Organometallic Chemistry

The Palladium-Catalyzed C–H Activation of Benzylic *gem*-Dialkyl Groups

Olivier Baudoin, Audrey Herrbach, and Françoise Guéritte*

The activation of C(sp^3)–H bonds is one of the current challenges in chemistry that is expected to have a major impact on both industrial and academic research. In the past years, it was shown that C–H bond activations in alkanes can be performed by low- and high-valent transition-metal complexes and in stoichiometric and catalytic processes, giving rise to synthetically useful and structurally diverse functionalized hydrocarbons.[1]

The high energy barrier of C–H bond cleavage is lowered when it is preceded by cyclometalation, which is initiated by precoordination of the metal complex to a carbon or heteroatom in the molecule. This precoordination directs

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[*] Dr. O. Baudoin, Dr. A. Herrbach, Dr. F. Guéritte
Institut de Chimie des Substances Naturelles, CNRS
Avenue de la Terrasse, 91198 Gif-sur-Yvette (France)
Fax: (+33) 1-6907-7247
E-mail: baudoin@icsn.cnrs-gif.fr

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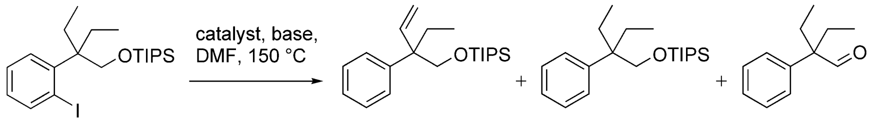
the metal center to the vicinity of the C–H bond to be broken. Among transition metals, it was shown that palladium(0) is particularly suitable for this process since the precoordination step can arise from the oxidative insertion into a carbon–halogen bond, such as that occurring in cross-coupling reactions. Indeed, a number of intramolecular arylations that proceed by catalytic C–H activation of arenes have been described.[2] Much less data is available regarding catalytic activation of a C(sp^3)–H bond through cyclometalation. In particular, it was shown that benzylic or α-benzylic C–H bonds can be cleaved through cyclometalation from Pd^{II} intermediates, giving rise to homo- or cross-coupling products.[3–6] In this report, we describe our own findings regarding the catalytic C–H activation of benzylic *gem*-dialkyl groups, which occurs by formation of five- and six-membered palladacycles, and gives rise to benzocylobutadienes and olefins, respectively, without formation of homo- or cross-coupling products.

During the course of our studies directed to the synthesis of bridged biaryls with antimitotic properties, we found that a mixture of olefin **1b**, the protodeiodinated compound **1c**, and aldehyde **1d** was obtained in different ratios when phenyl iodide **1a** was heated at 150 °C in DMF in the presence of a palladium catalyst and a base [Eq. (1), Table 1]. Initially, cesium carbonate was used as base, and different palladium catalysts were tested (entries 1–7). Thus, in the presence of a phosphane-free catalyst, olefin **1b** was the major product, accompanied by starting material **1a** and by-product **1c** (entry 1). When a phosphane ligand was added, the starting iodide was completely converted into the mixture of **1b** (major product) and **1c** (entries 2–7). Among the ligands tested, tri-*o*-tolylphosphane gave the highest yield of **1b** (entry 6). From these results, it seems that a bulky triarylmonophosphane gives better results than other types of phosphanes in this reaction. Among triarylmonophosphanes with large cone angles—PPh_3 (145°), P(*o*-tol)$_3$ (194°), and P(mesityl)$_3$ (212°) (entries 3, 6, and 7)[7]— P(*o*-tol)$_3$ seems to have the optimal bulkiness for this reaction. Interestingly aldehyde **1d** was formed in substantial amounts when PPh_3 and dppp were employed as ligands (entries 3 and 5). In most other cases **1d**, which probably arises from desilylation and dehydrogenation of the resulting primary alcohol, was formed in negligible quantities. The influence of the base was then assessed (entries 8–11). Among the bases tested, K_2CO_3 (entry 8) and K_3PO_4 (entry 9) gave the highest yields of **1b** and the highest **1b**:**1c** ratio. Besides, high-boiling solvents other than DMF (e.g. dimethyl sulfoxide, xylenes) gave lower yields of **1b** (data not shown). In DMF, the reaction did not proceed at temperatures below 140–150 °C. Repeating the reaction under the optimal conditions (entries 8–9) with 5 mol % palladium acetate and 10 mol % phosphane gave the same results as with 10 mol % palladium. However, lower yields were obtained when less than 5 mol % palladium was employed (data not shown).

Using the optimal conditions, i.e. Pd(OAc)$_2$/P(*o*-tol)$_3$ as the catalyst and K_2CO_3 as the base, we evalulated the scope of this new dehydrogenation reaction with a number of different substrates (Table 2).[8] These were obtained in few steps from commercially available iodo- or bromobenzenes according to procedures described in our previous reports.[9] First, the influence of the benzylic R substituent and of the halogen X was studied (entries 1–8). As shown with iodides **1a, 2a, 3a**, and **4a**, substrates with relatively large R groups gave higher yields of olefin than those with smaller groups. Remarkably, phenyl bromides **5a** and **6a** gave olefins **1b** and **4b**, respectively, in high yield and with no protodehalogenated by-products (entries 5 and 6), in contrast to the reactions of the corresponding iodides **1a** and **4a**. The same temperature (150 °C) was required for the reactions of bromides and iodides. In contrast, the chloro ethyl ester ($R = CO_2Et$, $X = Cl$) was not reactive under these conditions. The fact that the reaction of bromides is more efficient than that of iodides may be related to the high reactivity of the latter at this temperature and consequently their higher propensity to undergo protodehalogenation. Nitrile **7a** gave olefin **7b** as the sole product in 65 % yield, indicating again that substrates with smaller R groups give lower yields. The methoxymethyl(MOM)-protected tertiary alcohol **8a** gave only 11 % yield of olefin **8b**. In this case, the use of protecting groups other than MOM (Me, Ac, TES) did not prove more satisfactory. These data indicate that the reaction is quite dependent on the nature of the benzylic R substituent, with poor reactivity when an oxygen atom is directly attached to the quaternary carbon atom, perhaps



(1)

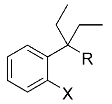
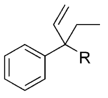
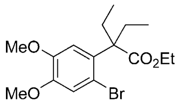
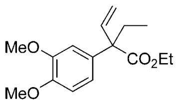
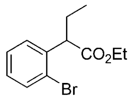
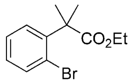
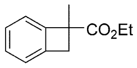
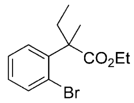
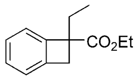
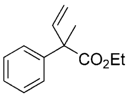
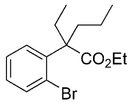
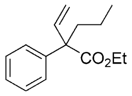
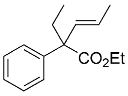
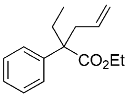
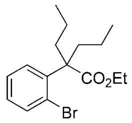
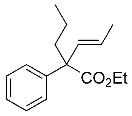
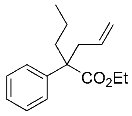
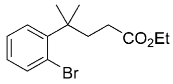
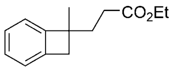
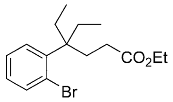
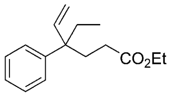
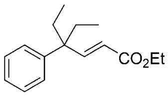
1a **1b** **1c** **1d**

Table 1: Optimization of the reaction conditions.[a]

Entry	Catalyst[a]	Base	**1a** [%][b]	**1b** [%][b]	**1c** [%][b]	**1d** [%]
1	Pd(OAc)$_2$	Cs_2CO_3	19	55	6	< 5
2	[PdCl$_2$(dppf)]	Cs_2CO_3	0	57	18	< 5
3	Pd(OAc)$_2$/PPh$_3$	Cs_2CO_3	0	39	7	28[c]
4	Pd(OAc)$_2$/P(*t*Bu)$_3$	Cs_2CO_3	0	58	6	< 5
5	Pd(OAc)$_2$/dppp	Cs_2CO_3	0	32	10	28[c]
6	Pd(OAc)$_2$/P(*o*-tol)$_3$	Cs_2CO_3	0	82	8	< 5
7	Pd(OAc)$_2$/P(mesityl)$_3$	Cs_2CO_3	0	75	6	< 5
8	Pd(OAc)$_2$/P(*o*-tol)$_3$	K_2CO_3	0	82	4	< 5
9	Pd(OAc)$_2$/P(*o*-tol)$_3$	K_3PO_4	0	83	5	< 5
10	Pd(OAc)$_2$/P(*o*-tol)$_3$	DBU	47	42	nd	< 5
11	Pd(OAc)$_2$/P(*o*-tol)$_3$	KOAc	56	32	nd	< 5

[a] Reaction conditions: 10 mol % palladium, 20 mol % phosphane (when used), 2 equiv base, DMF (0.1 mmol **1a** L^{-1}), 150 °C, 30 min. Abbreviations: dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, dppp = 1,3-bis(diphenylphosphanyl)propane, TIPS = triisopropylsilyl. [b] Yields after flash chromatography; **1a**:**1b**:**1c** ratio was determined by GC and ^1H NMR analysis. [c] Yield of isolated product.

Table 2: Dehydrogenation of phenyl iodides and bromides.[a]

Entry	Phenyl halide	Products[b]	Yield [%][c]
1	 **1a**: $\mathrm{R=CH_2OTIPS}$, $\mathrm{X=I}$	 **1b**	82 (4)
2	**2a**: $\mathrm{R=CH_2OTES}$, $\mathrm{X=I}$	**2b**	12 (2)
3	**3a**: $\mathrm{R=CO_2Me}$, $\mathrm{X=I}$	**3b**	47 (8)
4	**4a**: $\mathrm{R=CO_2Et}$, $\mathrm{X=I}$	**4b**	62 (6)
5	**5a**: $\mathrm{R=CH_2OTIPS}$, $\mathrm{X=Br}$	**1b**	83 (0)
6	**6a**: $\mathrm{R=CO_2Et}$, $\mathrm{X=Br}$	**4b**	83 (0)
7	**7a**: $\mathrm{R=CN}$, $\mathrm{X=Br}$	**7b**	65 (0)
8	**8a**: $\mathrm{R=OMOM}$, $\mathrm{X=Br}$	**8b**	11 (7)
9	 **9a**	 **9b**	93
10	 **10a**	–	0
11	 **11a**	 **11b**	60[d]
12	 **12a**	 **12b** +  **12c** 95:5	71
13	 **13a**	 **13b** +  **13c** +  **13d** 73:19:8	75
14	 **14a**	 **14b** +  **14c** 81:19	74
15	 **15a**	 **15b**	78
16	 **16a**	 **16b** +  **16c** 86:14	80

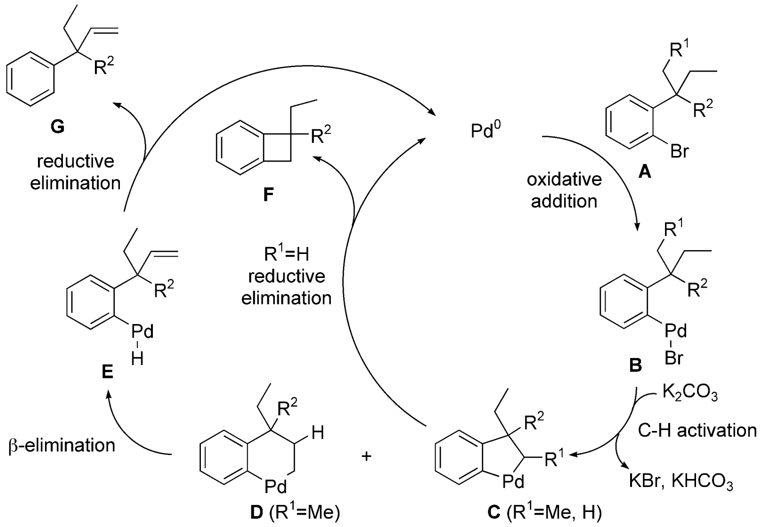
[a] Reaction conditions: 10 mol% Pd(OAc)$_2$, 20 mol% P(*o*-tol)$_3$, 2 equiv K$_2$CO$_3$, DMF, 150 °C, 30 min.[8] Abbreviation: TES = triethylsilyl. [b] The ratio of regioisomers was determined by GC analysis. [c] After flash chromatography; yields in brackets refer to the protodehalogenated by-product (see **1c**, Table 1). [d] Reaction time: 90 min.

due to electronic effects. By contrast, as shown with bromide **9a**, it seems that substituted benzenes can be employed successfully, though more examples are still needed.

Next, the influence of different benzylic alkyl groups was evaluated (entries 10–16) starting from bromophenyl ethyl esters **10a**–**16a**. When only one ethyl group was present, no reaction occurred (entry 10). With a *gem*-dimethyl group, substrate **11a** (entry 11) is obviously unable to undergo double-bond formation. The benzocyclobutene **11b** was formed exclusively in 60% yield, and a longer time (90 min) was necessary for the reaction to reach completion. A related example of benzocyclobutene formation, concomitant with homocoupling, was described by Dyker.[3d] The controlled formation of **11b** (without homocoupling) may provide convenient access to functionalized benzocyclobutenes, which are traditionally difficult to synthesize and which, in particular, are useful substrates for Diels–Alder reactions and intermediates in the synthesis of natural products.[10] Starting from dissymmetric methyl ethyl bromide **12a**, a 95:5 mixture of the two possible products **12b** and **12c** was obtained in 71 % yield, showing that the formation of the cyclobutarene is much preferred over the olefin. When the ethyl propyl bromide **13a** was employed, a 73:19:8 mixture of regioisomeric olefins **13b, 13c**, and **13d** was obtained in 75 % yield, showing that the dehydrogenation of the less substituted alkyl group is predominant. With the symmetrical dipropyl bromide **14a**, a 81:19 mixture of regioisomers **14b** and **14c** was obtained in 74 % yield, and **14b** has exclusively the *E* geometry (like **13c**). Thus, as shown with **13a** and **14a**, it seems that the dehydrogenation of the *n*-propyl group occurs such as to give the thermodynamically more stable product with the more substituted double bond.

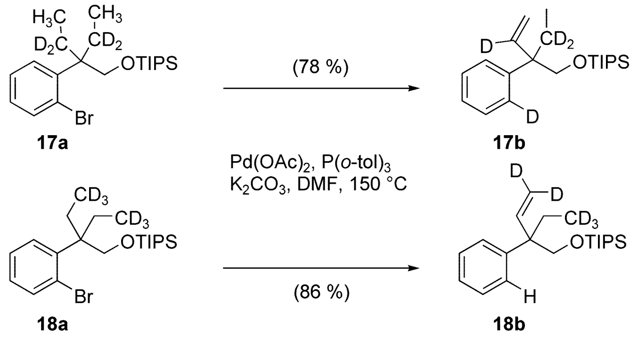
Finally, the two-carbon homologated compounds **15a** and **16a** were reacted in order to determine whether the conjugated double bond was formed preferentially as a consequence of thermodynamic factors. In the case of *gem*-dimethyl bromide **15a**, the benzocyclobutene **15b** was formed exclusively in 78 % yield. Similarly, with *gem*-diethyl bromide **16a**, both olefins **16b** and **16c** were formed (80 % yield), but in a 86:14 ratio in favor of the nonconjugated product **16b**. These data suggest again that steric factors prevail in this reaction.

A plausible mechanism for the formation of olefins (when alkyl groups have at least two carbons) or benzocyclobutenes (when at least one alkyl group is a methyl) is shown in Scheme 1. The oxidative addition of Pd^0 to phenyl bromide **A** gives rise to intermediate **B**, which would undergo C–H activation of one of the alkyl C–H bonds to give either the five-membered palladacycle **C** or the six-membered palladacycle **D**. If a methyl group is present ($R^1 = H$), intermediate **C** is formed and gives directly benzocyclobutene **F** by reductive elimination. If alkyl groups having at least two carbons are present ($R^1 = Me$, Et), both five- and six-membered palladacycles can explain the formation of olefin **G** by β-elimination followed by reductive elimination from the palladium hydride intermediate **E**.[11]



Scheme 1. Mechanistic proposal for the formation of olefins and benzocyclobutenes.

In order to determine whether palladacycle **C** or **D** is involved in the formation of olefin **G**, the dehydrogenation was conducted with deuterated bromides **17a** and **18a** (Scheme 2). The corresponding olefins **17b** and **18b**, having



Scheme 2. Deuterium-labeling experiments.

a deuterium atom and an hydrogen atom, respectively, in the place of the bromine, were obtained in good yield.[12] These experiments show that the deuterium or hydrogen atom incorporated on the benzene ring originated from the carbon α to the quaternary benzylic position and lends support for the six-membered palladacycle intermediate **D** in Scheme 1. The observation of terminal olefins **13d** and **14c** in the dehydrogenation of propyl-containing substrates (Table 2) also argues in favor of intermediate **D** (with β-elimination from the terminal position).[11] Thus, it appears that benzocyclobutenes **F** and olefins **G** are formed initially through C–H activation at the α- and β-benzylic position, respectively, (**B**→**C** or **D**). When the competition between the two routes leading to **F** and **G** is allowed (Table 2, entries 12, 15), the route leading to cyclobutarene **F** is preferred, perhaps because of steric factors or because in this case no β-elimination step is involved.

In conclusion, we have reported a novel palladium-catalyzed C–H activation of *gem*-dialkyl groups on bromo- and iodobenzenes to give olefins or benzocyclobutenes. This process is simple, efficient, and regioselective and utilizes common reagents. The reaction products are valuable molecules containing a quaternary stereocenter as well as a new chemical function (olefin, cyclobutene) potentially useful for further reactions. A full description of the synthesis and physical data of reaction substrates and products as well as further development of the methodology will be reported in due course.

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Keywords: alkenes · C–H activation · catalysis · dehydrogenation · palladium

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[1] For reviews, see: a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; b) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; c) Y. Guari, S.

Sabo-Etienne, B. Chaudret, *Eur. J. Inorg. Chem.* **1999**, 1047–1055; d) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514.

[2] a) J. Hassa, M. Sévignon, C. Gozzi, E. Schultz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; b) A. M. Echavarren, B. Gómez-Lor, J. J. González, O. de Frutos, *Synlett* **2003**, 585–597.

[3] a) G. Dyker, *Angew. Chem.* **1992**, *104*, 1079–1081; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1023–1025; b) G. Dyker, *J. Org. Chem.* **1993**, *58*, 6426–6428; c) G. Dyker, *Chem. Ber.* **1994**, *127*, 739–742; d) G. Dyker, *Angew. Chem.* **1994**, *106*, 117–119; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 103–105.

[4] M. Catellani, E. Motti, S. Ghelli, *Chem. Commun.* **2000**, 2003–2004.

[5] a) J. L. Portscheller, H. C. Malinakova, *Org. Lett.* **2002**, *4*, 3679–3681; b) J. L. Portscheller, S. E. Lilley, H. C. Malinakova, *Organometallics* **2003**, *22*, 2961–2971.

[6] a) B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 11856–11857; b) B. Sezen, R. Franz, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 13372–13373.

[7] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313–348.

[8] Representative procedure: A dry resealable Schlenk tube containing a magnetic rod was charged with bromide **6a** (145 mg, 0.48 mmol), palladium acetate (11 mg, 0.048 mmol), tri-*o*-tolylphosphane (30 mg, 0.097 mmol), and potassium carbonate (134 mg, 0.97 mmol). The Schlenk tube was evacuated and backfilled with argon twice, then capped with a rubber septum. Dry *N,N*-dimethylformamide (3 mL) was injected under argon, then the septum was replaced by a screwcap and the mixture was stirred at 150 °C (preheated oil bath) for 30 min. After cooling, the mixture was diluted with diethyl ether and filtered through celite. The organic solution was washed with water, dried over magnesium sulfate, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, heptanes) to afford olefin **4b** as an oil (88 mg, 83 %); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.86$ (t, $J = 7.3$ Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 2.18 (m, 2H), 4.18 (q, $J = 7.2$ Hz, 2H), 5.03 (d, $J = 17.7$ Hz, 1H), 5.31 (d, $J = 11.1$ Hz, 1H), 6.38 (dd, $J = 17.7$, 10.8 Hz, 1H), 7.27 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 9.2$, 14.0, 29.3, 57.9, 60.8, 115.9, 126.6, 127.3, 128.1, 139.6, 142.0, 174.3 ppm; IR (film) $\tilde{\nu} = 2975$, 1729 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}NaO_2$ $[(M+Na)^+]$: 241.1204, found: 241.1212.

[9] a) C. Pascal, J. Dubois, D. Guénard, F. Guéritte, *J. Org. Chem.* **1998**, *63*, 6414–6420; b) C. Pascal, J. Dubois, D. Guénard, L. Tchertanov, S. Thoret, F. Guéritte, *Tetrahedron* **1998**, *54*, 14737–14756.

[10] a) G. Mehta, S. Kotha, *Tetrahedron* **2001**, *57*, 625–659; b) A. K. Sadana, R. K. Saini, W. E. Billups, *Chem. Rev.* **2003**, *103*, 1539–1602.

[11] In the case of propyl groups ($R^1 = Et$), it could be possible that the terminal methyl C–H bond is activated selectively to form a seven-membered palladacycle giving the terminal olefin, and that isomerization of the double bond occurs afterwards to give the mixture of olefins.

[12] Selected physical data: **17b**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (s, 3H), 0.99 (m, 21H), 3.86 (d, $J = 9.9$ Hz, 1H), 3.96 (d, $J = 9.3$ Hz, 1H), 5.02 (m, 1H), 5.21 (m, 1H), 7.15–7.33 ppm (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 8.5$, 12.0, 18.0, 26.5, 50.1, 68.7, 113.8, 125.9 (*C*H-Ar), 127.3 (*C*D-Ar), 127.7 (*C*H-Ar), 127.8 (*C*H-Ar), 128.0 (*C*H-Ar), 143.3, 144.2 ppm (*C*q-Ar); HRMS (EI) calcd for $C_{18}H_{25}D_4OSi$ $[(M-iPr)^+]$: 293.2239; found: 293.2242. **18b**: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.98$ (m, 21H), 1.91 (m, 2H), 3.86 (d, $J = 8.8$ Hz, 1H), 3.95 (d, $J = 9.2$ Hz, 1H), 6.01 (m, 1H), 7.14–7.35 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 8.5$, 11.9, 17.9, 26.8, 50.1, 68.6, 113.9, 125.8 (*C*H-Ar), 127.7 (*C*H-Ar), 127.9 (*C*H-Ar), 143.2, 144.1 ppm (*C*q-Ar); HRMS (EI) calcd for $C_{18}H_{24}D_5OSi$ $[(M-iPr)^+]$: 294.2302; found: 294.2312.