ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Palladium-Catalyzed Oxidative Rearrangement of Diaryl Alkenyl Carbinols to β,β-Diaryl α,β-Unsaturated Ketones

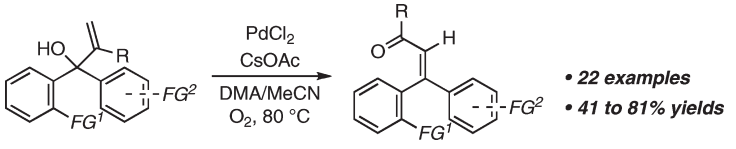
David Rosa and Arturo Orellana*

Department of Chemistry, York University, 440 Chemistry Building, 4700 Keele Street, Toronto, ON, Canada M3J 1P3

aorellan@yorku.ca

Received May 14, 2011

ABSTRACT



An unusual oxidative palladium-catalyzed rearrangement of diaryl alkenyl carbinols to β,β-diaryl α,β-unsaturated ketones is described. The geometry of the alkene product is not determined by the electronic nature of the aryl substitutents but rather is determined by substitution pattern on the aryl rings. The reaction proceeds in good yields, utilizes oxygen at atmospheric pressure as the terminal oxidant, and tolerates a variety of functional groups on the aryl rings.

Tremendous advances in transition metal catalysis have revolutionized synthetic organic chemistry. In particular, palladium catalyzed reactions have found widespread use, and progress in this area continues unabated.[1] We have been interested in studying the palladium-catalyzed chemistry of tertiary alcohols[2] proceeding through a carbon–carbon bond cleavage step.[3] In earlier reports,[4] we have documented carbon–carbon bond forming reactions of palladium homoenolates.[5] In these instances, the formation of the homoenolate moiety occurred *via* the known palladium-catalyzed and strain-driven cleavage or ring-expansion of cyclopropanols and isopropenyl-*tert*-cyclobutanols, respectively. With an interest in developing a new entry into palladium homoenolates, we began studying tertiary allylic alcohols that do not benefit from ring strain as a driving force. Specifically, we envisioned that diaryl alkenyl carbinols[6,7] could give rise to a palladium homoenolate through electrophilic activation of the alkenyl function followed by an aryl 1,2-migration.[8] The resulting palladium homoenolate could then participate in further reactions.

(1) Reviews: (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *45*, 4442.

(2) For a review of palladium-catalyzed reactions of alcohols, see: Muzart, J. *Tetrahedron* **2005**, *61*, 9423.

(3) For reviews on palladium-catalyzed reactions proceeding through β-carboelimination, see: (a) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835. (b) Satoh, T.; Miura, M. *Top. Organomet. Chem* **2007**, *24*, 61. (c) Satoh, T; Miura, M. *Top. Organomet. Chem* **2005**, *14*, 1. (d) Kuwajima, I.; Nakamura, E. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, Germany, 1990; Vol. 155, p 1. (e) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 2, p 441. (f) Kuwajima, I. *Pure Appl. Chem.* **1988**, *60*, 115.

(4) (a) Schweinitz, A.; Chtchemelinine, A.; Orellana, A. *Org. Lett.* **2011**, *13*, 232. (b) Rosa, D.; Orellana, A. *Org. Lett.* **2011**, *13*, 110.

(5) For a good entry into the palladium homoenolate literature, see: (a) Molander, G. A.; Jean-Gerard, L. *J. Org. Chem.* **2009**, *74*, 1297. For a concise overview of homoenolate chemistry see: (b) Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt., K. A. *J. Am. Chem. Soc.* **2009**, *131*, 8805.

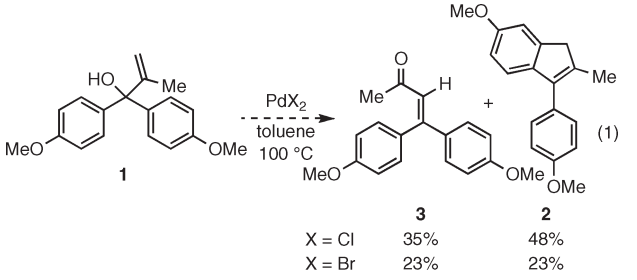
(6) Diaryl alkenyl carbinols were readily prepared by either addition of alkenyllithiums or Grignard reagents to the corresponding benzophenones, or addition of aryllithiums to the corresponding unsaturated ketones. See Supporting Information for details.

(7) This substrate class has not been explored extensively. For the synthesis of epoxides through palladium-catalyzed carboetherification, see: Hayashi, S; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052.

(8) For selected examples of aryl 1,2-migration in transition-metal-catalyzed reactions, see: (a) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762. (b) Dudnik, A. S.; Grevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195.

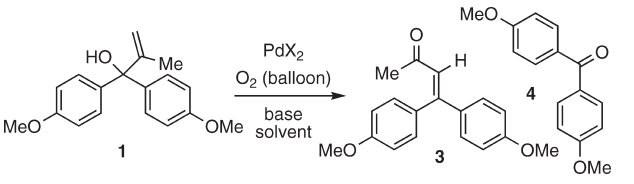
10.1021/ol201177t

In initial experiments, treatment of tertiary allylic alcohol **1** with stoichiometric amounts of palladium(II) salts did not promote the desired aryl 1,2-shift, but rather resulted in the formation of indene **2** and β,β-diaryl α,β-unsaturated ketone **3** (eq 1). The formation of arylated indene **2** is likely the result of ionization of the allylic alcohol and intramolecular Friedel–Crafts reaction.[9] The formation of unsaturated ketone **3**,[10] in which a reorganization of the carbon framework associated with the allylic alcohols from a branched to a linear arrangement of carbon atoms has occurred, was unexpected and is not readily rationalized. We note in passing that 1,1-diaryl styrene systems of this type are useful synthetic intermediates, and that their hydrogenation leads to 1,1-diaryl fragments[11] that are valuable in drug discovery. More importantly, the unusual reactivity observed prompted us to study this reaction further.



We reasoned that the inclusion of a stoichiometric amount of inorganic base would prevent formation of aryl indenes. Under these conditions the reaction provided a mixture of ketone **3** and benzophenone, the latter product likely arising through palladium-catalyzed β-carboelimination of the isopropenyl fragment. Further optimization focused on using catalytic amounts of palladium in the presence of a co-oxidant (Table 1). It was quickly established that common oxidants (Cu and Ag salts, DDQ) did not ameliorate the reaction. The use of molecular oxygen as the terminal oxidant[12] was explored using a variety of solvents with limited success. However, the use of dimethylacetamide (DMA)[13] resulted in a significantly increased yield. A screen of palladium(II) sources and bases revealed $PdCl_2$ and CsOAc to be optimal. Finally, the use of DMA/MeCN solvent mixture significantly diminished the generation of benzophenone.

Table 1. Reaction Optimization[a,g]



	solvent[b]	Pd source[c]	base	time (h)	yield (%)[d] (**3**:**4**)[e]
1	MeCN[f]	$PdCl_2$	Cs_2CO_3	20	16 (100:0)
2	DMF	$PdCl_2$	Cs_2CO_3	20	26 (85:15)
3	NMP	$PdCl_2$	Cs_2CO_3	20	35 (72:28)
4	DMA	$PdCl_2$	Cs_2CO_3	20	76 (81:19)
5	DMA	$PdBr_2$	Cs_2CO_3	10	68 (70:30)
6	DMA	$PdCl_2MeCN_2$	Cs_2CO_3	10	68 (78:22)
7	DMA	$PdCl_2(PPh_3)_2$	Cs_2CO_3	24	39 (67:33)
8	DMA	$PdCl_2$	K_2CO_3	10	80 (69:31)
9	DMA	$PdCl_2$	Na_2CO_3	10	74 (72:28)
10	DMA	$PdCl_2$	$NaHCO_3$	10	90 (72:28)
11	DMA	$PdCl_2$	Ag_2CO_3	48	26 (50:50)
12	DMA	$PdCl_2$	NaOAc	10	80 (51:49)
13	DMA	$PdCl_2$	KO^{t}Bu	10	77 (82:18)
14	DMA	$PdCl_2$	CsOAc	10	80 (88:12)
15	DMA[f,h]	$PdCl_2$	CsOAc	10	80 (98:2)

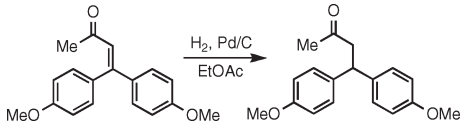
[a] All reactions were conducted on a 0.11 mmol scale at a 0.1 M concentration using 20 mol % of the palladium catalyst and 1.1 equiv of base. [b] All reactions were conducted at 100 °C unless otherwise noted. [c] $Pd(OAc)_2$ and $PdTFA_2$ did not yield any unsaturated ketone. [d] Combined isolated yield of benzophenone and unsaturated ketone. [e] Ratio determined by quantitative ^{1}H NMR of crude reaction mixtures. [f] Reactions conducted at 80 °C. [g] A catalyst loading study revealed that as little as 1 mol % of $PdCl_2$ could be used. However, the reaction required 72 h to reach completion. For convenience a catalyst loading of 20 mol % was used on all subsequent reactions. [h] A 3:1 ratio of DMA/MeCN was used.

Next, we conducted a series of experiments aimed at expanding the scope of this reaction (Table 2). Not surprisingly, the carbinol derived from benzophenone provided the expected product in good yield (entry 1). A substrate bearing a phenyl and an electron-rich aryl ring provided a 1:1 mixture of products in good yield (entry 2). Substituting the phenyl ring with an electron-poor aryl ring did not affect the product distribution (entry 3). Likewise, the use of a substrate bearing two *ortho*-substituted aryl rings also resulted in a 1:1 mixture of products (entry 4). Taken together, these results suggest that the process is insensitive to the electronic nature of the aryl ring. In contrast, the use of a substrate bearing only one *ortho*-substituted aryl ring resulted in the formation of a single product (entry 5).[14]

A series of substrates bearing one *ortho*-susbtituted aryl ring were subjected to the optimized reaction conditions to explore the generality of this selectivity (Figure 1). In all cases studied only the product having a *cis*-relationship between the *ortho*-substituted ring and acyl moiety was

(9) Smith, C. D.; Rosoch, G.; Mui, L.; Batey, R. *J. Org. Chem.* **2010**, *75*, 4716.

(10) The structure of ketone **3** could be readily assigned based on calculation of the chemical shift for the vinyl proton and characterizaion of its hydrogenation product. See Supporting Information for full details.



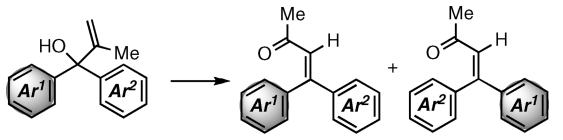
(11) For a leading reference on the enantioselective hydrogenation of 1,1-diaryl alkenes, see: Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881.

(12) Reviews: (a) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854. (b) Stahl, S. S. *Science* **2005**, *309*, 1824. (c) Stahl, S. *Angew. Chem., Int. Ed.* **2003**, *43*, 3400.

(13) (a) Mitsudome, T.; Mizumoto, K.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 1238. (b) Mitsudome, T.; Umetani, T.; Nozaka, N.; Mori, K.; Mizugaki, T.; Ebitami, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *68*, 5236.

(14) The double bond geometry of all products arising from unsymmetrical carbinols was determined using nuclear Overhauser difference (NOE) experiments. See Supporting Information for details.

Table 2. Effect of Aryl Substitution on Product Distribution[a]



entry	Ar^1	Ar^2	yield[b]	ratio[c]
1			78%	n.a.
2	MeO		73%	1:1
3	MeO	F_3C	49%	1:1
4	MeO	H_3C	68%	1:1
5	MeO		71%	1:0

[a] All reactions were conducted at 0.1 M concentration using 20 mol % of $PdCl_2$, 1.1 equiv of CsOAc, and a DMA/MeCN ratio of 3:1 (v/v). [b] Isolated yields. [c] Determined using ^1H NMR of crude reaction mixtures.

observed, regardless of the electronic nature of the rings (entries 1 to 14). This suggests that the geometry-determining step in the reaction is influenced by the steric demands of the aryl groups. A variety of functionalized aryl groups are tolerated in this reaction including alkyl- (entries 1 and 10), alkoxy- (entries 1 to 8, 10 to 12, and 14), trifluoromethyl- (entries 6 and 11), vinyl- (entry 7), chloro- (entries 3 and 14), fluoro- (entries 4 and 13) and bromo- (entry 12) substituted aryl rings. The fact that chloro-, bromo-, and vinyl substituents do not participate in any palladium-catalyzed side reactions is particularly interesting. Furthermore, it is important to note that although the majority of examples explored bear an *ortho*-methoxy-substituted aryl group[15] (entries 1–8), the nature of this substituent does not appear to be an important factor. Indeed, substrates bearing a variety of other functional groups at the *ortho*-position, including phenyl (entry 9), methyl (entry 10), trifluoromethyl (entry 11), bromo (entry 12), fluoro (entry 13), and chloro (entry 14), display the same reactivity and selectivity.

Substrates bearing heterocycles did not provide the expected products but rather formed the ketone resulting from carboelimination of the isopropenyl unit or gave intractable reaction mixtures (not shown). The nature of the alkene component in the substrate also has a profound

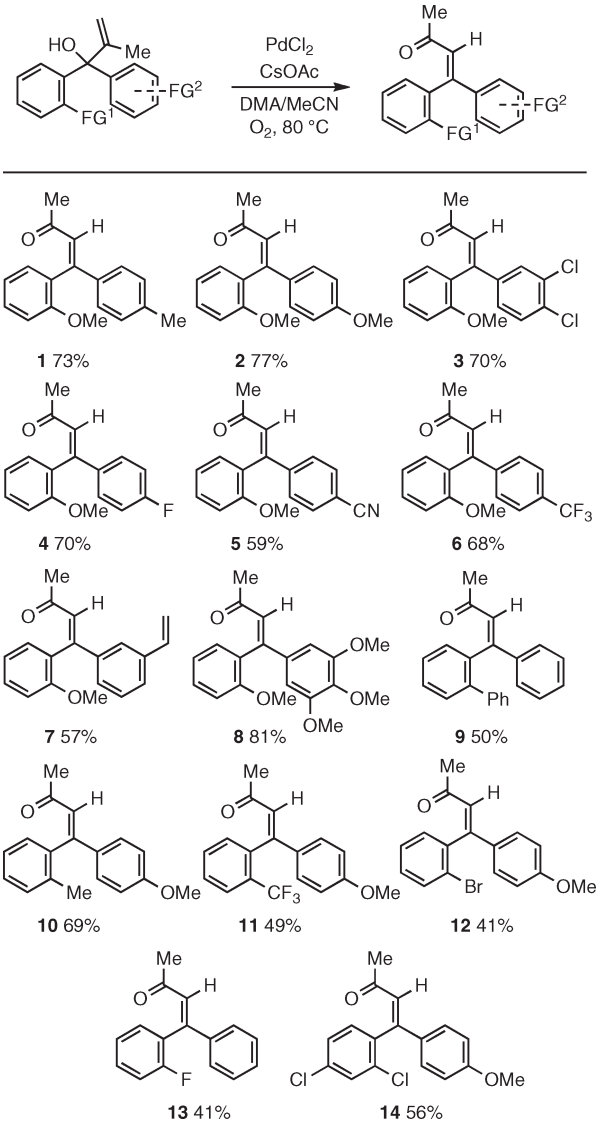


Figure 1. Selective product formation with substrates bearing *ortho*-substituted aryl rings.

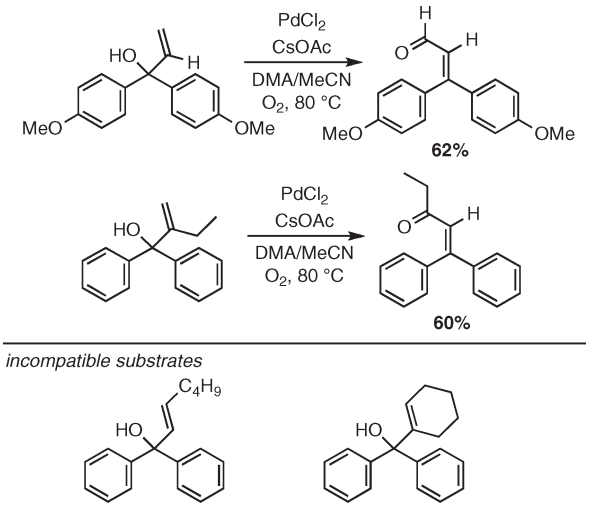
effect on the success of this reaction. Substrates bearing isopropenyl (Tables 1 and 2, and Figure 1), vinyl, and 2-(1-butenyl) groups provide the rearranged products in good yields, while those bearing 1-(*trans*-1-hexenyl) or cyclohexenyl groups react sluggishly and provide intractable mixtures of products (Scheme 1).

At present, we cannot offer a clear mechanistic picture for this unusual reaction. However, we have begun probing its mechanism. A number of studies have documented the palladium-catalyzed β-carboelimination of aryl fragments from triaryl carbinols to generate arylpalladium(II) intermediates.[16] In particular, the selective β-carboelimination of *ortho*-substituted aryl rings from tertiary carbinols has been ascribed to steric effects.[17] We have conducted a number of crossover experiments to explore the possibility of a

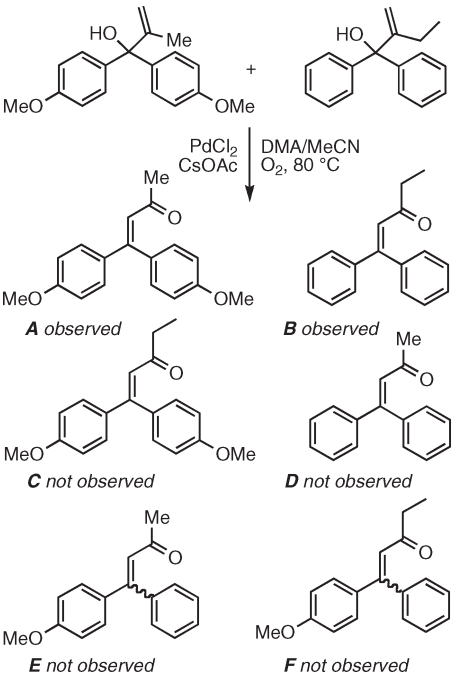
(15) A number of benzophenones were prepared in one step from salicylaldehyde using the palladium-catalyzed cross-coupling with aryl halides. See: Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, *25*, 823.

(16) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

Scheme 1. Effect of Alkene Variation



Scheme 2. Crossover Experiment



palladium-catalyzed β-carboelimination of the aryl or alkenyl groups in the present reaction (Scheme 2).[18] For example, when two substrates derived from two different benzophenones and bearing different alkenyl groups were subjected to the optimized reaction conditions, only products **A** and **B** were observed. Although some of the corresponding benzophenones (not shown) could be detected, no evidence of products **C** or **D**, resulting from an exchange of the alkenyl moiety, or products **E** or **F**, arising from exchange of the aryl substituents, was observed. This experiment suggests that the mechanism of this reaction does not involve fragmentation of the starting material into two reactive partners but rather proceeds in an intramolecular fashion. Further studies aimed at elucidating the mechanism of this transformation are underway.

In conclusion, we have discovered an unusual palladium-catalyzed oxidative rearrangement of alkenyl diaryl carbinols to β,β-disubstituted α,β-unsaturated ketones. This reaction provides a single geometric isomer of the products when one *ortho*-substituted aryl ring is incorporated in the substrate, proceeds in good yields, tolerates a variety of functional groups on the aryl rings, and utilizes oxygen at atmospheric pressure as the terminal oxidant.

Acknowledgment. We gratefully acknowledge the support of this work from York University and the Natural Sciences and Engineering Research Council of Canada. We thank Dr. Howard N. Hunter (York University) for assistance in conducting NOE difference experiments.

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

(17) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236.

(18) See Supporting Information for experimental details.