A Dramatic Effect of the Reaction Conditions on the Course of a Palladium-Catalyzed Cyclization of an Alkene Bearing a Vinyl Bromide and a Nucleophile: A New Route to the *trans*-Hydrindane System

Isabelle Coudanne, Jaume Castro and Geneviève Balme *

Laboratoire de chimie organique I, associé au CNRS, Université Claude Bernard, CPE, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France.

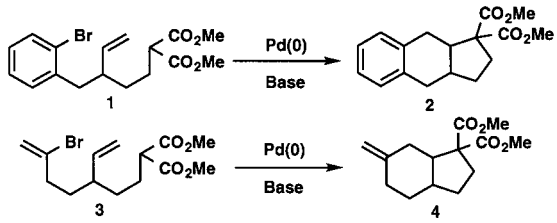
Fax: Int.33.4.72.43.12.14. E-mail: balme@univ-lyon1.fr

Received 3 May 1998

Abstract: Upon treatment with catalytic Pd(dppe) in the presence of KH, the malonate derivative **3** underwent a Wacker-type cyclization leading exclusively to compound **4** having the *trans*-hydrindane system. However, the course of the cyclization is dramatically dependent on the reaction conditions, mainly on the nature of the base. In the presence of a carbonate, a quaternary ammonium salt and the catalytic system ($Pd(OAc)_2$ + PPh_3) the cyclization of the same substrate **3** led only to compounds resulting from an initial Heck reaction of the vinyl bromide on the neighbouring olefin.

The hydrindane framework is found in many biologically active natural products and therefore numerous strategies for the construction of this skeleton have been reported.[1]

In light of the excellent stereocontrol inherent in the cyclization[2] of the malonate derivative **1** using the "Wacker-type" reaction developed in our group, it was of interest to determine whether a *trans*-hydrindane system might be prepared from **3** in a stereocontrolled fashion using this methodology (Scheme 1).

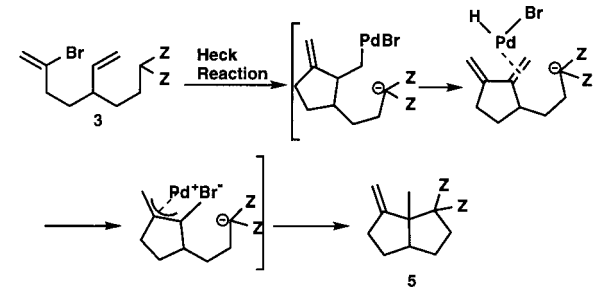


Scheme 1

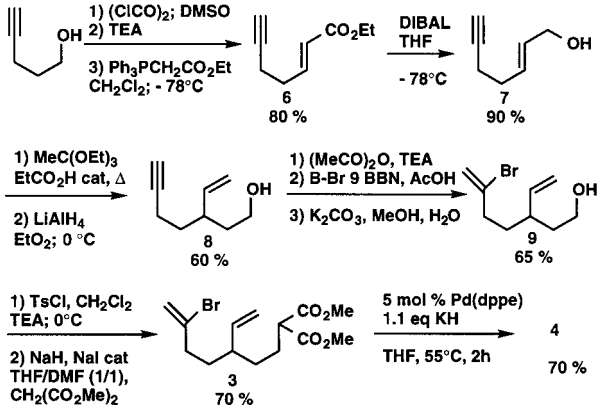
However, in earlier papers,[3] we reported that this palladium-catalyzed cascade cyclization could compete with the classical intramolecular Heck reaction by slightly changing the nature of the nucleophile. [4]

Therefore, we reasoned that, from the same substrate **3**, it would also be possible to obtain another bicyclic compound by favoring the competing Heck reaction. Indeed we hoped that, since 5-*exo* cyclizations are usually preferred to 6-*endo* in intramolecular Heck reactions,[5] the palladium mediated addition of the vinyl bromide to the double bond via an *exo* mode would first occur followed by a palladium migration to form a π-allylpalladium intermediate. An intramolecular displacement of palladium by the carbon nucleophile would lead to bicyclic compound **5** (Scheme 2).

The requisite vinyl bromide **3** was prepared from pent-4-yn-1-ol as illustrated in Scheme 3. Oxidation under Swern conditions followed by *in situ* Wittig condensation[6] afforded the ester **6** which was reduced with diisobutylaluminium hydride to provide the allyl alcohol **7**. Then the ester obtained by thermal Claisen-Johnson rearrangement[7] was reduced with lithium aluminium hydride. The resulting alcohol **8** was then acylated with acetic anhydride in the presence of triethylamine. Bromoboration of the carbon-carbon triple bond of this acetate with commercial B-Br-9-BBN followed by protonolysis with acetic acid[8] and subsequent treatment with potassium carbonate in methanol gave the



Scheme 2



Scheme 3

vinyl bromide **9**. Mesylation of this alcohol followed by reaction with the sodium enolate of dimethyl malonate gave the vinyl bromide **3**.[9]

With cyclization precursor **3** in hand, we first focused our attention on the construction of the hydrindane system.

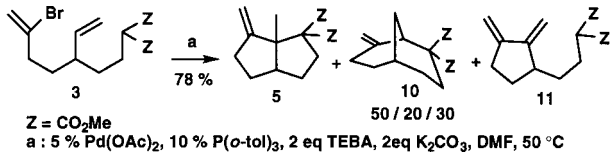
Therefore, taking advantage of our previous experience, the same reaction conditions[1] as used for **1** (1.1 equivalent of KH, 5 mol% Pd(dppe), THF, 55°C) were applied to substrate **3**. These conditions provided the bicyclic compound **4** as a single isomer and no traces of any other product could be detected by GC or NMR.

The structure of **4** was established by NMR experiments[10] in deuterobenzene at 300 MHz and confirmed by an X-ray crystallographic analysis.[11]

In agreement with the results obtained in the palladium-promoted cyclization of compound **1**, the annelation of the vinyl bromide **3** was highly diastereoselective and afforded only the *trans*-hydrindane **4** in 70% yield (Scheme 5).

Having established that the efficient synthesis of the *trans*-hydrindane skeleton could be effected under these conditions, we next turned our attention to the synthesis of the biquinane **5** by favoring the Heck reaction. We considered altering the reaction conditions for the cyclization of compound **3** in order to determine whether the intramolecular version of Weinreb's[4] three component reaction would

work on this compound. Then, using the reaction conditions developed by that group[4b] (5% $Pd(OAc)_2$, 10% P(*o*-tol)$_3$, 1.5 equiv. NaH, 2 equiv *n*-Bu_4Cl in DMF at 50°C) the attempted cyclization of substrate **3** failed; the NMR and GC/MS spectra of the crude reaction product revealed the presence of a major product identified as **4** along with three minor untractable products. In order to enhance the formation of compounds resulting from the Heck reaction i.e. to favour the alkene insertion of the organopalladium halide over the nucleophilic attack of the malonate, the substrate **3** was subjected to reaction conditions developed by Jeffery[12] and slightly modified by Larock[13] in which weaker bases than sodium hydride are used. So, by only changing the nature of the base ($KHCO_3$ instead of NaH) the cyclization of the dimethyl malonate derivative **3** gave a 50/20/30 mixture[14] of bicyclic compounds **5** and **10** along with the diene **11** in 78 % combined yield. In this case, compound **4** was not formed (Scheme 4). Our efforts to exclusively obtain compound **5**, resulting from the Heck reaction were only partially successful due to two competitive reactions. Indeed, the formation of the bridged compound resulted from an initial 6-*endo* ring closure followed by a palladium migration to form a π-allylpalladium intermediate whereas that of the diene was due to the slow nucleophilic attack of the π-allyl intermediate leading to a competing β-hydride elimination.

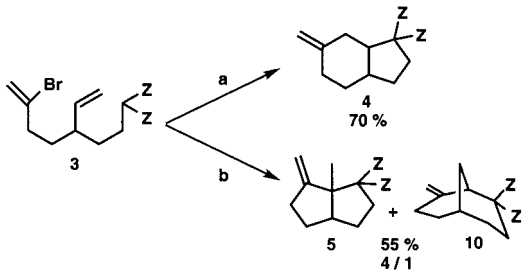


Scheme 4

Numerous attempts were realized in order to improve the chemoselectivity in favor of product **5** and to prevent or reduce the formation of diene **11**. Along this line, different bases (K_2CO_3, $KHCO_3$, Na_2CO_3, $NaHCO_3$), solvents (THF, DMSO, NMP, DMF, CH_3CN), palladium catalysts ($Pd(OAc)_2$, $Pd(dba)_2$, $Pd(PPh_3)_4$) with or without added phosphine ligand (PPh_3, P(*o*-tol)$_3$) in the presence or absence of quaternary ammonium salts were screened. Best results were obtained by using 5% $Pd(OAc)_2$ as the palladium source with 10% PPh_3 as ligand in the presence of 2 equiv. of a quaternary ammonium salt (benzyltriethylammonium chloride or TEBA) and 2 equiv. of carbonate bases (K_2CO_3 or $KHCO_3$) in DMF at 60°C. These conditions gave an inseparable 70/15/15 mixture of the three compounds **5**, **10** and **11** in 85% combined yield. Fortunately, as intermolecular Diels-Alder reactions of bis-exocyclic 1,3-dienes are well known[15] the treatment of the mixture with dimethyl acetylenedicarboxylate (DMAD) in toluene allowed to separate **11** from the two bicyclic products. This produced[16] a 4:1 mixture of the fused and the bridged bicyclic compounds **5** and **10** in a combined yield of 55 %.

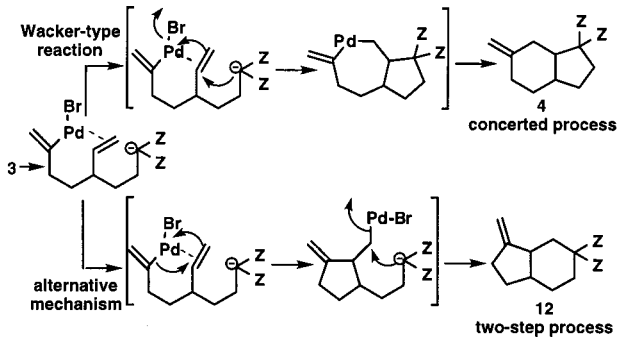
In conclusion, we have shown that the palladium tandem catalyzed biscyclization (Wacker-type reaction) can be performed on the dimethyl malonate derivative **3** providing a new route to the *trans*-hydrindane system. By changing the reaction conditions, it was possible, from the same substrate **3** to obtain selectively compounds resulting from an initial Heck reaction.

Moreover, we observed that there is often a misunderstanding[17] concerning the mechanism of the new reaction that we have been developing in our group. As far as we are concerned, we explained the result of the cyclization by an activation of the olefinic double bond by complexation of the electrophilic palladium species which initiates the



Scheme 5

nucleophilic attack of the malonate. Then, a reductive elimination of the palladacycloheptane derivative lead to the cyclic product **4**[18] (Scheme 6). An alternative pathway has been considered by some authors.[19] They suggested that it might be a two-step reaction with insertion of the alkene (Heck reaction) giving an alkylpalladium derivative which would then be attacked by the malonate without undergoing elimination of β-hydrogen. According to this mechanism, the cyclization of compound **3** would lead to another bicyclic compound **12**. Thus, the alternative hypothesis on the reaction path can undoubtedly be excluded.



Scheme 6

In addition to its synthetic interest, this study has then clarified the mechanism of the biscyclization reaction in ruling out this alternative mechanism.

References and Notes

(1) (a) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 6745. (b) Tamao, K.; Nagata, Y. Ito; Maeda, K.; Shiro, M. *Synlett* **1994**, 257. (c) Satoh, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 2278 and references cited therein. (d) Shibasaki, M.; Boden, J.D.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.

(2) Coudame, I.; Balme, G. *Synlett* **1998**, 998.

(3) (a) Vittoz, P.; Bouyssi, D.; Traversa, C.; Goré, J.; Balme, G. *Tetrahedron Lett*. **1994**, *35*, 1871. (b) Bouyssi, D.; Coudanne, I.; Uriot, H.; Goré, J.; Balme, G. *Tetrahedron Lett*. **1994**, *35*, 1871.

(4) Interestingly, recent studies by Weinreb's group have shown that a novel variation of the Heck reaction can be applied on substrates which contain a vinyl halide, an olefin and a nucleophile leading to various carbo- and heterobicyclic compounds. Nevertheless, it is important to note that the Weinreb's three component reactions were never applied to substrates which could be involved in the

Wacker-type reaction: (a) Nylund, C.S.; Klopp, J.M.; Weinreb, S.M. *Tetrahedron Lett.* **1994**, *35*, 4287. (b) Nylund, C.S.; Smith, D.T.; Klopp, J.M.; Weinreb, S.M. *Tetrahedron* **1995**, *51*, 9301.

(5) (a) Shi, L.; Narula, C.K.; Mak, K.T.; Kao, L.; Xu, Y.; Heck, R.F. *J. Org. Chem.* **1983**, *48*, 3894. (b) Grigg, R.; Stevenson, P.; Worakun, T.J. *Tetrahedron* **1988**, *44*, 2033. (c) Meyer, F. E.; Ang, K.H.; Steinig, A.G.; de Meijere, A. *Synlett* **1994**, 191. (d) Henniges, H.; Meyer, F.E.; Schick, U.; Funke, F.; Parsons, P.J.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11503.

(6) Ireland, R.E.; Norbeck, D.W. *J. Org. Chem*. **1985**, *50*, 2198.

(7) Ziegler, F.E. *Chem. Rev.* **1988**, *88*, 1423.

(8) Hara, S.; Dojo, H.; Takinani, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(9) The product ratio was determined by integration of the vinyl proton peaks in the ^{1}H NMR spectrum.

(10) *Experimental procedure for the « Wacker-type reaction » (preparation of compound* **4***)*: on the one hand, a suspension of 50% KH in mineral oil (122 mg, 1.3 mmol) was washed with pentane (2 x 20 ml) and then suspended in anhydrous THF (5 ml). The malonate derivative **3** (300 mg, 0.9 mmol),was added and the resultant mixture was stirred at room temperature for 15 min. On the other hand, the palladium(0) complex was preformed at 50°C in THF (3ml) by reaction of $Pd(OAc)_2$ (10.1 mg, 0.045 mmol, 5 mol%) and dppe (18 mg, 0.045 mmol, 5 mol%). Then the addition of this Pd(0) solution was made at room temperature via a cannula on the malonate anion prepared above and the reaction mixture was heated at 55°C and stirred at this temperature for 2 hours. The solution was then filtered through a short pad of silica gel and the solvent removed under reduced pressure. The residue was purified by flash chromatography with petroleum ether/ Et_2O 85/15 to afford **4** as a colorless solid (160 mg, 70%).
Compound **4**: ^{1}H -NMR (300 MHz, C_6D_6, δ ppm) (assignment facilitated by selective irradiations) 4.72 (2H, m); 3.40 (3H, s); 3.30 (3H, s); 2.96 (1H, dd, *J*=12.35, 2.3 Hz); 2.72 (1H, dt, *J*=14.0, 8.80 Hz); 2.18 (1H, dq, *J*=13.60, 2.05 Hz); 2.14 (1H, td, *J*=11.95, 2.32 Hz); 2.03 (1H, ddd, *J*=13.3, 10.6, 2.3 Hz); 1.89 (1H, t, *J*=12.8 Hz); 1.8-1.7 (1H, m); 1.7-1.6 (3H, m); 1.5-1.0 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$) 173, 172.2, 147.8, 109.4, 61.7, 52.8, 52.4, 52.1, 42.7, 37.2, 34.2, 33.1, 32.3, 30.9. MS, m/z (relative intensity): 220 (23), 192 (43), 160 (31), 145 (27), 133 (46), 120 (100), 106 (96), 91 (49), 77 (27), 59 (36), 41 (29), 39 (20).

(11) Bond distances (Å) and bond angles (°) of compound 4: O1-C11 1.201(3), C1-C10 1.573(4), C4-C6 1.510(5), O2-C11 1.319(4), C1-C11 1.519(4), C6-C7 1.540(4), O2-C12 1.454(4), C1-C13 1.507(4), C7-C8 1.517(4), O3-C13 1.197(3), C2-C3 1.518(3), C8-C9 1.550(4), O4-C13 1.316(3), C2-C8 1.530(4), C9-C10 1.535(5), O4-C14 1.456(4), C3-C4 1.514(4), C1-C2 1.563(4), C4-C5 1.314(4), C11-O2-C12 115.7(3), C3-C2-C8 111.4(2), C8-C9-C10 103.0(3), C13-O4-C14 116.4(2), C2-C3-C4 108.3(2), C1-C10-C9 107.0(2), C2-C1-C10 103.1(2), C3-C4-C5 122.9(3), O1-C11-O2. 124.0(3), C2-C1-C11 109.6(2), C3-C4-C6 115.2(2), O1-C11-C1 124.6(3), C2-C1-C13 112.1(2), C5-C4-C6 121.9(3), O2-C11-C1 111.3(2), C10-C1-C11 111.0(2), C4-C6-C7 111.2(3), O3-C13-O4 123.0(3), C10-C1-C13 110.3(2), C6-C7-C8 109.0(3), O3-C13-C1 125.4(3), C11-C1-C13 110.5(2), C2-C8-C7 110.6(2), O4-C13-C1 111.5(2), C1-C2-C3 119.4(2), C2-C8-C9 101.1(2), C1-C2-C8 104.1(2), C7-C8-C9 116.1(3).

(12) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun*. **1984**, 1287. (b) Jeffery, T. *Synthesis* **1987**, 70.

(13) Larock, R.C.; Baker, B.E. *Tetrahedron Lett.* **1988**, *29*, 905.

(14) The structure assigned to each compound was in full accord with its spectral (^{1}H and ^{13}C NMR, IR, MS) characteristics. All yields are based on isolated material except where inseparable isomers were formed for which ratios were determined by GC and ^{1}H NMR spectroscopy.

(15) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley: New York, **1990**.

(16) *Optimized experimental procedure for the Heck reaction (preparation of compound* **5** *and* **10***)*: on the one hand, the malonate derivative **3** (200 mg, 0.6 mmol), was stirred at room temperature for 10 min with K_2CO_3 (120 mg, 1.2 mmol, 2 equiv). On the other hand, a mixture of $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 5 mol %) and PPh_3 (15.7 mg, 0.06 mol, 10 mol %) in 5 ml of DMF was stirred under a nitrogen atmosphere at 60°C until a homogeneous solution was obtained. Then the addition of this Pd(0) solution was made at room temperature via a cannula on the malonate anion prepared above followed by the addition of TEBA (273 mg, 1.2 mmol, 2.0 equiv). The mixture was heated for 12 h at 55°C. After completion of the reaction (GC), the reaction mixture was quenched with water and extracted with ether. The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography with petroleum ether/ Et_2O 90/10 to give **5**, **10** and **11** in a ratio of 75/15/15 (130 mg, 85%). This mixture of three compounds was placed in 3 ml of toluene and 20 mg (0.14 mmol) of dimethyl acetylenedicarboxylate was added. The solution was heated at reflux for 3 h. Removal of the solvent under reduced pressure and flash chromatography of the residue with petroleum ether/Et_2O 90/10 gave an inseparable mixture of fused and bridged bicyclic compounds **5** and **10** in a ratio of 4:1 (combined 85 mg, 55%). A further careful flash chromatography allowed isolation of small amounts of each compound:
Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 4.9 (1H, m); 4.8 (1H, m); 4.7 (1H, m); 3.70 (3H, s); 2.7 (1H, quint, *J*=5 Hz), 2.5-2.3 (2H, m); 2.3-1.9 (3H, m); 1.8-1.5 (3H, m); 1.39 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) 171.8, 171.0, 158.3, 107.9, 69.3, 57.7, 52.2, 51.8, 51.6, 35.5, 35.4, 31, 29.7, 23.5. MS, m/z (relative intensity): 192 (32), 145 (48), 133 (25), 120 (100), 113 (51), 108 (22), 91 (24), 77 (24), 59 (18), 41 (13).
Compound **10** : ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 4.8 (1H, m); 4.7 (1H, m); 3.75 (3H, s); 3.64 (3H, s); 3.2 (1H, m); 2.63-1.5 (11H, dd, *J*=14.34, 6.25 Hz); 2.54 (1H, dd, *J*=14.05, 10.05 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 171.7, 171.2, 148.2, 111.2, 58.6, 52.6, 52.4, 43, 32.6, 31, 30.8, 28.6, 26.5. MS, m/z (relative intensity): M^+ 252 (7), 220 (7), 192 (53), 160 (16), 145 (16), 132 (36), 120 (100), 106 (36), 91 (41), 77 (30), 59 (31), 41 (23).

(17) See for example: Boden C.; Pattenden, G. *Contemporary Organic Synthesis* **1996**, *3*, 19.

(18) Balme, G.; Bouyssi, D.; Goré, J.; Faure, R.; Van Hemelryck, B. *Tetrahedron* **1992**, *48*, 3891.

(19) (a) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Synthesis*, John Wiley & Sons, Chichester: **1995**; p. 156; (b) Negishi, E.I.; Copéret, C.; Ma, S.; Liou, S.Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.