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Remote Substituent Control of the Regioselectivity of the Aryl- and Vinylpalladation of 7-Oxabicyclo[2.2.1]heptenes.

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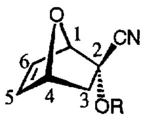
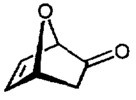
Abstract: Pd-catalyzed arylations of 2-*exo*-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-yl acetate and 7-oxabicyclo[2.2.1]hept-5-en-2-one are regio- and stereoselective giving products of H_2(HCOOH) and $Me_3SiC{\equiv}CH$ coupling in which the aryl group ($4\text{-}MeOC_6H_4$) prefers the *exo* position of C(5) whereas the Pd-catalyzed vinylations with methyl-2-iodoacrylate prefers the *exo* position of C(6) center.

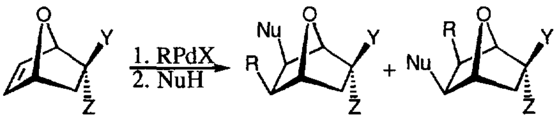
Enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives (+)-**1** and (+)-**2** ("naked sugars of the first generation")[1] are useful chirons in the synthesis of natural products [2] and of compounds of biological interest.[3] The stereoselective introduction of a carbon residue at C(3) can use aldolisation[4] and alkylation, at C(5) or C(6), radical additions.[2a,b, 5,6] The Heck Pd-catalyzed reactions[7] can be conducted, as we have shown,[8] under mild conditions in water. The carbapalladation of bicyclic alkenes can be followed by trapping the alkylpalladium intermediates with alkynes, a process investigated by Larock et al.[9] and by Torii et al.[10] This powerful tandem reaction could increase the synthetic potential of the "naked sugars" if it could be regioselective (**3** → **4** + **5**). We report that the regioselectivity of the aryl- and vinylpalladations of (±)-**1b** and (±)-**2** is controlled by the remote substituents at C(2). Interestingly, the vinylations with methyl (Z)-2-iodoacrylate have opposite regioselectivity than the Pd-catalyzed arylations. The intermediate alkylpalladium derivatives were trapped with HCOOH or with $Me_3SiC{\equiv}CH$, the latter process allowing one the introduce two different *exo*-carbon functionalities at C(5) and C(6) of the "naked sugar" with good regioselectivities (see Table 1,2).



1a R = (1*S*)-camphanoyl
1b R = Ac



(+)-**2**

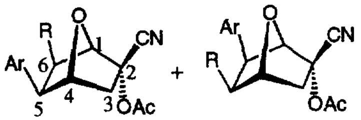
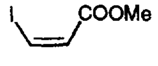
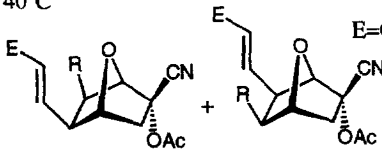


3 **4** **5**

The treatment of the Diels-Alder adduct of furan to 1-cyanovinyl acetate (**1b**)[11] with *p*-methoxyiodobenzene (3 eq.), Et_3N (2.5 eq.), HCOOH (3eq.), Ph_3P (0.4 eq.)[12] and $Pd(OAc)_2$ (0.1 eq.) in THF (40°C, 36 h) gave a 74% yield of a 84:16 mixture of products of *exo* arylation **6** and **7**.[13] When HCOOH was replaced by trimethylsilylacetylene (3 eq.) and adding CuI (0.1 eq., 40°C, 8 h), a 83:17 mixture of products of anionic coupling **8**[14] and **9** (43%) was obtained together with unreacted **1b** (30%) and $MeOC_6H_4C{\equiv}CSiMe_3$ (ca.

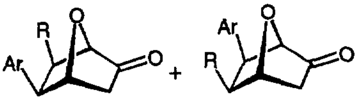
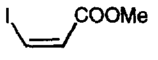
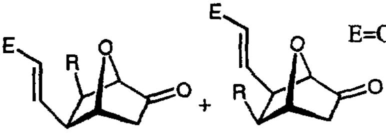
25%). The latter reaction could be run in CH_3CN/H_2O using TPPTS (0.1 eq., trisodium triphenylphosphine-*meta*trisulfonate) instead of Ph_3P and $(i\text{-}Pr)_2NEt$ (2.5 eq.) instead of Et_3N without any CuI promoter.[8a] This led to a 79:21 mixture of **8** and **9** with a 50% yield (after separation by flash chromatography). Under similar conditions (Table 2), the arylpalladation of enone (±)-**2** provided a 80:20 mixture of **10**[15] and **11** (66%, trapping with HCOOH) and a 78:22 mixture of products of three component coupling **12** and **13** (73%, trapping with $Me_3SiC{\equiv}CH$ in THF).[16]

Table 1. Carbapalladation of bicyclic alkene **1b**

Iodide	Trapping agent	Catalyst	Conditions	Products	(Yield)	Product ratio
 ≡ A						
A + HCOOH (3eq.)		10% $Pd(OAc)_2$ 40% PPh_3	2.5 eq. NEt_3 THF, 40°C	**6** R = H	**7** (74%)	84:16
A + TMSC≡CH (3eq.)		idem	+ CuI (10%)	**8** R = $Me_3SiC{\equiv}C$	**9** (43%)	83:17
A + TMSC≡CH (3eq.)		5% $Pd(OAc)_2$ 10%TPPTS	2.5 eq. $(i\text{-}Pr)_2NEt$ H_2O/CH_3CN, 40°C	**8**	**9** (50%)	79:21
 ≡ B				 E=COOMe		
B + HCOOH (3eq.)		10% $Pd(OAc)_2$ 40% PPh_3	2.5 eq. NEt_3 THF, 50°C	**14** R = H	**15** (49%)	26:74[a)]
B + TMSC≡CH (3eq.)		idem	+ CuI (10%)	**16** R = $Me_3SiC{\equiv}C$	**17** (50%)	25:75[b)]

a) **14** was a 1:1 mixture of the (E)- and (Z) acrylate; **15** was a 97:3 mixture of the (E)- and (Z)-acrylate
b) separated by flash chromatography on silica gel; only (E)-acrylates.

Table 2. Carbapalladation of bicyclic alkene (±)-**2**

Iodide	Trapping agent	Catalyst	Conditions	Products	(Yield)	Product ratio
 ≡ A						
A + HCOOH (3eq.)		10% $Pd(OAc)_2$ 40% PPh_3	2.5 eq. NEt_3 THF, 40°C	**10** R = H	**11** (66%)	80:20
A + TMSC≡CH (3eq.)		idem	+ CuI (10%)	**12** R = $Me_3SiC{\equiv}C$	**13** (73%)	78:22
A + TMSC≡CH (3eq.)		5% $Pd(OAc)_2$ 10%TPPTS	2.5 eq. $(i\text{-}Pr)_2NEt$ H_2O/CH_3CN, 40°C	**12**	**13** (60%)	75:25
 ≡ B				 E=COOMe		
B + HCOOH (3eq.)		10% $Pd(OAc)_2$ 40% PPh_3	2.5 eq. NEt_3 THF, 50°C	**18** R = H	**19** (49%)	54:46[a)]
B + TMSC≡CH (3eq.)		idem	+ CuI (10%) 60°C	**20** R = $Me_3SiC{\equiv}C$	**21** (67%)	40:60

a) **18** was a 63:37 mixture of (E)- and (Z)-acrylate; **19** was pure (E)-acrylate

When the bicyclic alkene **1b** was treated with methyl (Z)-2-iodoacrylate (3 eq.), HCOOH (3 eq.), Et_3N (2.5 eq.), PPh_3 (0.4 eq.) and $Pd(OAc)_2$ (0.1 eq.) in THF (50°C, 12 h) a 26:74 mixture of the products of *exo* vinylation **14** and **15** (49%) was obtained. Under similar conditions and using $Me_3SiC{\equiv}CH$ instead of HCOOH, the products of vinylation and acetylenation **16** and **17**[17] were obtained with the same regioselectivity (Table 1). With enone (±)-**2** (Table 2) the same type of products were observed with somewhat lower regioselectivities. The vinylation coupled with the hydrogenation (HCOOH) gave a 54:46 mixture of (E)-acrylates **18** and **19** (49%). As for the vinylation of **1b** that gave **14** + **15**, incomplete (Z) → (E) isomerisation of the acrylate moieties of **18** + **19** was seen.[10] Using $Me_3SiC{\equiv}CH$ as trapping agent, the vinylation of (±)-**2** with methyl (E)-2-iodoacrylate provided a 40:60 mixture of **20** and **21** (67%).[18] All the compounds **6-21** were fully characterized by their spectral data and their structures were established by their 2D-NOESY ^1H-NMR spectra (400 MHz).

Steric factors are not expected to play a role on the regioselectivity of the carbapalladations of **1b** and **2** since the *exo* face of these bicyclic alkenes interact with the Pd complexes. Both the cyanoacetate and carbonyl moieties act as remote electron-withdrawing groups[19] and this favors the arylpalladations of C(5), the center the most remote from them.[7] The reversal of the regioselectivity between the aryl and vinylpalladations cannot be explained before it is established whether the product determining step is the β-insertion from the alkene-Pd complexes to the corresponding alkyl-Pd species or the subsequent quenching of the latter species with HCOOH or $Me_3SiC{\equiv}CH$. Alternatively, the regioselectivities could parallel the relative stabilities of these intermediates. Work is underway in our laboratories to put these hypotheses on firmer ground. Our preliminary results, however, demonstrate that remote substituents can control the regioselectivity of Heck carbapalladations and can be used to construct asymmetric polyfunctional systems. All the compounds described here can be prepared optically pure in both their enantiomeric forms.[1]

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[3] See e.g.: Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487; Vogel, P. *Chim. Oggi* **1992**, 9-15; Ferritto, R.; Vogel, P. *Tetrahedron Lett.* **1995**, *36*, 3517-3518.

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[13] Data for **6**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 7.17-7.29, 6.83-6.90 (2m, 4 H), 5.26 (d, ^3J=5.4, HC(1)), 4.58 (d, ^3J=5.7, HC(4)), 3.82 (s, MeO), 2.95 (dd, ^3J=4.8, ^3J=9.0, H_{endo}C(5)), 2.59 (dd, ^2J=13.8, ^3J=5.7, H_{exo}C(3)), 2.43 (dd, ^2J=13.6, ^3J=9.0, H_{endo}C(6)), 2.23 (s, OAc) 2.01 (d, ^2J=13.8, H_{endo}C(3)), 1.84 (ddd, ^2J=13.6, ^3J=5.4, ^3J=4.8, H_{exo}C(6)); HRMS Calcd for $C_{16}H_{17}O_4N$: 287.11575; Found: 287.11570. Data for **7**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 7.16-7.22, 6.84-6.90 (2m, 4 H), 4.97 (s, HC(1)), 4.86 (m, HC(4)), 3.81 (s, MeO), 3.27 (dd, ^3J=5.3, ^3J=8.8, H_{endo}C(6)), 2.76 (m, H_{exo}C(3)), 2.26 (s, OAc), 2.19 (m, H_{endo}C(5)), 1.92 (d, ^2J=13, H_{endo}C(3)), 1.78-1.89 (m, H_{exo}C(5)).

[14] Data for **8**: m.p. 145-148°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 7.2, 6.8 (2m, 4 H), 5.16 (s, HC(1)), 4.77 (d, ^3J=5.9, HC(4)), 3.79 (s, MeO), 3.52 (d, ^3J=8.9, H_{endo}C(6)), 3.21 (d, ^3J=8.9, H_{endo}C(5)), 2.82 (dd, ^2J=14, ^3J=5.9, H_{exo}C(3)), 2.22 (s, OAc), 1.94 (d, ^2J=14, H_{endo}C(3)), 0.01 (s, Me_3Si); Anal Calcd for $C_{21}H_{25}O_4SiN$: C 65.77, N 3.65, H 6.57; Found: C 65.67, N 3.82, H 6.55.

[15] Data for **10**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 7.22-7.28, 6.84-6.91 (2m, 4 H), 4.75 (d, ^3J=5.8, HC(4)), 4.58 (d, ^3J=6, HC(1)), 3.82 (s, MeO), 3.11 (dd, ^3J=9.1, ^3J=4.9, H_{endo}C(5)), 2.56 (dd, ^2J=17.4, ^3J=5.8, H_{exo}C(3)), 2.31 (dd, ^2J=13.4, ^3J=9.1, H_{endo}C(6)), 2.16 (d, ^2J=17.4, H_{endo}C(3)), 1.84 (m, H_{exo}C(6)); HRMS Calcd for $C_{13}H_{14}O_3$: 218.094292; Found 218.094370.

[16] Data for **12**: m.p. 92°C; ^{1}H-NMR (400 MHz, C_6D_6) δ_H: 7.24, 6.89 (2dm, ^3J=8.7), 4.46 (s, HC(1)), 4.34 (d, ^3J=5.9, HC(4)), 3.45 (s, MeO), 3.00 (d, ^3J=8.9, HC(6)), 2.64 (d, ^3J=8.9, HC(5), NOE with signals at 7.24, 1.38), 1.91 (dd, ^2J=17.4, ^3J=5.9, H_{exo}C(3)), 1.38 (d, ^2J=17.4, H_{endo}C(3)), 0.02 (s, Me_3Si); HRMS Calcd for $C_{18}H_{22}O_3Si$: 314.133821; Found: 314.133722. Data for **13**: ^{1}H-NMR (400 MHz, C_6D_6) δ_H: 7.20, 6.83 (2dm, ^3J=8.7), 4.56 (d, ^3J=5.9, HC(4)); 4.33 (s, HC(1)), 3.42 (s, MeO), 2.98 (d, ^3J=8.9, HC(6), NOE with 7.20), 2.71 (d, ^3J=8.9, HC(5), NOE with H_{endo}C(3)), 1.90 (dd, ^2J=17.4, ^3J=5.9, H_{exo}C(3)), 1.40 (d, ^2J=17.4, H_{endo}C(3)), 0.03 (s, Me_3Si).

[17] Data for **16**: m.p. 150°C; ^{1}H-NMR (400 MHz, C_6D_6) δ_H: 7.16 (dd, ^3J=15.7, 9.8), 5.77 (d, ^3J=15.7), 5.12 (s, HC(1)), 3.72 (d, ^3J=5.9, HC(4)), 3.52 (s, MeOOC), 3.05 (d, ^3J=8.4, HC(6)), 2.19 (dd, ^2J=14.1, ^3J=5.9, H_{exo}C(3)), 1.95 (dd, ^3J=9.8, 8.4, HC(5), NOE with signals at 7.16, 1.03), 1.46 (s, Ac), 1.03 (d, ^2J=14.1, H_{endo}C(3)), 0.20 (s, Me_3Si); Anal. Calcd for $C_{18}H_{23}O_5SiN$: C 59.81, N 3.88, H 6.41; Found: C 59.72, N 3.87, H 6.47. Data for **17**: m.p. 107°C; ^{1}H-NMR (400 MHz, C_6D_6) δ_H: 7.18 (dd), 5.79 (d), 4.64 (s), 4.16 (d), 3.47 (s, MeO), 2.57 (dd, NOE with signal at 7.18), 2.28 (d, NOE with H_{endo}C(3)), 2.06 (dd), 1.36 (s, Ac), 0.98 (d), 0.21 (s, Me_3Si); Anal. Calcd for $C_{18}H_{23}O_5SiN$: C 59.81, N 3.88, H 6.41; Found: C 59.86, N 3.83, H 6.32.

[18] Data for **20**: ^{1}H-NMR (400 MHz, C_6D_6) δ_H: 7.21 (dd, ^3J=15.7, 10.0), 5.74 (d, ^3J=15.7), 4.32 (s, HC(1)), 3.92 (d, ^3J=6.1, HC(4), NOE with HC(5)), 3.53 (s, MeOOC), 2.70 (d, ^3J=8.6, HC(6)), 1.94 (dd, ^3J=10.0, 8.6, HC(5), NOE with HC(4)), 1.77 (ddm, ^2J=17.5, ^3J=6.1, H_{exo}C(3)), 1.18 (d, ^2J=17.5, H_{endo}C(3)), 0.20 (s, Me_3Si); HRMS Calcd for $C_{15}H_{20}O_4Si$: 292.113085; Found: 292.112976. Data for **21**: ^{1}H-NMR (400 MHz, C_6D_6) δ_H: 7.19 (dd, ^3J=15.6, 9.8), 5.69 (d, ^3J=15.6), 4.38 (d, ^3J=6.0, HC(4)), 3.82 (s, HC(1), NOE with HC(6)), 3.49 (s, COOMe), 2.35 (d, ^3J=8.6, HC(5), NOE with HC(4)), 2.24 (dd, ^3J=9.8, 8.6, HC(6)), 1.75 (dd, ^3J=6.0, ^2J=17.5, H_{exo}C(3)), 1.19 (d, ^2J=17.5, H_{endo}C(3)), 0.24 (s, $SiMe_3$); HRMS Calcd for $C_{15}H_{20}O_4Si$: 292.113085; Found: 292.113257.

[19] For reactions with strong electron-demand the homoconjugated carbonyl group can be electron-releasing, see e.g.: Carrupt, P.-A.; Vogel, P. *J. Org. Chem.* **1990**, *55*, 5696-5700.

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