility of ARO products, we were interested in using functionalized nucleophiles to make multicyclic products using a ring-breaking/ring-making strategy. Such compounds are biologically interesting scaffolds for pharmaceutical research.[2] Previously, it was found that **1a** underwent radical cyclization in the presence of $HSnBu_3$ to give a benzofuran skeleton (Scheme 1).[3] In an effort to introduce further functionalization by trapping the species following the furan-forming step, we chose the Heck reaction, which has become a very important tool for the formation of carbon−carbon bonds.[4]

The accepted catalytic cycle of the Heck reaction involves oxidative addition, carbon−palladium insertion, and β-hydride elimination.[5] It is well established that both insertion and elimination steps are cis-stereospecific. In some cases, such as α,β-unsaturated carbonyl compounds or styrene-type

Scheme 1



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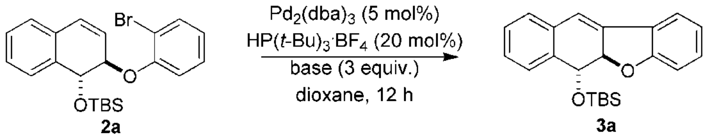
(1) For a review, see: (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58. ARO using heteroatom nucleophiles: (b) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, in press. (c) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259−270. ARO using carbon-based nucleophiles: (d) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311−1314. (e) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804−1805.

(2) (a) Gordaliza, M.; Castro, M. A.; Miguel Del Corral, J. M.; San Feliciano, A. *Curr. Pharmaceut. Des.* **2000**, *6*, 1811−1839. (b) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, *55*, 8967−8976 and references therein.

10.1021/ol035354k CCC: $25.00

Table 1. Effect of Amine Base on the Intramolecular Heck Reaction



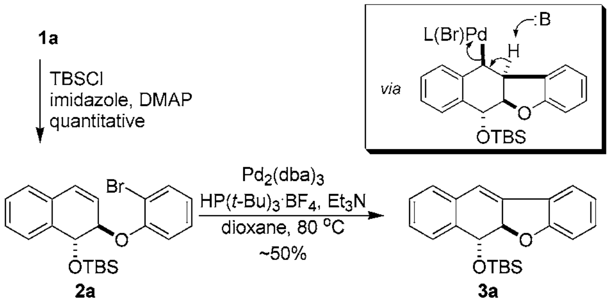
entry	base	temp	yield[a] (**3a** + **2a**%)	entry	base	temp	yield[a] (**3a** + **2a**%)
1	Et_3N	80 °C	52 + 4	7	TMEDA	60 °C	23 + 66
2	*i*Pr_2NEt	80 °C	37 + 0	8	*i*Pr_2NH	60 °C	87 + 0
3	Cy_2NMe	80 °C	48 + 0	9	morpholine	60 °C	53 + 32
4	proton sponge	80 °C	52 + 35	10	Et_2NH	60 °C	63 + 8
5	DABCO	60 °C	94 + 0	11	piperidine	60 °C	28 + 53
6	DBU	60 °C	21 + 54	12	pyrolidine	60 °C	51 + 32

[a] Yields (both the product **3a** and starting material **2a**) were measured by HPLC using naphthalene as an internal standard following aqueous $NaHCO_3$ workup and hexane extraction of the crude reaction mixture.

systems, formal *trans*-elimination is possible.[6] However, the yields are generally low and the scope is limited. Herein, we report a high-yielding synthesis of tetracyclic compounds from ARO products (e.g., **1a**) via a mild-condition intramolecular Heck reaction with *trans*-elimination.

Milder conditions for the Heck reaction have been extensively studied in recent years.[7] Fu and Hartwig have found that electron-rich and sterically hindered phosphine ligands (e.g., P(t-Bu_3)) facilitate oxidative addition and allow for the use of less reactive aryl bromides at room temperature.[8] To eliminate possible complications of the free OH group, the ring-opening product **1a** was protected as the *tert*-butyldimethylsilyl (TBS) ether (**2a**) in quantitative yield.[9] Exposure of **2a** to $Pd_2(dba)_3$/HP(t-Bu)$_3$·BF_4 in the presence of Et_3N gave the unusual intramolecular Heck product **3a** in moderate yield (Scheme 2).[10]

Scheme 2



With the hypothesis that the base removes a proton from the benzylic palladium intermediate in an *anti*-periplanar fashion in the rate-determining step,[11] the geometry and basicity of the base were believed to be important parameters for the reaction. Therefore, a number of bases with varying sterics and basicity were screened (Table 1). Generally, inorganic bases such as K_2CO_3, Cs_2CO_3, and K_3PO_4 were ineffective, presumably due to their strong basicity as well as their low solubility in organic solvents. Most amines tested showed some reactivity. The best amine found was 1,4-diazabicyclo[2,2,2]octane (DABCO) (Table 1, entry 10). Compared to Cy_2NMe, the standard base reported by Fu and Buchwald,[12] DABCO is a less sterically hindered tertiary amine base with an optimal shape for proton extraction.

Further optimization revealed that dioxane as well as other solvents, including toluene and THF, worked well under milder conditions (40 °C). The catalyst loading could be decreased to 2 mol% Pd (Pd/L = 1:2) with prolonged reaction times (normally complete within 60 h). Interestingly, Pd(P(t-Bu)$_3$)$_2$ usually gave lower turnover numbers (TON), presumably due to the absence of a Pd(0)-stabilizing dba

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(3) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677−1679.

(4) For reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (c) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371−7395.

(5) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427−436.

(6) Some recent examples: (a) Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104−109. (b) Shea, K. M.; Lee, K. L.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 2353−2356. (c) For examples before 1999, see: Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957−1970 and references therein.

(7) Review: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(8) (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000. (c) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677−2678.

(9) Unprotected substrates yielded a complicated mixture of products. Other protecting groups such as Me, MOM, and TMS gave incomplete conversion or low yields of the desired Heck product even under optimized conditions.

(10) Air- and moisture-stable HP(t-Bu)$_3$·BF_4 was used as a replacement for P(t-Bu)$_3$: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

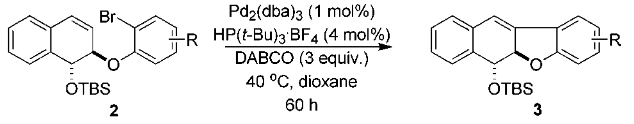
(11) (a) Adams, N. J.; Bargon, J.; Brown, J. M.; Farrington, E. J.; Galardon, E.; Giernoth, R.; Heinrich, H.; John, B. D.; Maeda, K. *Pure Appl. Chem.* **2001**, *73*, 343−346. (b) ref 3a. (c) Although the mechanism via epimerization of the benzylic center by an external Pd(0) attack followed by *cis*-elimination cannot be completely excluded, we believe that this mechanism is unlikely because of steric hindrance. Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832−5840.

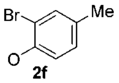
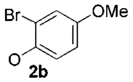
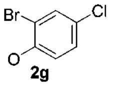
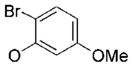
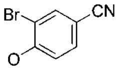
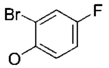
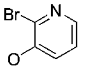
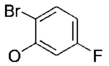
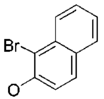
(12) (a) Gurtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107−3112. (b) ref 8b.

ligand, preventing aggregation.[13] Excess ligand (Pd/L = 1:4) was found to slow the reaction significantly. Though it is known that cationic palladium catalysts generally accelerate the Heck reaction,[14] in our case, it was found that use of silver salts to generate a cationic Pd species completely inhibited the reaction.

The optimized conditions were then applied to different substrates.[15] Most substitution patterns on the aryl bromide moiety give excellent yields (Table 2), including electron-rich (Table 2, entries 2, 3), fluoro- and chloro-substituted (Table 2, entries 4, 5, 7), and heterocyclic (Table 2, entry 9) systems. This suggests that oxidative addition occurs rapidly regardless of the electronics of the aryl bromide. Lower yields were obtained for the naphthyl substrate **2j** (Table 2, entry 10), despite the use of elevated temperatures and higher catalyst loadings, presumably due to steric hindrance that disfavored elimination.

Table 2. Intramolecular Heck Reaction with Substituents on the Bromophenoxy Moiety

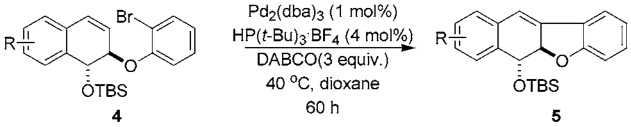


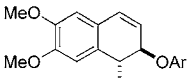
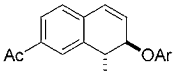
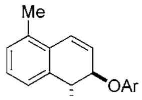
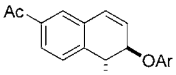
entry	OAr	yield (%)[a]	entry	OAr	yield (%)[a]
1	 **2a**	**3a** 92	6	 **2f**	**3f** 96
2	 **2b**	**3b** 96	7	 **2g**	**3g** 90
3	 **2c**	**3c** 91	8	 **2h**	**3h** 91
4	 **2d**	**3d** 96	9	 **2i**	**3i** 95
5	 **2e**	**3e** 97	10	 **2j**	**3j** 83[b]

[a] Isolated yield by column chromotography. [b] $Pd_2(dba)_3$ (10 mol%), $HP(t\text{-}Bu)_3{\cdot}BF_4$ (40 mol %), 80 °C for 20 h.

Substituents on the dihydronaphthalene moiety were found to influence the reactivity and yields. With electron-rich substituents (Table 3, entry 1), the reaction proceeded more slowly, requiring higher temperatures in order to obtain an excellent yield. Electron-withdrawing groups conjugated (Table 3, entry 3) with the double bond did not affect the reactivity; however, side reactions did increase significantly.[16] The isomer **4d** was more reactive and gave the expected product in high yield. Surprisingly, *ortho*-substituted dihydronaphthalene (Table 3, entry 2) gave excellent yield despite forming a hindered benzylic palladium intermediate.

Table 3. Intramolecular Heck Reaction with Substituents on the Dihydronaphthalene Moiety

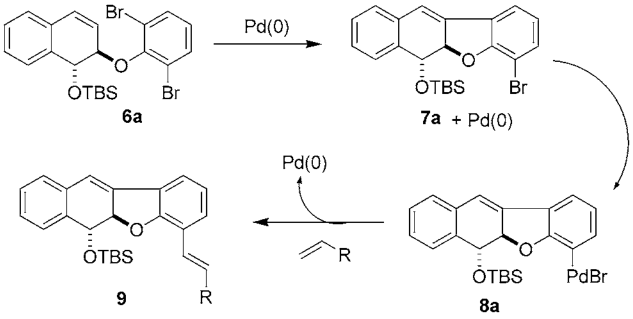


entry	substrate	yield (%)[a]	entry	substrate	yield (%)[a]
1	 **4a**	**5a** 93[b]	3	 **4c**	**5c** 55
2	 **4b**	**5b** 97	4	 **4d**	**5d** 92

[a] Isolated yields using column chromotography. [b] At 70 °C.

When the standard conditions were applied to the dibromo-substituted substrate **6a**, the reaction failed to give the expected monobromo product **7a** even at elevated temperatures (80 °C). This is presumably due to the Pd catalyst reacting with **7a** to yield **8a**, which cannot react further (Scheme 3).

Scheme 3



To allow for catalytic turnover, an external Heck acceptor (2 equiv of olefin) was added. This double-Heck reaction proceeded smoothly to yield **9** in good to excellent yields for different dibromo substrates and olefins (Tables 4 and 5). One of the double-Heck products **9a** was unambiguously characterized by X-ray crystallography (Figure 1). In no case did the reaction proceed in the absence of an external olefin.

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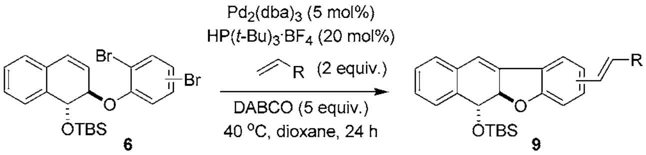
[13] Commercially available (from STREM) $Pd(P(t\text{-}Bu)_3)_2$ was used. When this catalyst was used, the TON was lower than 10 and a palladium mirror was formed inside the reaction flask.

[14] Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.

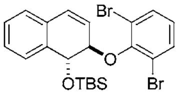
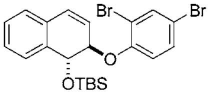
[15] All substrates are racemates obtained from the Rh-catalyzed ring-opening reaction followed by TBS protection. See Supporting Information for their preparation.

[16] For possible side reactions, see Pd-catalyzed triarylation on η^6-1,2-dihydronaphthalene−$Cr(CO)_3$ complexes: Dongol, K. G.; Matsubara, K.; Mataka, S.; Thiemann, T. *Chem. Commun.* **2002**, 3060−3061.

Table 4. Double-Heck Reaction of Dibromo Substrates and an External Acceptor



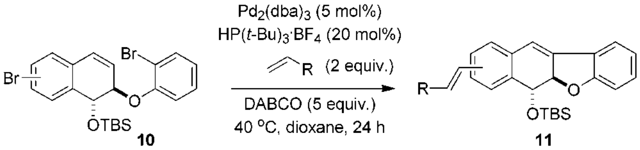
6 → 9

entry	substrate	olefin	product/yield (%)[a]
1	 **6a**	CO_2Et	**9a** 88
2		CO_2-t-Bu	**9b** 81
3		Ph	**9c** 85
4	 **6b**	CO_2Et	**9d** 94
5		CO_2-t-Bu	**9e** 91
6		Ph	**9f** 92
7		Me CO_2Me	**9g** 74 (E/Z=1.6:1)

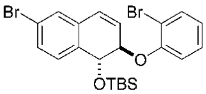
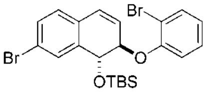
[a] Isolated yields using column chromotography.

Mechanistically, it is difficult to determine which Heck reaction occurs first when the two bromo substituents are nonequivalent (**6b**, **10a**, **10b**). However, treatment of **6a** under the double-Heck reaction conditions allowed for the isolation and characterization of the monobromo intermediate **7a**, indicating that the intramolecular Heck reaction occurs much faster than the intermolecular Heck process.

Table 5. Double-Heck Reaction of Dibromo Substrates and an External Acceptor



10 → 11

entry	substrate	olefin	product/yield (%)[a]
1	 **10a**	CO_2Et	**11a** 81
2		Ph	**11b** 85
3	 **10b**	CO_2Et	**11c** 67
4		Ph	**11d** 57

[a] Isolated yields using column chromotography.

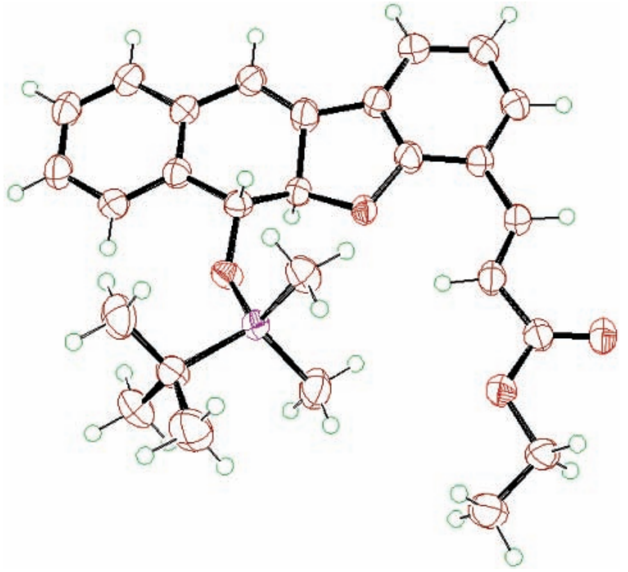


Figure 1. X-ray structure of compound **9a** from the double-Heck reaction. Only one of the enantiomers from the racemic crystal is shown.

In summary, we have discovered a palladium catalyst for the intramolecular Heck reaction with dihydronaphthalene substrates under mild conditions. The combination of Pd$_2$(dba)$_3$/HP(t-Bu)$_3$·BF$_4$ and DABCO gives unusual *anti*-hydride elimination products in good to excellent yields. For dibromo substrates, an external olefin can be added so that a second conventional Heck reaction can proceed. Further exploration of the reaction scope, mechanistic studies, and total syntheses of related natural products or their analogues are currently under investigation.

Acknowledgment. We thank NSERC (Canada), AstraZeneca (Montreal), and the University of Toronto for the funding of this research. We also thank Dr. Alan Lough for X-ray structure determination. Y.-Q.F. thanks the University of Toronto for financial support in the form of doctoral fellowships.

Supporting Information Available: Crystallographic data, full experimental details, and characterization, including ^{1}H and ^{13}C NMR spectroscopic data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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