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A Sequential Pd/Norbornene-Catalyzed Process Generates *o*-Biaryl Carbaldehydes or Ketones via a Redox Reaction or 6*H*-Dibenzopyrans by C–O Ring Closure

Elena Motti,[†] Nicola Della Ca',[†] Di Xu,[†,‡] Anna Piersimoni,[†] Elena Bedogni,[†] Zhi-Ming Zhou,[‡] and Marta Catellani*,[†]

Dipartimento di Chimica and CIRCC, Università di Parma, Parco Area delle Scienze, 17/A, 43124 Parma, Italy, and R&D Centre for Pharmaceuticals, School of Chemical Engineering and the Environment, Beijing Institute of Technology, Beijing, P. R. China, 100081

marta.catellani@unipr.it

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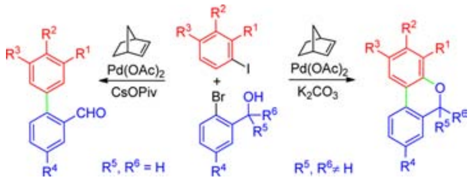
ABSTRACT



***o*-Biaryl carbaldeydes and ketones are obtained through the one-pot reaction of *o*-aryl iodides with *o*-bromobenzyl alcohols under the catalytic action of Pd and norbornene, in the presence of a base. The same reaction can also give dibenzopyrans by Pd and norbornene catalysis with a different termination, leading to C–O ring closure. In both cases the process first leads to a five-membered palladacycle, which controls C–C coupling, then to a seven-membered oxapalladacycle, which gives aldehydes and ketones or dibenzopyrans.**

In the course of our studies aimed at working out new methods to achieve ordered reaction sequences by means of Pd and norbornene joint catalysis,[1] we have shown that a variety of biphenyl derivatives can be prepared by reaction of ortho-substituted aryl iodides with aryl bromides, followed by irreversible termination steps leading to C–C, C–N, or C–O bond formation.

We have now found that the one-pot reaction of an ortho-substituted aryl iodide with a 2-bromobenzyl alcohol derivative under catalysis of Pd and norbornene in the presence of a base leads to *o*-biaryl carbaldehyde **3** and to 6*H*-dibenzo[*b,d*]pyran **4**, the former by an intramolecular oxidation–reduction process involving hydrogen migration from the benzylic group to the aromatic carbon of the other ring and the latter by C–O coupling (Scheme 1).

Amazingly, the hydroxymethyl group of the bromobenzyl alcohol remains unaffected through the series of steps leading to unsymmetrical aryl–aryl coupling and eventually reacts with the biaryl-bonded Pd intramolecularly.

In the effort to optimize the reaction conditions we observed that the use of PPh$_3$ as a ligand negatively affected the yield due to the formation of byproducts and set out to work out a ligandless reaction. We varied the base, the solvent, and norbornene equivalents as well as the temperature. We were delighted to find that the use of CsO$_2$CCMe$_3$ (cesium pivalate) allowed us to obtain *o*-biaryl carbaldehyde **3** selectively and in satisfactory to excellent yield.

[†] Università di Parma.

[‡] Beijing Institute of Technology.

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Scheme 1. *o*-Biaryl Carbaldehyde and 6*H*-Dibenzo[*b*,*d*]pyran by Pd/Norbornene Catalysis[2]

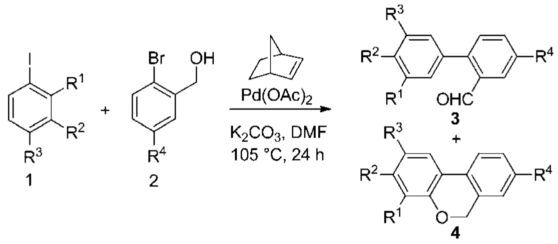
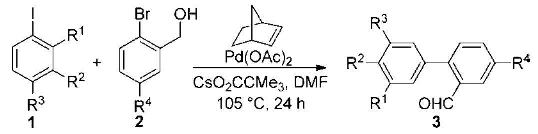


Table 1. Synthesis of *o*-Biaryl Carbaldehydes[a]



entry	R^1	R^2	R^3	R^4	**3** (yield %)[b]
1	Me	H	H	H	66 (78)[c]
2	Me	Me	H	H	66 (79)
3	Me	H	Me	H	92 (99)
4	Me	H	OMe	H	91 (99)[c]
5	Et	H	H	H	68 (80)[d]
6	*i*-Pr	H	H	H	90 (99)
7	*i*-Pr	H	H	OMe	91 (99)
8	*i*-Pr	H	H	Cl	62 (78)[d]
9	*sec*-Bu	H	H	H	93 (99)
10	(CH=CH)$_2$		H	H	74 (86)
11	(CH=CH)$_2$		OMe	H	90 (98)
12	CF$_3$	H	H	H	68 (81)[d]
13	Me	OMe	OMe	H	92 (98)[c]
14	*n*-Pr	H	H	4,5-OMe	88 (95)[d]
15	*i*-Pr	H	H	4,5-OMe	95 (99)

[a] Reaction conditions: molar ratio of **1**, **2**, Pd(OAc)$_2$, norbornene, and CsO$_2$CCMe$_3$ 20:20:1:10:50; 105 °C for 24 h. DMF as solvent, under N$_2$; 2.2 × 10^{-3} mmol Pd(OAc)$_2$/mL DMF. [b] Isolated yield on the amount of charged aryl iodide. In parentheses: yield based on reacted aryl bromide. Dibenzopyrans **4**, when present, have been estimated by ^{1}H NMR to range from 1 to 5%. Byproducts mainly derive from the reaction of aryl iodide with norbornene and have been reported previously.[1a,3] [c] Molar ratio of norbornene to Pd = 5:1. [d] Molar ratio of norbornene to Pd = 20:1.

Thus, reaction of 2-isopropyliodobenzene and 2-bromobenzyl alcohol, in the presence of Pd(OAc)$_2$ and norbornene, using CsO$_2$CCMe$_3$ in DMF, at 105 °C for 24 h, led to the formation of 3′-isopropyl[1,1′]-biphenyl-2-carbaldehyde (**3**; R^1 = *i*-Pr; R^2, R^3, R^4 = H) in 90% yield, together with a small amount, if any, of the corresponding dibenzo[*b*,*d*]pyran derivative (Table 1).

As shown in Table 1, the reaction led to compounds **3** with good to excellent yields, which are significantly enhanced in the presence of bulky groups ortho to the aryl iodide (e.g., entries 6 and 9) as well as in the presence of electron-releasing groups in the aromatic ring of both the iodide (entries 4 and 13) and the bromide (entries 14 and 15). Electron-releasing substituents in the iodoarene are required since, with the exception of CF$_3$,[3] electron-withdrawing groups favor the reaction with a second molecule of iodoarene rather than with the bromobenzyl alcohol.

As pointed out in our previous works,[1] norbornene, although acting catalytically, must be used in excess to Pd to counteract competitive reactions. A too large excess has a negative effect, however, because of the tendency of certain substrates to retain norbornene and incorporate it into organic compounds.[1] Different ratios to Pd (from 5 to 20:1 molar ratio), depending on substituents on both aryl halides, have therefore to be used. As previously pointed out, the base of choice turned out to be CsO$_2$CCMe$_3$, with poorer results being obtained, in terms of both conversion and selectivity, with other bases such as KO$_2$CCMe$_3$, K$_2$CO$_3$, Cs$_2$CO$_3$, or Na$_2$CO$_3$, and NaOAc or KOAc, used in excess over that required for neutralizing acidity.

This procedure allows access to a large number of substituted *o*-biaryl carbaldehydes, which are useful intermediates for fragrances, pharmaceutical compounds, and other fine chemicals;[4] moreover, in view of the simplicity of the one-pot procedure, the availability of the starting materials, and the modular approach, which allows a facile change of the building blocks, this ligandless Pd-catalyzed sequence offers a valuable alternative to other procedures.[5]

At this point, we wondered how aryl bromides, containing a substituted hydroxymethyl group in the ortho position, as in the case of **5** (Table 2) would behave. As shown in Table 2 the reaction led to the expected ketone **6** together with 6*H*-dibenzopyran derivative **7**. K$_2$CO$_3$ proved to be the base of choice and allowed us to obtain the ketone with a yield up to 85% (entry 3; R^5 = Me). Passing from the methyl group to the phenyl one (entry 6; R^5 = Ph) led to the dibenzopyran derivative predominantly. The decrease of the norbornene ratio to Pd had a beneficial effect in entries 1 and 2. Other variations of reaction conditions did not exert a positive influence on the outcome.

Finally, we carried out the reaction using tertiary benzyl alcohols **8**, as reported in Table 3. In this case, as could be expected in view of the lack of hydrogen to be abstracted, the reaction was found to be very selective and led, with good to excellent yields, to the dibenzopyran derivative **9**.

Ring closure to dibenzopyran derivative was also strongly favored by the geminal group effect (Table 3).[7] The base of choice turned out to be K$_2$CO$_3$. The trend

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(2) See the Supporting Information for details.

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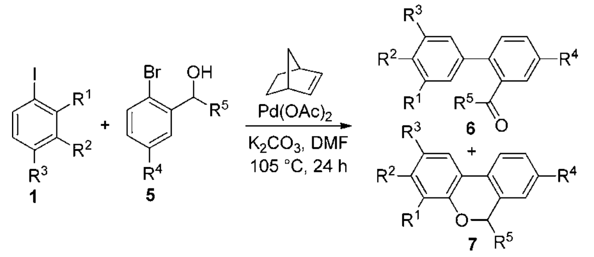
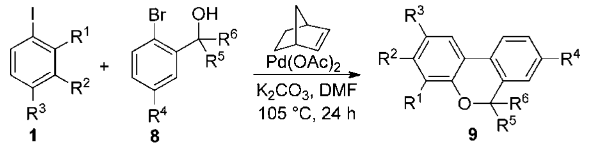
Table 2. Synthesis of *o*-Biaryl Ketones and Dibenzo[*b*,*d*]pyrans[a]



entry	R^1	R^2	R^3	R^5	**6** (yield %)[b]	**7** (yield %)[b]
1	Me	H	H	Me	43[c]	37[c]
2	Me	H	OMe	Me	78[c]	8[c]
3	Me	OMe	OMe	Me	85	9
4	$(CH{=}CH)_2$		H	Me	24	49
5	$(CH{=}CH)_2$		OMe	Me	80	16
6[d]	Me	H	H	Ph	11	50

[a] Reaction conditions: molar ratio of **1**, **5** (R^4 = H), $Pd(OAc)_2$, norbornene, and K_2CO_3 20:20:1:20:50; 105 °C for 24 h. DMF as solvent, under N_2; 2.2 × 10^{-3} mmol of $Pd(OAc)_2$/mL of DMF. [b] Isolated yield. [c] Molar ratio of norbornene to Pd = 10:1. [d] 1-Methyl-9-phenylfluoren-9-ol[6] was also formed in 11% isolated yield likely through coupling of the activated hydroxymethyl carbon with the Pd-bonded aryl carbon.

Table 3. Synthesis of Dibenzo[*b*,*d*]pyrans[a]



entry	R^1	R^2	R^3	R^4	R^5	R^6	**9** (yield %)[b]
1	Me	H	H	H	Me	Me	79[c]
2	*i*-Pr	H	H	H	Me	Me	75[c]
3	$(CH{=}CH)_2$		H	H	Me	Me	66
4	Me	H	Me	H	Me	Me	98
5	Me	H	H	H	Me	Et	84[c]
6	*n*-Pr	H	H	H	Me	Et	90
7	*i*-Pr	H	H	H	Me	Et	92
8	$(CH{=}CH)_2$		H	H	Me	Et	98
9	Me	H	H	H	Et	Et	95[c]
10	*n*-Pr	H	H	H	Et	Et	98
11	$(CH{=}CH)_2$		H	H	Et	Et	80
12	OMe	H	H	H	Et	Et	90
13	Me	H	H	OMe	Et	Et	99
14	*n*-Pr	H	H	OMe	Et	Et	99
15	$(CH{=}CH)_2$		H	OMe	Et	Et	98
16	Me	H	H	Cl	Et	Et	97

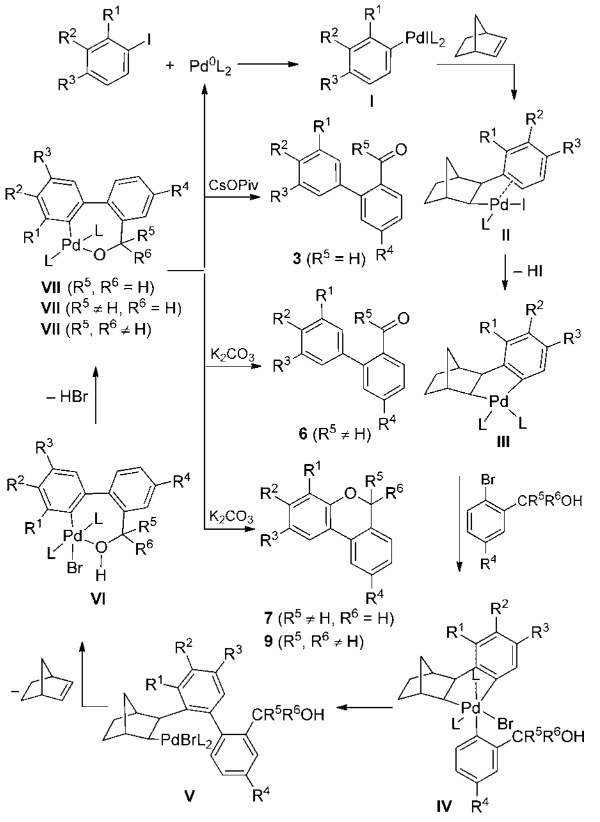
[a] Reaction conditions as in Table 2. [b] Isolated yield. [c] Molar ratio of the substrate to Pd = 50:1.

observed for the substituent effect is the same as that previously mentioned for Table 1. In addition the reaction appears to be compatible with a variety of R^5 and R^6 substituents. No reaction is observed in the absence of norbornene.

Dibenzopyrans are widely present in natural substances and in pharmaceuticals. Their basic structure is contained in the important class of cannabinoids.[8]

The proposed reaction pathway for the reactions shown in Tables 1−3 is outlined in Scheme 2. The aryl iodide oxidatively adds to Pd(0),[9] and then norbornene stereoselectively inserts into the C−C bond of **I** giving **II**,[10] which cyclizes to **III**[11] through Csp^2−H activation.[12] Oxidative addition of the aryl bromide has been recently shown to proceed through the Pd(IV) complex **IV**[13] thanks to the presence of an ortho substituent in palladacycle **III**.[14] This step is followed by reductive elimination leading to intermediate **V**, which, owing to steric factors, readily undergoes norbornene deinsertion to the aryl-Pd(II) species **VII** (via **VI**).[15] In the presence of the appropriate base intermediate **VII** generates both the cyclic (**7** and **9**) and the carbonyl (**3** and **6**) containing species together with Pd(0).

Scheme 2. Proposed Reaction Pathway



Oxapalladacycles, condensed with simple arenes instead of the biaryl unit of **VI** and **VII**, have been prepared by

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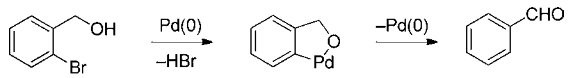
trapping them with tertiary phosphines or other stabilizing ligands.[15] Cyclic ether formation has been the object of much work in the past years.[16]

Recently the formation of dibenzopyrans starting from tertiary *o*-bromobenzyl alcohols similar to **9**, using Pd(OAc)$_2$ as the catalyst, Cs$_2$CO$_3$ as a base, and phosphines as ligands, was reported by Satyanarayana et al.[17] This methodology substantially differs from ours, because of the presence of phosphines, the absence of norbornene, the use of only bromobenzyl alcohol for the construction of the biaryl structure, and the termination step (ipso substitution). As a consequence, the dibenzopyrans formed differ by the substituents, which belong only to the bromobenzyl alcohols, and also by the junction of the two aryl groups, which occurs between the two carbon atoms originally bonded to the bromide. Biarylaldehydes or ketones have been found to be not accessible through this procedure because, if primary or secondary bromobenzyl alcohols are used, β-hydrogen elimination readily occurs with formation of aldehydes or ketones[16c−e,17] before coupling to biaryls might take place; for example, the following reaction (Scheme 3) has been reported.[17]

Scheme 3. Benzaldehyde from *o*-Bromobenzyl Alcohol



This problem does not arise in our case, as no benzaldehyde is being formed. The aryl iodide indeed reacts with Pd(0) in preference to the poorly reactive bromobenzyl alcohol to give **I**. Hydrogen transfer from the hydroxymethyl group through a redox process does not occur until **VII** is formed. Although intermolecular hydrogen transfer reactions[18] able to terminate a Pd-catalyzed reaction sequence have been reported by us and others,[19] the bromobenzaldehyde expected to result from such a process was not detected. Thus, the behavior observed in the present research, which involves oxidation to aldehyde in one ring of the biaryl unit and reduction of the C−Pd bond in the other, appears to be unprecedented.

In summary, we have reported a new one-pot method for preparing *o*-biaryl carbaldehydes and ketones or condensed 6*H*-dibenzo[*b*,*d*]pyrans, in most cases with good to excellent selectivity, through oxapalladacycles formed in the final stage of the reaction sequence that leads to biarylpalladium intermediates.

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

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The authors declare no competing financial interest.