

Alkenes were distilled and treated with activated alumina to remove impurities and alkyl hydroperoxide. The reaction was carried out in a glass vial or a round-bottomed flask containing a magnetic stir bar under 1 atm of molecular oxygen as described previously.^[21] 2-Cyclohexen-1-one was usually used as an internal standard. The homogeneous reaction solution was periodically sampled and analyzed by gas chromatography on a TC-WAX capillary column and by NMR spectroscopy. The amounts of oxygen consumed were measured with a gas burette. It was confirmed for the oxygenation of cyclooctene that no reaction proceeded without catalysts. Turnover numbers were calculated as moles of products per mole of **1**.

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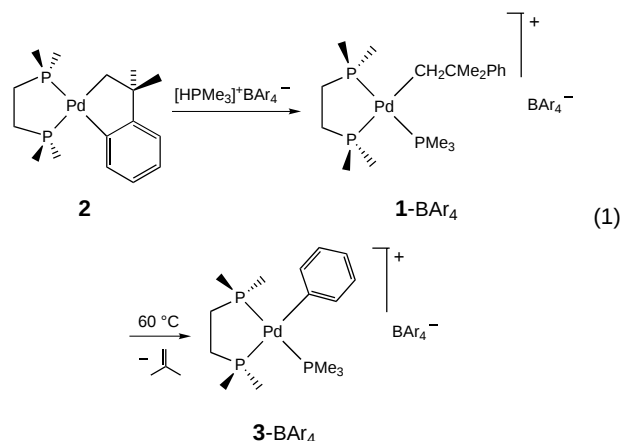
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Cleavage of the C_{alkyl}–C_{aryl} Bond of [Pd–CH₂CMe₂Ph] Complexes**

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The cleavage and functionalization of strong C–C single bonds^[1] by transition metal compounds is an important transformation,^[2–6] which is relevant to Ziegler–Natta catalysis^[7] and to other organometallic processes.^[8, 9] Aryl elimination by activation of a β -C_{alkyl}–C_{aryl} bond^[5] is the microscopic reverse of the migratory insertion of an alkene into a M–C_{aryl} bond, a relevant step of the Heck reaction^[8] and of the SHOP process.^[9] Herein we report on the conversion of a [Pd–CH₂CMe₂Ph]⁺ moiety into the corresponding phenyl derivative, [Pd–Ph]⁺, and the subsequent functionalization of the latter by conventional C₂H₄ migratory insertion chemistry to produce C₆H₅CH=CH₂.

The cationic complex [Pd(CH₂CMe₂Ph)(dmpe)(PMe₃)]⁺ (**1**) (dmpe = Me₂PCH₂CH₂PMe₂) can be generated by reacting the palladacycle [PdCH₂CMe₂-*o*-C₆H₄](dmpe)] (**2**)^[10] with [HPMe₃]⁺BAR₄[–] (Ar = 3,5-C₆H₃(CF₃)₂). At 60 °C it under-



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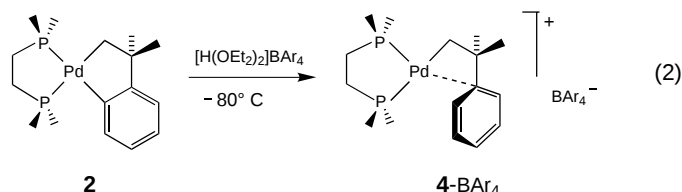
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Supporting information (kinetic data and reaction rates for the transformation **1** → **3** catalyzed by **4**) for this article is available on the WWW under <http://www.angewandte.com> or from the author.

goes very slow thermolysis ([Eq. (1)], $t_{1/2} \approx 60$ h) to give the phenyl derivative **3**-BAR₄^[11] along with isobutene (GC-MS analysis). A formally three-coordinate cationic complex [Pd(CH₂CMe₂Ph)(dmpe)]⁺ (**4**), in which the highly electrophilic metal is stabilized by an auxiliary π, η^1 interaction with the *ipso*-carbon atom of the phenyl group appears as a likely intermediate.^[12] Hence, we have prepared the BAR₄[−] salt of this cation [Eq. (2)] by the low-temperature protonation of



the palladacycle **2** with [H(OEt₂)₂]BAR₄. Similarly to related palladium metallacycles^[12] selective cleavage of the Pd–C_{aryl} bond is observed, leading to **4**-BAR₄ in quantitative yield [Eq. (2)]. Spectroscopic data for **4** (see Experimental Section) are in accord with the proposed structure. In particular, the *ipso*-carbon atom displays a ¹³C{¹H} signal at $\delta = 119.6$ (dd, ²J_{C,P} = 6, 12 Hz). This matches closely the corresponding resonance in the PMe₃ analogue and in the structurally related, X-ray characterized compound [Pd(CH₂CMe₂-Ph)(OTf)(PMe₃)]^[12] ($\delta = 123.5$, dd, ²J_{C,P} = 4, 12 Hz and $\delta = 21.8$, d, ²J_{C,P} = 13 Hz, respectively). The above observation is in agreement with the existence of a Pd–C_{ipso} π, η^1 bonding interaction, which was confirmed by an X-ray structure determination^[13] (Figure 1). Other Pd complexes that display

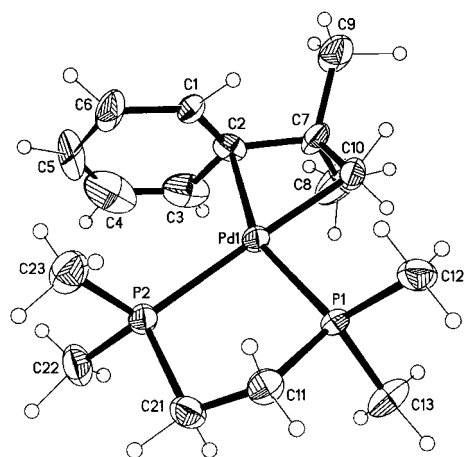
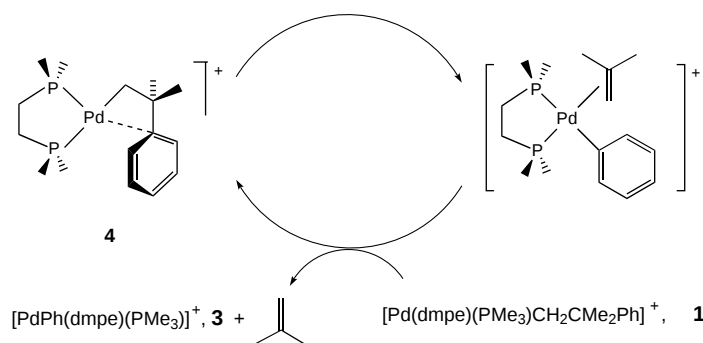


Figure 1. Structure of the cation **4** (ORTEP view; the BAR₄[−] counterion has been omitted for clarity). Selected bond lengths [Å] and angles [°]: Pd1–C10 2.065(7), C7–C10 1.531(11), Pd1–C2 2.343(6), Pd1–P1 2.220(2), Pd1–C1 2.511(8), Pd1–P2 2.363(2), C2–C7 1.530(10); P1–Pd1–P2 86.67(7), Pd1–C10–C7 98.3(5), C2–Pd1–C10 66.2(3), Pd–C2–C7 87.5(4).

similar Pd...aryl interactions (either π, η^1 or π, η^2) have been reported.^[14] It is also worth noting that the structural data obtained for **4** are strikingly similar to those calculated by Rösch et al.^[15] by density functional theory (DFT) methods for [Pd(CH₂CH₂Ph)(C(NH₂)₂)]⁺, which was considered as a model for the insertion step of the Heck reaction.

Complex **4** undergoes intricate thermolysis in CH₂Cl₂, THF, or Et₂O as the solvent to give isobutene, along with C₆H₆,

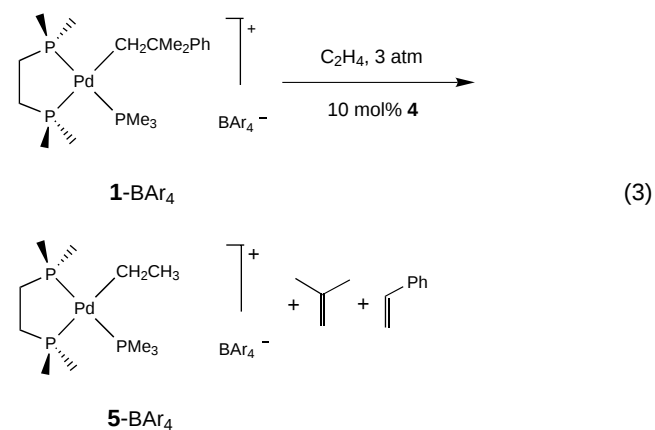
C₆H₅CMe₃, and smaller amounts of other unidentified volatile materials. An uncharacterized mixture of inorganic compounds is also formed. This complexity is, however, foreseeable since the extrusion of isobutene from **4** would generate a highly labile, thermally unstable 14-electron phenyl complex, [PdPh(dmpe)]⁺. Notwithstanding, we have found that the β -Ph elimination reaction of **1** can be made catalytic in the presence of **4** (10 mol %). Thus, a sample of compound **1** converts cleanly under these conditions into [Pd(Ph)(dmpe)(PMe₃)]⁺ (**3**) and CH₂=CMe₂ (Scheme 1). Kinetic measurements show a zero-order dependence on

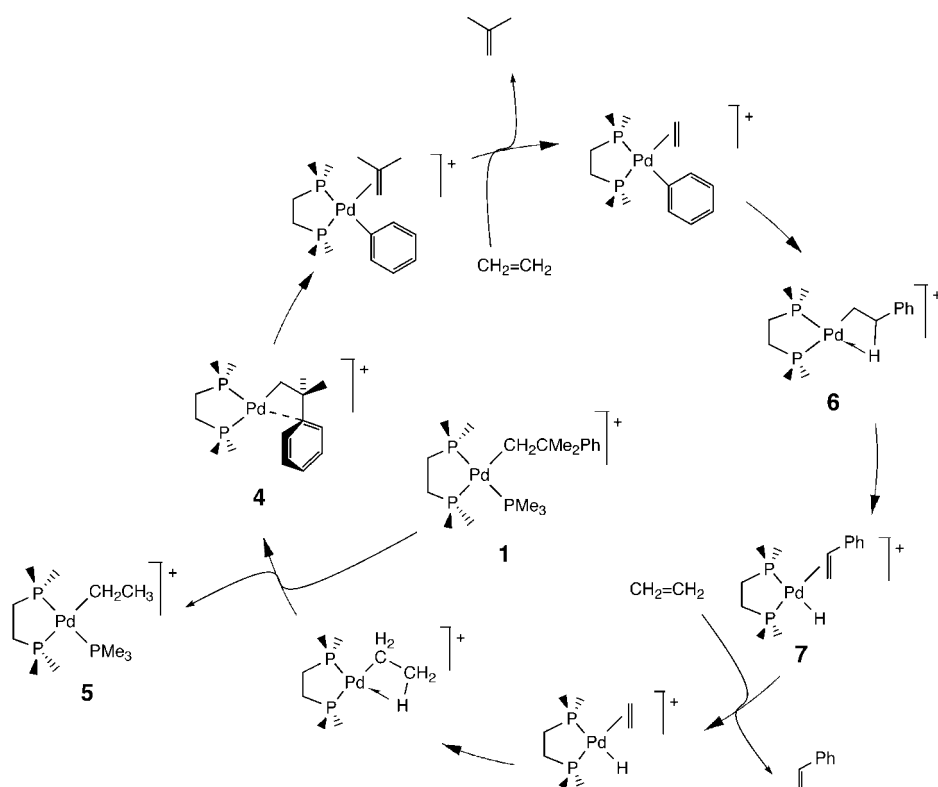


Scheme 1. β -Ph elimination reaction of **1** in the presence of **4**.

1, while the concentration of **4** remains steady during the process. The apparent rate constant exhibits a direct dependency on the concentration of **4**, a value of $2.7 \times 10^{-4} \text{ s}^{-1}$ has been obtained at 60 °C for the overall first-order rate constant. It seems likely that C–C bond cleavage is the rate-determining step.

As already pointed out, the β -Ph elimination can be considered as the microscopic reverse of the olefin insertion step of the Heck reaction. Whereas it is evident that the electrophilicity of the cationic palladium center has a decisive influence in the deinsertion, it seems probable that the irreversibility of this process is a consequence of the steric requirements posed by the insertion of isobutene into the Pd–Ph bond. In accord with these assumptions, C₂H₄ is able to induce the reverse reactivity, and undergoes insertion under the conditions of Equation (3) to produce a mixture of the ethyl derivative **5**, isobutene, and styrene. Scheme 2 depicts a



Scheme 2. Proposed reaction pathway for the overall transformation of **1** to **5**.

likely reaction pathway for the overall transformation. Like in the Heck reaction, the phenethyl intermediate **6**, undergoes facile β -H elimination. In our base-free system, the $[\text{Pd}-\text{H}]^+$ complex inserts another molecule of C_2H_4 and gives rise to a $[\text{Pd}-\text{Et}]^+$ group which becomes stabilized by the coordination of PMe_3 .^[16] It is interesting to note here the ability of the dmpe ligand to promote the olefin extrusion or insertion as compared to the corresponding PMe_3 system.^[12] This might be rationalized on the basis of the smaller steric hindrance posed by the dmpe ligand to the planar transition state required for the mentioned processes.^[15, 17]

In summary, we have shown that the unstrained $\text{C}_{\text{alkyl}}-\text{C}_{\text{aryl}}$ bond of the neophyl ligand becomes readily activated when bonded to an electrophilic palladium center. Effecting this thermal activation under ethylene allows the coupling of this molecule with the phenyl fragment that results from the cleavage of the $\text{C}_{\text{alkyl}}-\text{C}_{\text{aryl}}$ bond to produce styrene along with isobutene.

Experimental Section

4: $[\text{H}(\text{OEt})_2]\text{BAR}_4$ (0.22 g, 0.25 mmol) was added to a cooled (-30°C) solution of the metallacyclic complex **2**^[10] (0.97 g, 0.25 mmol) in CH_2Cl_2 (20 mL). After the cooling bath had been removed, the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum and the residue was extracted with Et_2O (20 mL). The product was isolated as colorless crystals by partial concentration of the solvent, addition of some petroleum ether, and cooling to -20°C overnight. Yield: 0.28 g, 91%. Elemental analysis (%) calcd for $\text{C}_{48}\text{H}_{41}\text{BF}_4\text{P}_2\text{Pd}$: C 46.01, H 3.30; found: C 46.08, H 3.29; ^1H NMR (CD_2Cl_2 , 20°C): δ = 1.09 (dd, $^3J_{\text{H,P}}$ = 5.5, 8.1 Hz, 2H; CH_2), 1.37 (s, 6H; CMe_2), 7.42 (m, 1H; CH arom.), 7.67 (m, 2H; CH arom.), 7.73 (m, 2H; CH arom.); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C) AX

spin system, $\delta_{\text{A}} = 13.6$, $\delta_{\text{X}} = 32.7$, $J_{\text{AX}} = 29.6$ Hz; $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C): δ = 18.9 (dd, $^2J_{\text{C,P}} = 19$, 34 Hz; CH_2), 32.7 (d, $^4J_{\text{C,P}} = 5$ Hz; CMe_2), 41.6 (d, $^3J_{\text{C,P}} = 3$ Hz; CMe_2), 119.6 (dd, $^2J_{\text{C,P}} = 6$, 12 Hz; C_q arom.), 122.2 (d, $J_{\text{C,P}} = 2$ Hz; CH arom.), 128.6 (s; CH arom.), 133.1 (s; CH arom.).

5: A solution of **1** (0.33 g, 0.25 mmol), **4** (0.030 g, 0.025 mmol), and toluene (50 μL ; internal GC standard) in diethyl ether (20 mL) was transferred to a Fischer–Porter pressure reactor, charged with ethylene (3 bar) and heated at 60°C for 24 h. GC analysis of the resulting yellow solution revealed the formation of styrene (0.25 mmol), isobutene (0.20 mmol), *tert*-butylbenzene (ca. 0.03 mmol), and minor amounts of unidentified volatile products. A $^{31}\text{P}\{^1\text{H}\}$ spectrum of this crude mixture showed full conversion to **5** (ca. 90% purity). The solution was evaporated and the residue extracted with petroleum ether and filtered. Evaporation to dryness left the crude product as an oily solid, which was obtained as pale green crystals by recrystallization from a petroleum ether/ Et_2O (2:1) mixture. Yield: 0.18 g, 60%. Elemental analysis (%) calcd for $\text{C}_{43}\text{H}_{42}\text{BF}_4\text{P}_2\text{Pd}$: C 42.16, H 3.46; found: C 42.21, H 3.27; ^1H ^{31}P NMR (CD_2Cl_2 , 20°C): δ = 1.11 (t, $^3J_{\text{H,H}} = 8.0$ Hz, 3H; CH_3CH_2), 1.41 (q, 2H; CH_3CH_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C): δ = -18.6 (dd, $^2J_{\text{PP}} = 386$, 39 Hz), 16.1 (dd, $^2J_{\text{PP}} = 39$, 26 Hz), 30.1 (dd, $^2J_{\text{PP}} = 386$, 26 Hz);

$^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C): δ = 11.9 (d, $^2J_{\text{C,P}} = 87$ Hz; CH_2), 15.2 (m, partially hidden by dmpe signals, CH_3).

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A Readily Available, Highly Potent E-Selectin Antagonist

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Excessive infiltration of leukocytes from blood vessels into surrounding tissues can cause acute or chronic inflammatory disorders such as reperfusion injuries, stroke, psoriasis, rheumatoid arthritis, or respiratory diseases.^[1] An early step in the cascade of events which finally leads to leukocyte extravasation—their rolling on activated endothelial cells—is mediated by selectin–carbohydrate interactions.^[2] The adverse effects could thus be prevented by selectin blockade. The tetrasaccharide sialyl Lewis^x (**1**, Scheme 1) is a weak^[3] ligand for E-, P- and L-selectin^[4] and became a lead to discover more potent inhibitors.^[5] To assess our E-selectin antagonists we used a static, cell-free ligand-binding assay which measures inhibition under equilibrium conditions.^[6] Sialyl Lewis^x ($\text{IC}_{50} = 1000\text{--}2000$ μM) was tested on each plate to allow direct comparison of data from different test plates. Thus, we obtained relative IC_{50} values (see Table 1). To further profile our compounds we developed a dynamic in vitro assay which allows to monitor E-selectin-dependent rolling of neutrophils on activated endothelial cells under shear stress and, hence, mimics the nonequilibrium in vivo conditions^[7] (see Table 1). Recently we described the promising E-selectin inhibitor **2** (Scheme 1), which showed good activities in both the static (rel. $\text{IC}_{50} = 0.030$) and the dynamic ($\text{IC}_{50} = 10$ μM) assay.^[8] Here we report on our search for simplified analogues of **2** which led to the discovery of **3** (Scheme 1) being the most potent small-molecule E-selectin antagonist to date ($\text{IC}_{50} = 1\text{--}2$ μM in the dynamic flow assay).

To simplify **2** we designed compound **4** (Scheme 1) with a glucal-derived moiety instead of the glucosamine residue. Furthermore, the benzamide in **2** was replaced by the corresponding anilide. We expected compound **4** to be readily available from the earlier described advanced intermediate **5**, which can be assembled from building blocks **6–9** in eight steps in an overall yield of $> 30\%$ (Scheme 2).^[9] The primary hydroxyl group of **5** was oxidized to yield the carboxylic acid **10**, which was then coupled with 3,4-dimethoxyaniline to give **11** (Scheme 2). Hydrogenolytic removal of the benzyl protecting groups proceeded smoothly (**12**), but subsequent cleavage of all three benzoyl groups to obtain **4** failed. Transesterification using NaOMe (1.1 equiv) gave clean removal of the gal-4 and the gal-6 benzoyl groups leading to partly protected compound **13**^[10] (Scheme 2). The gal-2 benzoate remained untouched. Harsher conditions (aqueous NaOH; 50°C) resulted in decomposition, most probably

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