π-Allyl Palladium Complexes as Efficient and Powerful Alternative for Nucleophilic Substitution on Bicyclo[3.1.0]hexane Sulfonates: Regio-, Chemo- and Stereoselectivity

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Abstract: The preparation of cyclopropylidene bicyclo[3.1.0]hexane derivatives has been performed on both *exo*- and *endo*-bicyclo[3.1.0]hexane sulfonates, through nucleophilic substitution via π-allyl palladium complexes. While the *endo*- and *exo*-configurations do not particularly affect the selectivities of the products, on the other hand, the 'hard' or 'soft' nature of nucleophiles dramatically enhances the conservation or not of the integrity of the cyclopropane rings.

Key words: palladium, chemoselectivity, complexes, nucleophilic additions, regioselectivity, ring-opening

Several years ago, Schöllkopf[1] studied the acetolysis of *exo*- and *endo*-bicyclo[3.1.0]hexane *p*-toluenesulfonates and observed that the *exo*-ester **1a** was recovered unchanged to the extent of more than 90% after three months at 150 °C in (acetate buffered) acetic acid (k_{rel} << 0.01) while the *endo*-ester **1b** underwent a very fast reaction (k_{rel} = 25000) to produce the cis-2-cyclohexen-1-yl acetate (**2**) through a strain free cyclohexenyl cation generated by an inward disrotatory cyclopropyl ring-opening (Figure 1).

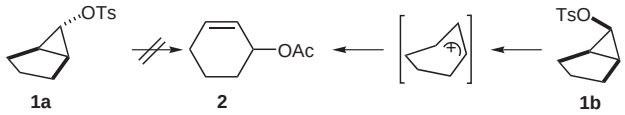
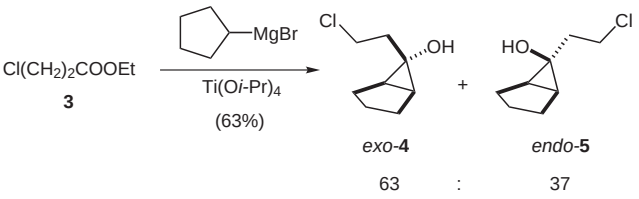


Figure 1

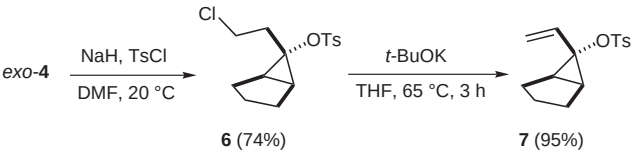
In our recent work,[2] we related that the titanium(IV)-mediated cyclopropanation of cyclopentylmagnesium bromide with ethyl β-chloropropionate (**3**, Kulinkovich reaction[3]) led in 63% yield to a mixture of (*exo*/*endo* = 63:37) 6-(2′-chloroethyl)bicyclo[3.1.0]hexane-6-ols **4a**,**b** separable by silica gel chromatography (Scheme 1).

With the aim to achieve nucleophilic substitutions on cyclopropyl moieties and to compare with Schöllkopf's results, the sulfonates of both *exo*-**4** and *endo*-**5** were readily prepared.



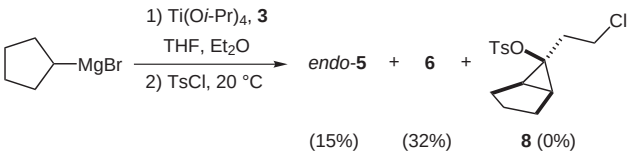
Scheme 1

Thus, the *exo*-alcohol **4** was esterified to the tosylate **6** then dehydrochlorinated to furnish 1-vinylcyclopropyltosylate (**7**) in 70% overall yield (Scheme 2).



Scheme 2

However, we were unfortunately unable to reproduce the same sequence with the *endo*-alcohol **5**. Indeed, the tosylation reaction failed, certainly due to steric hindrance. Confirmation of our hypothesis was brought by the fact that, while trapping the cyclopropanation reaction with tosyl chloride before final hydrolysis, a mixture of *exo*-tosylate **6** and *endo*-alcohol **5** was isolated, while no trace of *endo*-sulfonate **8** was detected (Scheme 3).



Scheme 3

To overcome this problem, the formation of the mesylate *endo*-**9** could constitute an alternative, but the dehydrochlorination of this sulfonic ester would probably lead to the undesired spirocyclopropylsulfonate **10** as previously reported on a similar compound[4] (Scheme 4) through base-induced deprotonation of the mesyloxymethyl

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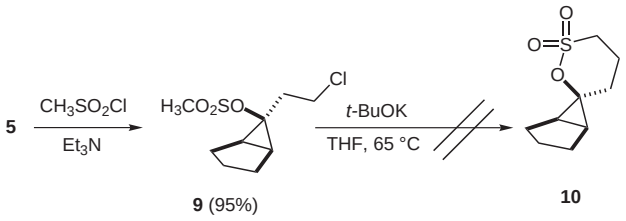
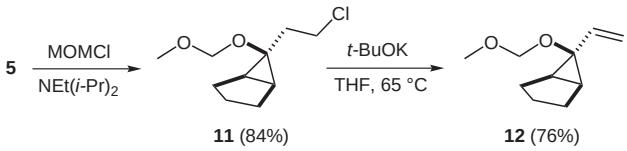
group, followed by substitution of chloride and cyclization.



Scheme 4

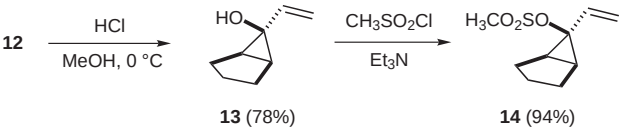
Having nonetheless attempted the reaction, the chlorosulfonate **9** proved unstable and thus unsuitable for pursuing any further development.

Finally, the solution consisted in protecting the alcohol function as a MOM-ether **11** followed by dehydrochlorination to afford the vinylcyclopropane **12** (Scheme 5).



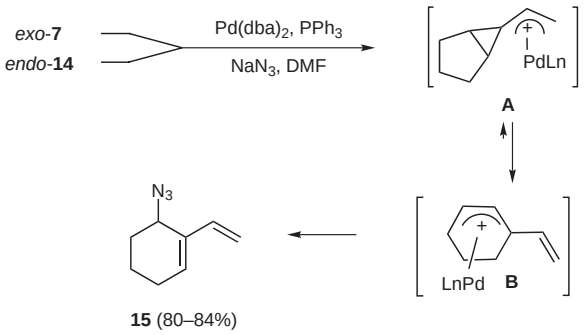
Scheme 5

Generation of the cyclopropanol **13** proceeded smoothly and subsequent esterification yielded the expected air sensitive mesylate **14** (Scheme 6). We note here that the tosylation (NaH, TsCl) of the alcohol **13** proved unsuccessful just as for the parent chloride **5**.



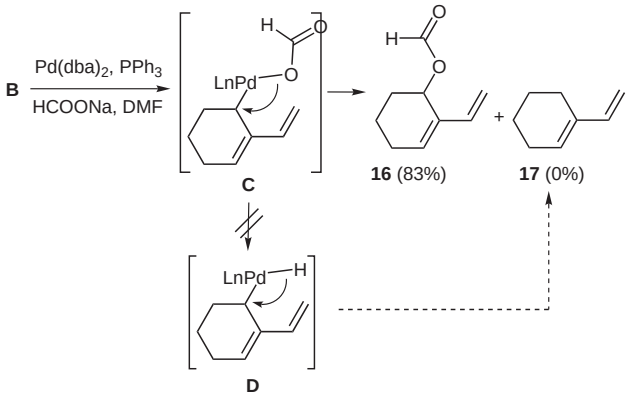
Scheme 6

Nucleophilic substitution was carried out on both tosylate *exo*-**7** and mesylate *endo*-**14** by sodium azide. When the reaction was performed without catalyst, even in refluxing THF or at 70 °C in DMF, no reaction occurred even for the presumed very reactive *endo*-compound **14**. However, in the presence of a catalytic amount of palladium(0) at –10 °C, azide **15**[5] was quantitatively isolated as a single product just as in the case of mesylate *exo*-**7**. Both these results are the opposite to those of Schöllkopf. The mechanism implies the formation of an initial π-allyl palladium complex **A** from the *exo*- or *endo*-sulfonates which rapidly evolves by ring-opening toward a new internal π-allyl intermediate **B**, itself then undergoing nucleophilic attack leading to the azide **15** (Scheme 7). Such a 2-aminocyclohexen-2-yl skeleton has been reported in the literature and is present in natural[6] and bioactive[7] products.



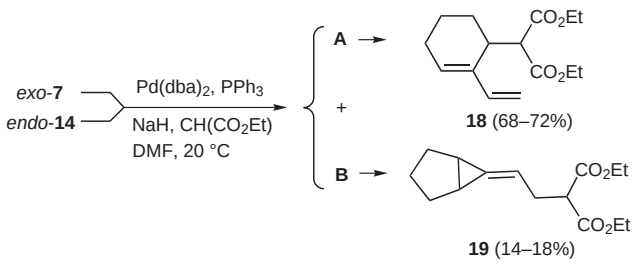
Scheme 7

On the other hand, the use of sodium formate as a nucleophilic reductive agent in the palladium-catalyzed hydrogenolysis only gave the *O*-formyl cyclohexene **16**.[8] As depicted in Scheme 8, no trace of the expected vinylcyclohexene **17** (generated from decarboxylation then reductive elimination of the complexes **C** and **D**, respectively) was isolated even when carrying out the reaction with dppe as palladium ligand.[9]



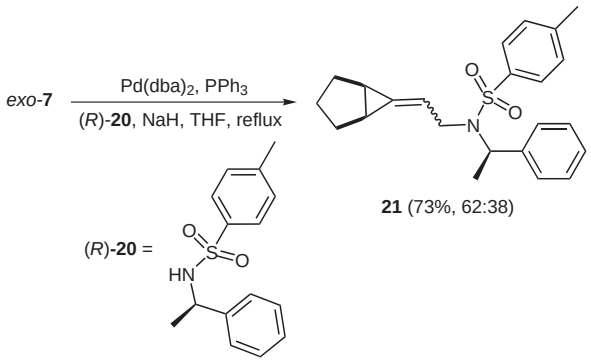
Scheme 8

Surprisingly, when the palladium-catalyzed nucleophilic substitution was performed using ethyl malonate, beside the formation of the expanded cyclohexene **18**,[10] cyclopropylidene **19**[11] was also obtained. The latter, which retains the integrity of the [3.1.0]hexane results from direct Pd-assisted nucleophilic substitution. The ratio for **18**:**19** was steadily at 68:32 whatever the *endo*- or *exo*-sulfonate starting material used (Scheme 9). The synthetic utility of such products has been reported in the literature.[12]



Scheme 9

Finally, and interestingly, the nucleophilic substitution performed using sulfonamide **20** provided only cyclopropylidene **21**[13] as a 62:38 inseparable mixture of diastereomers (Scheme 10).



Scheme 10

In conclusion, we describe herein an efficient preparation of both highly interesting vinylcyclohexene derivatives and fused cyclopropylidene derivatives. Finally, in the nucleophilic substitutions that we developed on such compounds, it is shown that the configurations of the starting sulfonates are not restrictive, as compared with previous data from Schöllkopf. The extension of this efficient pathway to other nucleophiles and towards enantioselective syntheses is currently under investigation.

References and Notes

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(5) **6-Azido-1-vinylcyclohex-1-ene (15)**
^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.33 (dd, *J* = 17.7, 10.9 Hz, 1 H), 6.06 (t, *J* = 3.9 Hz, 1 H), 5.30 (d, *J* = 17.7 Hz, 1 H), 5.08 (d, *J* = 10.9 Hz, 1 H), 4.12 (br s, 1 H), 2.32–2.00 (m, 3 H), 1.81–1.65 (m, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 137.4, 134.2, 132.8, 111.8, 53.9, 29.0, 25.4, 17.4. IR (neat): 2943, 2100, 1643 cm^{-1}. MS (EI): *m/z* (%) = 149 (4) [M$^+$], 120 (31), 93 (69), 91 (66), 79 (100), 77 (35). HRMS: *m/z* calcd for $C_8H_{11}N_3$: 149.0952; found; 149.0950.

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(8) **2-Vinylcyclohex-2-en-1-yl formate (16)**
^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 6.22 (dd, *J* = 17.5, 11.0 Hz, 1 H), 6.08 (t, *J* = 5.4 Hz, 1 H), 5.81 (m, 1 H), 5.09 (d, *J* = 17.5 Hz, 1 H), 4.98 (d, *J* = 11.0 Hz, 1 H), 2.35–1.80 (m, 3 H), 1.80–1.60 (m, 3 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 160.6, 136.8, 135.1, 133.4, 111.5, 64.8, 28.5, 25.5, 17.0. IR (neat): 2945, 1718, 1647 cm^{-1}. MS (EI): *m/z* (%) = 106 (95), 91 (100), 79 (35), 78 (45). MS (CI, NH_3): *m/z* (%) = 170 (100) [M$^+$ + 18]. HRMS (ES$^+$): *m/z* calcd for $C_{15}H_{22}O_4Na$: 289.1410; found: 289.1416.

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(10) **Diethyl (2-Vinylcyclohex-2-en-1-yl)malonate (18)**
^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.21 (dd, *J* = 17.6, 11.2 Hz, 1 H), 5.87 (t, *J* = 4.0 Hz, 1 H), 5.11 (d, *J* = 17.6 Hz, 1 H), 4.91 (d, *J* = 11.2 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 3.62 (d, *J* = 7.9 Hz, 1 H), 3.31 (m, 1 H), 2.25–2.10 (m, 2 H), 1.90–1.65 (m, 4 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.24 (q, *J* = 7.2 Hz, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.6, 138.6, 131.1, 114.3, 61.3, 61.1, 55.0, 54.8, 33.0, 25.7, 25.2, 18.0, 14.1, 13.9. IR (neat): 2936, 1732, 1641 cm^{-1}. MS (EI): *m/z* (%) = 175 (20), 161 (67), 160 (78), 133 (44), 119 (20), 115 (24), 106 (100), 91 (93), 79 (25), 78 (34). MS (CI, NH_3): *m/z* (%) = 267 (100) [M$^+$ + 1], 284 (52) [M$^+$ + 18]. HRMS (ES$^+$): *m/z* calcd for $C_{15}H_{22}O_4Na$: 289.1417; found: 289.1416.

(11) **Diethyl (2-Bicyclo[3.1.0]hex-6-ylideneethyl)malonate (19)**
^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.70 (t, *J* = 6.6 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 4 H), 3.46 (t, *J* = 7.5 Hz, 1 H), 2.71 (dd, *J* = 7.2, 6.6 Hz, 2 H), 1.92–1.65 (m, 8 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.0, 132.9, 115.2, 61.3, 52.0, 31.0, 29.6, 29.4, 21.2, 20.7, 20.5, 14.0. IR (neat): 2938, 2863, 1750, 1733 cm^{-1}. MS (EI): *m/z* (%) = 175 (37), 161 (20), 147 (37), 119 (100), 118 (44), 117 (27), 106 (51), 105 (20), 101 (33), 92 (27), 91 (81), 79 (31). MS (CI, NH_3): *m/z* (%) = 267 (67) [M$^+$ + 1], 284 (100) [M$^+$ + 18]. HRMS (ES$^+$): *m/z* calcd for $C_{15}H_{22}O_4Na$: 289.1417; found: 289.1415.

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(13) ***N*-(2{(1*R*,5*S*)-Bicyclo[3.1.0]hex-6-ylidene}ethyl)-4-methyl-*N*-[(1*R*)-1-phenylethyl] Benzenesulfonamide (21)**
^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.0 Hz, 4 H), 7.35–7.20 (m, 14 H), 5.52 (t, *J* = 6.5 Hz, 1 H, minor), 5.48 (t, *J* = 6.5 Hz, 1 H, major), 5.26 (q, *J* = 7.0 Hz, 1 H, major), 5.21 (q, *J* = 7.0 Hz, 1 H, minor), 3.90 (t, *J* = 6.5 Hz, 1 H, minor), 3.85 (t, *J* = 6.5 Hz, 1 H, major), 3.73 (d, *J* = 6.5 Hz, 1 H, major), 3.68 (d, *J* = 6.5 Hz, 1 H, minor), 2.45 (s, 6 H), 1.80–1.60 (m, 16 H), 1.49 (d, *J* = 7.0 Hz, 3 H, minor), 1.47 (d, *J* = 7.0 Hz, 3 H, major). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.8, 140.3 (major), 140.2 (minor), 138.8 (major), 138.6 (minor), 136.8, 133.1, 131.9, 129.5, 129.2, 128.1, 128.0, 127.7, 127.5, 127.3, 127.1, 117.3 (major), 117.2 (minor), 55.5 (minor), 55.3 (major), 45.6 (minor), 45.3 (major), 29.5 (major), 29.3 (minor), 21.5 (minor), 21.3 (major), 20.9, 20.5, 17.6 (minor), 17.1 (major). IR (neat): 2939, 2863, 1599 cm^{-1}. MS (EI): *m/z* (%) = 381 (3.4) [M$^+$], 276 (20), 207 (100), 155 (21), 120 (23), 105(69), 91 (33), 79 (20). HRMS: *m/z* calcd for $C_{23}H_{27}NO_2S$: 381.1757; found: 381.1752.