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Synthesis of Benzodiquinanes via Tandem Palladium-Catalyzed Semipinacol Rearrangement and Direct Arylation

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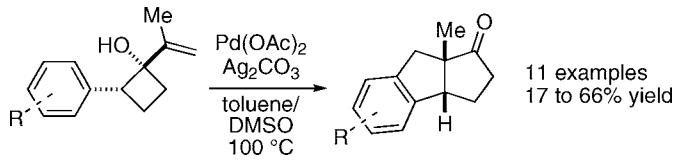
ABSTRACT



A palladium-catalyzed tandem semipinacol rearrangement/direct arylation reaction using α-aryl isopropenyl-*tert*-cyclobutanols has been developed. This reaction gives access to benzodiquinanes in moderate to good yields and tolerates alkyl-, alkoxy-, and halogen-substituted aryl groups.

Palladium-catalyzed reactions have had a great impact on our ability to construct complex molecules. Traditionally, palladium-catalyzed carbon−carbon bond forming cross-coupling reactions have required the use of an oxidative addition partner and an organometallic reagent.[1] More recently there has been significant focus on carbon−carbon bond-forming reactions that do not require the use of an oxidative addition partner, an organometallic partner, or either. Research into direct arylation reactions involving aryl- and benzylpalladium(II) intermediates has been particularly intense.[2] In contrast, reports of direct arylation reactions proceeding through alkylpalladium(II) intermediates are relatively rare,[3] reflecting the difficulties resulting from competitive β-hydride elimination processes.[4] Not surprisingly, alkylpalladium(II) intermediates incapable of β-hydride elimination have been strategically utilized in direct arylations. Methods to generate these intermediates include migratory insertion across a 1,1-disubstituted alkene and palladium-catalyzed fragmentation of 2,2-disubstituted *tert*-cyclobutanols.[5]

The indane and diquinane scaffolds are commonly occurring features in pharmaceutical agents and natural products.

(1) For reviews on traditional cross-coupling reactions, see: (a) Diederich, F.; Stang, P. J. Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For selected recent reviews on direct arylation, see: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (b) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (d) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res.* **2008**, *41*, 1512. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (h) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (i) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (j) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253.

(3) For a discussion, see: (a) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560. For examples of direct arylation with alkyl palladium(II) intermediates capable of β-hydride elimination see: (b) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (c) Hu, Y.; Yu, C.; Ren, D.; Hu, Q.; Zhang, L.; Cheng, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 5448.

(4) (a) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457. (b) Hartwig, J. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2009; Chapter 10, pp 398−402.

(5) For examples of direct arylation using alkylpalladium intermediates generated from cyclobutanol fragmentation, see: (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455. For the analogous reaction using cyclobutanone oximes, see: (c) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049.

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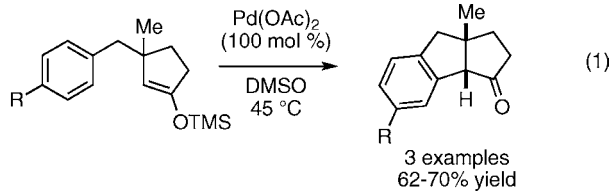
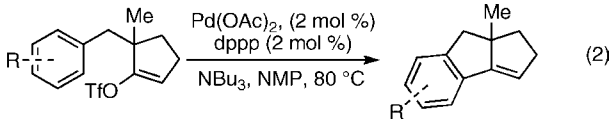
In contrast, the benzodiquinane[6] framework is relatively rare; nevertheless, its synthesis has attracted some attention. Sporadic reports of benzodiquinane synthesis initiated by oxidative addition of Pd(0) across an Ar−X bond have appeared.[7] In addition, two methods for the synthesis of benzodiquinanes via direct arylation have been developed. In 2002 Toyota and Ihara[8] reported a few examples of the direct coupling of palladium enolates with tethered aryl groups to generate benzodiquinanes (eq 1). One drawback of this method is the need for stoichiometric palladium. More recently, Willis[9] reported an efficient intramolecular direct arylation route to this class of compounds (eq 2).



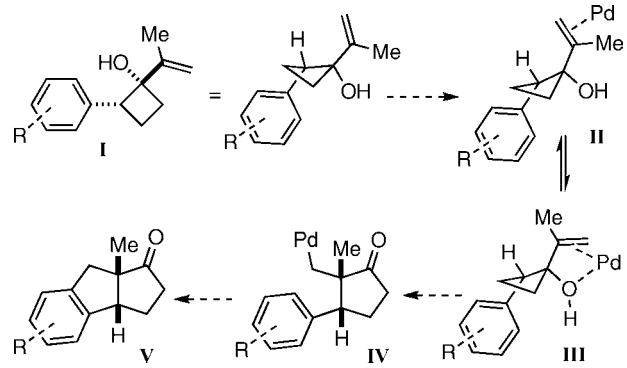
(1)



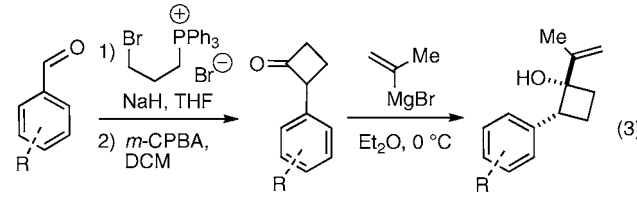
(2)

Our interest in expanding the chemistry of palladium homoenolates[10] and palladium-catalyzed strain-releasing reactions, coupled with the relatively few methods available for the synthesis of benzodiquinanes, prompted us to explore a new strategy for their preparation. We envisioned that the alkene function of an α-aryl substituted alkenyl *tert*-cyclobutanol **I** would coordinate with an electrophilic palladium intermediate and promote a 1,2-alkyl shift[11] to generate a palladium homoenolate **IV** (Scheme 1). We surmised that a certain degree of selectivity could be achieved if the palladium electrophile could coordinate the alkene and the hydroxy group simultaneously as in **III**.[12] The resulting palladium homoenolate could in principle participate in a direct arylation reaction to generate the target compound **V**.

Scheme 1. Proposed Synthesis of Benzodiquinanes



Substrates for this study could be readily prepared from the corresponding benzaldehydes using a three-step sequence involving methylenecyclopropane synthesis, oxidative rearrangement to an α-arylcyclobutanone, and diastereoselective 1,2-addition of an isopropenyl Grignard (eq 3).[13] Importantly, the synthesis of α-arylcyclobutanones is subject to enantioselective synthesis.[14]



(3)

Initial experiments conducted on *tert*-cyclobutanol **1** and using stoichiometric amounts of $PdCl_2$ resulted in the formation of the desired benzodiquinane product **2** in 10% yield (Table 1, entry 1). A suite of NMR experiments was used to establish the structure of the product, and NOE difference experiments confirmed the cis-fusion of the diquinane (inset). The use of 20 mol % $Pd(OAc)_2$ and molecular oxygen did not result in a significant improvement (entry 2). A further increase in yield was observed when Ag_2CO_3 was used as the base and oxidant in solvent mixtures containing DMSO (entries 4 to 7). The use of DMSO in toluene in an overnight reaction provided ketone **2** in 48% yield accompanied with a 16% yield of the α,β-unsaturated ketone **3** (entry 5). Under the same conditions, a 58% yield of **2** was obtained after 1 h (entry 6). A comparable yield was obtained when the reaction was conducted in DMSO after 5 h (entry 7). When CH_3CN was used as the sole solvent ketone **2** was obtained in 56% yield; however the reaction time was not practical (entry 8). Using a mixture of DMSO

(6) Buchanan, G. O.; Williams, P. G.; Feling, R. H.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2005**, *7*, 2731.

(7) Cascade Heck reaction: (a) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. Carbonylative polyene cyclization: (b) Copéret, C.; Ma, S.; Negishi, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2125. Reductive Heck reaction: (c) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764. Fragmentation of *tert*-cyclobutanols: (d) Ethirajan, M.; Oh, H.-S.; Cha, J. K. *Org. Lett.* **2007**, *9*, 2693. C(sp^3)−H activation: (e) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem.—Eur. J.* **2007**, *13*, 792. (f) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706.

(8) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293.

(9) Cruz, A. C. F.; Miller, N. D.; Willis, M. C. *Org. Lett.* **2007**, *9*, 4391.

(10) For a good entry into the metal homoenolate literature, see: (a) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74*, 1297. For examples of palladium homoenolate formation *via* directed C(sp^3)−H activation and subsequent cross-coupling, see: (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. For a recent example of formal homoenolate arylation, see: (e) Renaudat, A.; Ludivine, J.-G.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7261.

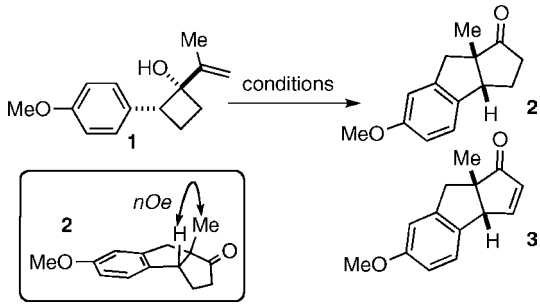
(11) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231.

(12) This type of coordination of alkenylcyclobutanols has been invoked before; see: (a) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850. (b) Nemoto, H.; Yoshida, M.; Fukumoto, K.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 907. (c) Yoshida, M.; Ismail, M. A.-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2629.

(13) See Supporting Information for details.

(14) Wang, B.; Shen, Y.-M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519.

Table 1. Reaction Development[a]



entry	PdX_2 (equiv)	base and oxidant (equiv)	solvent	time (h), *temp (°C)*	yield[c,d] (%)
1	$PdCl_2$ (1.0)	Cs_2CO_3 (1.1)	DMA	48, *80*	10
2	$Pd(OAc)_2$ (0.2)	K_2CO_3 (1.0) O_2 (ballon)	DMA	5, *100*	23
3	$Pd(OAc)_2$ (0.2)	Ag_2CO_3 (2.0)	DMF/ DMSO[b]	4, *100*	37
4	$Pd(OAc)_2$ (0.2)	Ag_2CO_3 (2.0)	CH_3CN/ DMSO[b]	68, *75*	48
5	$Pd(OAc)_2$ (0.1)	Ag_2CO_3 (2.0)	toluene/ DMSO[b]	14, *100*	48 (16)[d]
6	$Pd(OAc)_2$ (0.1)	Ag_2CO_3 (2.0)	toluene/ DMSO[b]	1, *100*	58
7	$Pd(OAc)_2$ (0.1)	Ag_2CO_3 (2.0)	DMSO	5, *100*	50
8	$Pd(OAc)_2$ (0.1)	Ag_2CO_3 (2.0)	CH_3CN	69, *75*	56
9	$Pd(OAc)_2$ (0.1)	Ag_2CO_3 (2.0)	toluene/ DMSO[b]	72, *85*	48 (29)[d]

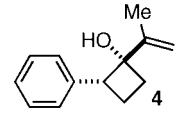
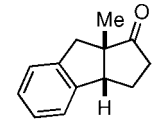
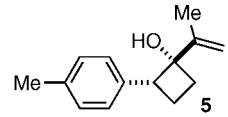
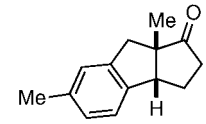
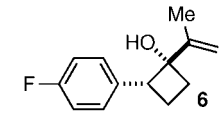
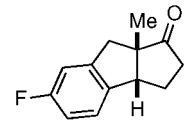
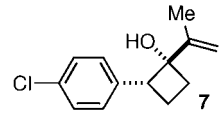
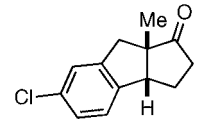
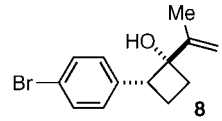
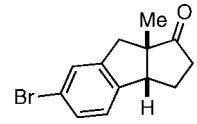
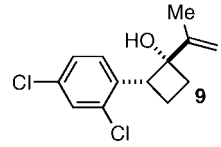
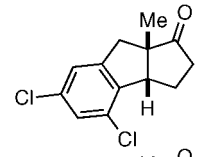
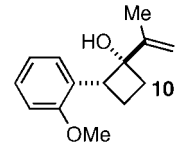
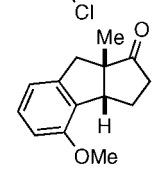
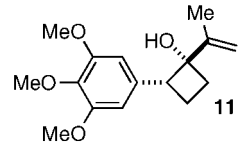
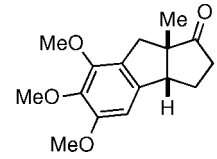
[a] All reactions were conducted on 30 mg of substrate at 0.14 M concentration. [b] A 5% solution of DMSO in the corresponding solvent was used. [c] Isolated yields of benzodiquinane **2**. [d] Yield of unsaturated benzodiquinane **3** in parentheses.

in toluene and reducing the reaction temperature to 85 °C increased the overall yield (**2** + **3**) of the reaction to 77% albeit over an extended reaction time (entry 9).

The scope of the reaction was explored using a toluene/DMSO solvent mixture at 100 °C to maintain short reaction times and avoid the formation of overoxidized product (Table 1, entry 6). A variety of substrates bearing methyl, alkoxy, and halogen substituents were readily prepared. The preparation of substrates bearing electrophilic substituents, (i.e., ketones or esters) on the aryl groups is hampered by the low nucleophilicity of the methylenecyclopropanes used for the synthesis of α-aryl cyclobutanones. Furthermore, ketones and esters would be subject to nucleophilic attack by the Grignard reagents and were therefore not explored.

Substrates bearing a phenyl or *p*-tolyl ring provided the benzodiquinane products in 48% and 66% yields, respectively (Table 2, entries 1 and 2). Substrates bearing *p*-fluorophenyl, *p*-chlorophenyl, and *o*,*p*-dichlorophenyl groups provided the benzodiquinane products in 45%, 48%, and 56% yields, respectively (entries 3, 4, and 6). A significantly lower yield was obtained with a substrate bearing a *p*-bromophenyl substituent, presumably due to an undesired oxidative addition to the aryl bromide (entry 5). Substrates bearing *o*-anisyl and 3,4,5-trimethoxyphenyl groups provided the benzodiquinane products in 53% yield (entries 7 and 8).

Table 2. Scope of the Benzodiquinane Synthesis[a,b]

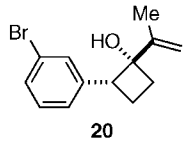
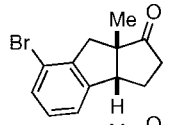
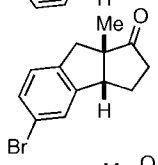
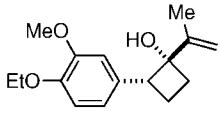
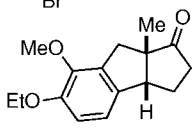
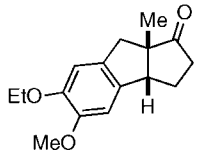
entry	cyclobutanol	benzodiquinane	yield
1			**12** 48%
2			**13** 66%
3			**14** 45%
4			**15** 48%
5			**16** 28%
6			**17** 56%
7			**18** 53%
8			**19** 53%

[a] All reactions were conducted on 30 mg of substrate and 20 mol % of $Pd(OAc)_2$ using the reactions conditions in Table 1, entry 6. [b] Isolated yields of the benzodiquinane products.

We explored the possibility of the halogen or alkoxy substituents exerting a directing effect during the direct arylation step (Table 3). Subjection of *tert*-cyclobutanol **20**, bearing a *m*-bromophenyl group capable of direct arylation at two distinct sites, provided benzodiquinanes **22** and **23** in a nearly 1:1 ratio and low yield. In contrast, the use of substrate **21**, bearing a 3-methoxy-4-ethoxyphenyl group, provided benzodiquinanes **24** and **25** in a 1:3.4 ratio and 48% overall yield.

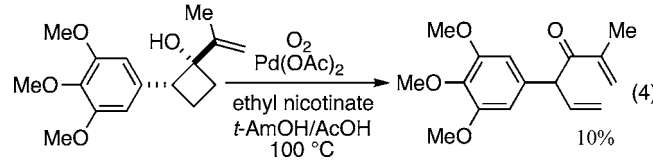
The generally moderate yields observed in this reaction suggest that at least one alternative reaction pathway leading to undesired products is available. For instance, we have observed the formation of products arising from a palladium-

Table 3. Regioselectivity of Benzodiquinane Synthesis[a,b]

entry	cyclobutanol	benzodiquinane	yield
1	 **20**	 **22**  **23**	17%
2	 **21**	 **24**  **25**	11% 37%

[a] All reactions were conducted using 20 mol % $Pd(OAc)_2$ using the reaction conditions in Table 1, entry 6. [b] Isolated yields of the benzodiquinane products.

catalyzed β-carboelimination[15] and β-hydride elimination process using the reaction conditions developed by Stoltz[16] for oxidative Heck reactions using electron-rich arenes (eq 3).



(4)

In conclusion, we have developed a new palladium-catalyzed route to the benzodiquinane scaffold using α-aryl isopropenyl-*tert*-cyclobutanols, proceeding through a semipinacol rearrangement and direct arylation. A variety of *tert*-cyclobutanols bearing alkyl-, halo-, and alkoxy-substituted aryl groups participate in this reaction and provide the desired products in moderate to good yields.

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

OL1026415

(15) For an early example of palladium-catalyzed β-carboelimination of alkenyl-*tert*-cyclobutanols under oxidative conditions, see ref 5b. For a related rhodium-catalyzed C−C activation of allenyl-*tert*-cyclobutanols, see: (b) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9294.

(16) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144.