Unexpected ring contraction of 1-aryl-cyclohexa-2,5-dienes under palladium catalysis

Raphaël Lebeuf, Frédéric Robert, and Yannick Landais*

Université de Bordeaux, Institut des Sciences Moléculaires, UMR-CNRS 5255,351, cours de la libération, 33405 Talence, Cedex, France
E-mail: *y.landais@ism.u-bordeaux1.fr*

Dedicated to Prof. Pierre Vogel on the occasion of his 70th anniversary

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.241

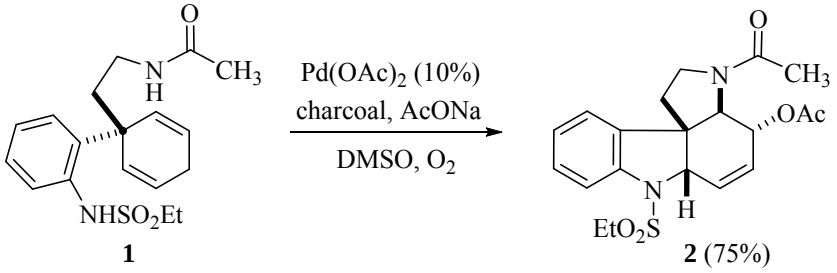
Abstract
The reaction of 1,1-disubstituted cyclohexa-2,5-dienes with aryl iodides in the presence of Pd(0) unexpectedly provided bicyclo[3.1.0] compounds in a very diastereocontrolled fashion in moderate to good yield. A tentative mechanism is proposed to rationalize this unusual reactivity of cyclohexadienes under palladium catalysis.

Keywords: Catalysis, Heck reaction, Wacker oxidation, palladium, cyclohexadienes, ring contraction

Introduction

1-Substituted cyclohexa-2,5-dienes constitute a versatile family of building blocks which continue to attract a wide interest.[1-4] Desymmetrization of such dienes has been carried out through a number of ways, leading to advanced intermediates in the synthesis of natural products. In the meantime, 1-silylcyclohexa-2,5-dienes and cyclohexa-2,5-diene carboxylic acids were shown to be valuable surrogate of tin hydride in radical processes.[4] Our continuous interest for this class of compounds[1,5,6] has led recently to the development of a methodology focused on a palladium-catalyzed aza-Wacker process[7-9] using 1-arylcyclohexa-2,5-dienes as precursors.[10] The pendant ethylamino moiety on the quaternary center was thus shown to add onto the dienyl system, affording the corresponding 5-membered ring along with a new conjugated diene, which could be functionalized further. For instance, starting from an *ortho*-substituted arylcyclohexa-2,5-diene such as **1**, this strategy offered a straightforward entry toward the tetracyclic core **2** of aspidosperma alkaloids (Scheme 1). Reoxidation of Pd(0) into Pd(II) is carried out using a stream of oxygen, the charcoal serving as to disperse the palladium catalyst, avoiding the

formation of metal colloids which precipitate during the reaction, thus limiting catalyst turn-over. Moderate to good yields of the cyclized product were thus observed using this protocol.



Scheme 1. Pd(II)-catalyzed aza-Wacker cascade.

The slow Pd(0) → Pd(II) reoxidation by oxygen (also producing hydrogen peroxide) may be circumvented using a Pd(0) source in the presence of an haloalkane (1,2-dichlorethane (DCE) or chlorobenzene), which upon oxidative addition generates a Pd(II) species. This strategy was used by Guram and Bei[11,12] for the oxidation of alcohols into ketones using a Pd(0) catalyst. Interestingly, this protocol is compatible with substrates bearing an olefinic moiety. Application of this strategy to our case was envisaged having in mind the possible competition between this oxidation and intermolecular Heck reaction, following a pathway depicted in Figure 1 below. A Heck reaction-heterocyclization could effectively take place after the regioselective aryl-palladation of the diene.[13-17] The regioselectivity of the process would be directed by the ethylamino group as in **I**, which upon reductive elimination would give rise to the bicyclic system **II** (Figure 1). Mechanisms have recently been put forward by Wolfe for such heterocyclizations, assuming the formation of a Pd-heteroatom bond preceding the cyclization, the C-Ar bond being generated through reductive elimination.[18-19] Based on these premises, we started a study on the reactivity of arylcyclohexadienes **3** with aryl iodides **4** in the presence of a Pd(II) catalyst. We report herein the addition of aryl halides onto dienes **3** and the unusual reactivity of the latter, which afford under these conditions cyclopropanes **5**. A tentative mechanism is provided to explain the unexpected formation of **5**.

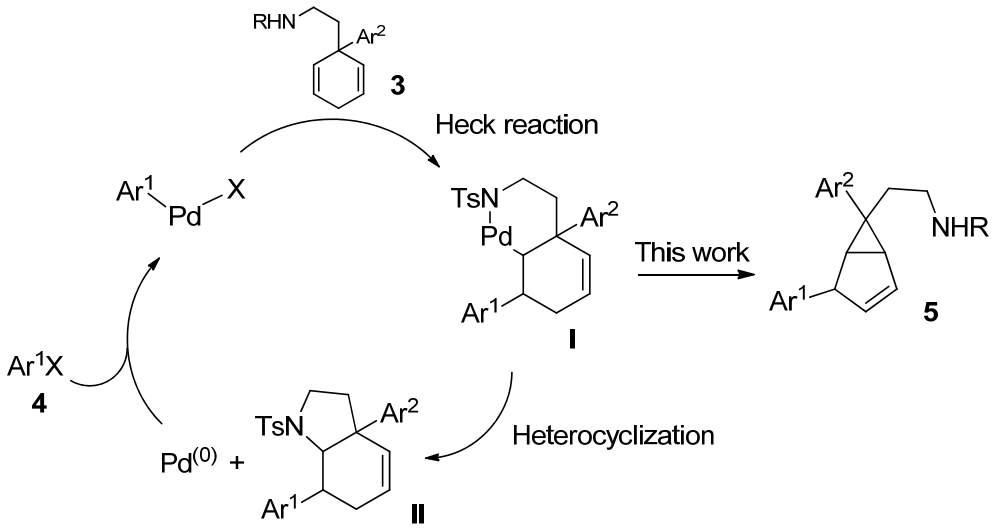
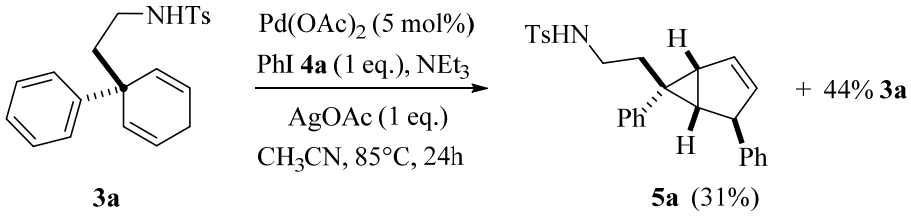


Figure 1. Intermolecular Heck reaction with 1-arylcyclohexa-2,5-dienes.

Results and Discussion

Cyclohexadienes **3a-d** were prepared through a Birch reductive alkylation using α-chloronitrile as electrophile, followed by the reduction of the nitrile into an amine, which was finally protected as a tosyl (**3a-b**) or a mesyl group (**3c-d**).[20-21] Our preliminary studies began by reacting cyclohexadiene **3a** with phenyl iodide **4a** in the presence of $Pd(OAc)_2$ under cationic Heck reaction conditions.[22] We observed no trace of heterocyclization product such as **II** in the mixture, which instead contained mainly starting material in 44% yield, an unexpected cyclopropane containing product **5a** (31%) and a third product (25%), which structure could not be determined (Scheme 2). **5a** was obtained as a single diastereomer with the tentative stereochemistry as shown.

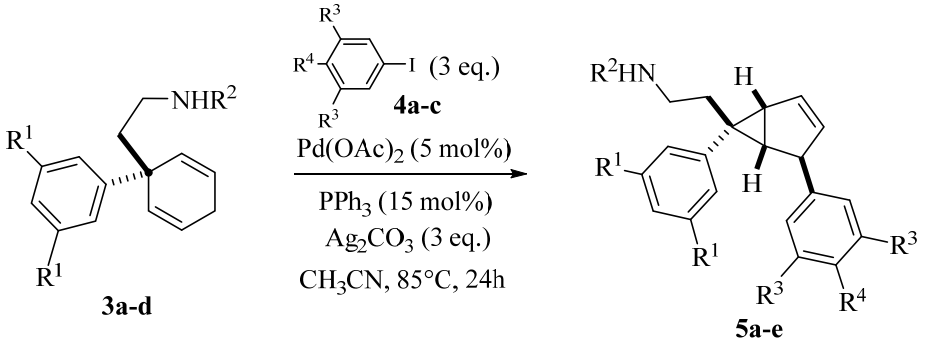


Scheme 2. Reaction of dienes **3a** and PhI under Heck conditions.

5a was finally obtained with higher efficiency using Ag_2CO_3 instead of AgOAc and in presence of triphenylphosphine, albeit as a 9:1 mixture of isomers (Table 1, entry 1). The reaction was extended to other aryl iodides including **4b-c** and arylcyclohexadienes **3b-d**. Under

these conditions, cyclopropanes **5b-e** were obtained as single isolated diastereomers with moderate to good yields, along with recovered starting material in some cases (entries 3-4).

Table 1. Reaction of dienes **3a-d** and aryl iodides **4a-c** under Heck conditions



Entry	**3**	R_1	R_2	**4**	R_3	R_4	**5**	Yield (%)[a]
1	**3a**	H	Ts	**4a**	H	H	**5a**	77
2	**3b**	OMe	Ts	**4b**	OMe	H	**5b**	52
3	**3c**	H	Ms	**4b**	OMe	H	**5c**	39 (51, brsm)[b]
4	**3d**	OMe	Ms	**4b**	OMe	H	**5d**	38 (49, brsm)[b]
5	**3a**	H	Ts	**4c**	H	OMe	**5e**	37

[a] Isolated yields. [b] Yields based on recovered starting material.

Our efforts to obtain crystals of **5a-e** suitable for X-ray structure determination unfortunately failed. ^{13}C NMR (DEPT) clearly shows the presence of two aliphatic CH_2 and three aliphatic CH, with chemical shifts in good agreement with a bicyclic structure bearing a cyclopropane ring. Complete 2D-NMR analysis of **5a** showed an absence of NOESY correlation between the benzylic proton and the contiguous cyclopropane CH, leading to the conclusion that these protons were *trans* to each other as in the structure shown. Further support to the above structure was obtained through DFT calculations of the ^{13}C NMR spectrum of **5c**, using a standardized method (B3LYP/6-311+G(2d,p)-SCRF//B3LYP/6-311+G(2d,p)) and established scaling factors.[23] The RMS deviation obtained for this compound (2.0338) was shown to be below the deviation obtained with the author's probe set used to validate the method (2.7992), thus supporting the above structure for **5c**. Computed chemical shifts and method parameters have been added after the description of **5c** in the experimental section.

A tentative mechanism to rationalize the formation of cyclopropanes **5a-e** is proposed in Figure 2 (Path A), which involves an oxidative addition of the catalyst into the C-I bond of the aryl iodides **4a-c**, followed by coordination of the Pd(II) to the nitrogen side chain. The addition of the resulting aryl-palladium species **Ia** onto one of the C=C bond of the diene **3a-d** is then facilitated by this chelation thus controlling the regio- and stereoselectivity of the process. The *syn*-addition of the resulting aryl-palladium **IIa** generates an alkyl-palladium **IIIa**, which cannot

evolve through a β-hydride elimination, but instead insert into the second olefin, forming the cyclopropane ring in **IVa**.[24,25] β-elimination finally affords **5a-e** and an hydrido-palladium species, which returns the Pd(0) catalyst. Starting the mechanism with a coordination of the nitrogen on palladium seems reasonable as only compounds bearing a sulfonyl moiety on nitrogen react by this way. Cyclohexadienes bearing amides or carbamates substituents remained unchanged under the reaction conditions. Sulfonamides being known as palladium ligands, their presence would be a prerequisite for this unusual reactivity profile.

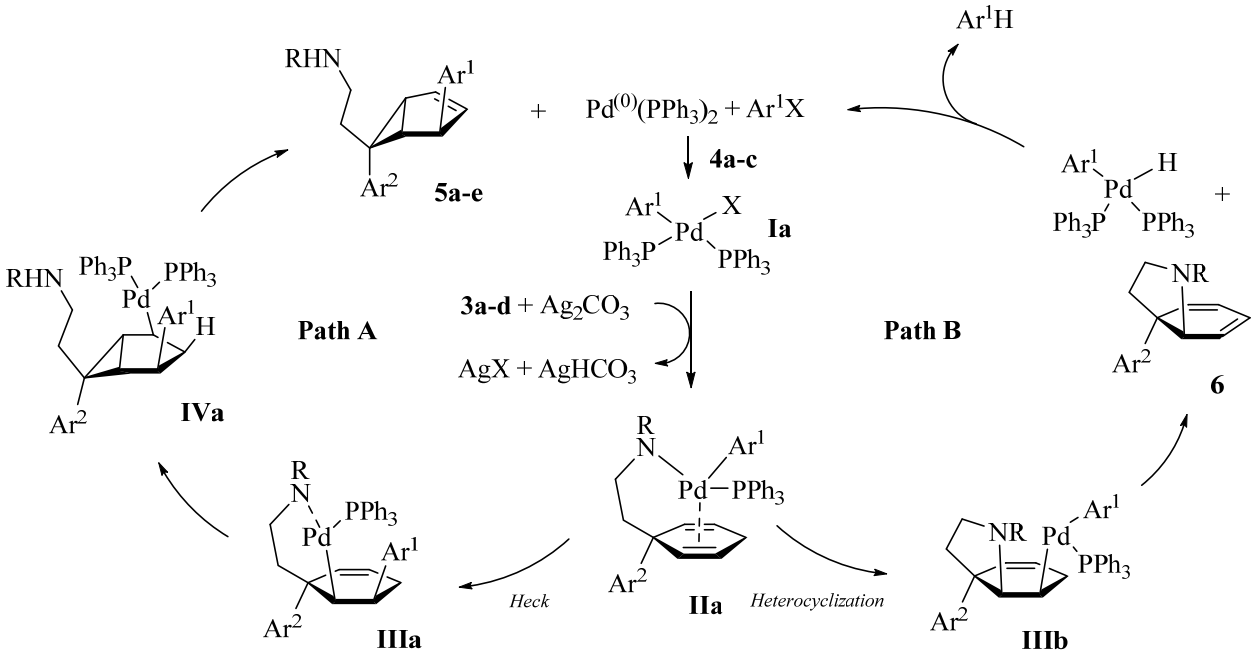
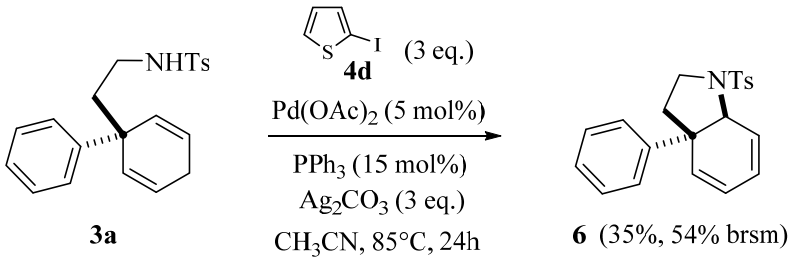


Figure 2. Putative mechanism for the formation of **5a-e** and **6** from 1-arylcyclohexa-2,5-dienes **3a-d**.

When the reaction was performed with electron-poor aryl iodides such as *p*-nitrophenyl iodide, no reaction took place. Interestingly, when cyclohexadiene **3a** was reacted with 2-iodothiophene **4d**, no trace of the corresponding cyclopropane was formed, but instead the product of heterocyclization **6** was observed, along with unreacted starting material (Scheme 3). **6** was previously prepared from **3a**[10] using Wacker type conditions ($Pd(OAc)_2$, pyridine, O_2 in xylene at 80°C). The formation of **6** may proceed through heterocyclization prior to β-hydride elimination as shown in Figure 2 (Path B). It is noteworthy that no Heck reaction on the resulting diene was observed. Although the yield of **6** is moderate, it has not been optimized and clearly indicates that with our substrates, 2-iodothiophene could be a good candidate to perform efficiently the reoxidation of Pd(0) in an aza-Wacker type process, as illustrated in Scheme 1.



Scheme 3. Reaction of diene **3a** and 2-iodothiophene **4c** under Heck conditions.

Conclusions

We reported above a unique reactivity of 1,1-disubstituted cyclohexa-2,5-dienes in the presence of electron-rich aryl iodides under Pd(0) catalysis. Under these Heck reaction conditions, one observed the unexpected formation of bicyclo[3.1.0] systems in a diastereocontrolled manner in moderate to good yields. To our knowledge, such a process has no precedent in the literature. When 2-iodothiophene **4d** was used as the aryl iodide partner, the cyclopropane was not formed, but instead we obtained an heterocycle (*e.g.* **6**) resulting from an aza-Wacker type process, the aryl iodide likely serving as to reoxidize Pd(0) into Pd(II) through an oxidative addition.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR were recorded on a Brüker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), Brüker AC-250 FT (^{1}H: 250 MHz, ^{13}C: 62.9 MHz), using solvent peak as internal reference or apparatus SR. The chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and hertz respectively. "*a"* means "apparent" for close coupling constant and the number of equivalent group are indicated after the sign "x". Carbon attribution C, CH, CH_2 and CH_3 were determined by ^{13}C, DEPT 135 and HMQC experiments. InfraRed (IR) spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. Melting points were uncorrected and determined by using a Büchi-Totolli apparatus. Merck silica gel (0.043-0.063 mm) was used for flash chromatography. CH_2Cl_2 (DCM) and acetonitrile were distilled under CaH_2. All reactions were carried out under nitrogen. Other reagents and starting materials were directly used as obtained commercially.

***N*-[2-(1-Phenyl-cyclohexa-2,5-dienyl)-ethyl]-methanesulfonamide (3c).** To a solution of 2-(1-Phenyl-cyclohexa-2,5-dienyl)-ethylamine[20,21] (536 mg, 2.69 mmol) in DCM (26 mL) was added triethylamine (760 µL, 5.42 mmol) and methanesulfonyl chloride (210 µL, 2.71 mmol) at 0°C. After stirring overnight at room temperature, the organic layer was washed with water then brine, dried over sodium sulfate and filtered. Evaporation of the solvents gave a white solid which was

purified through silica gel chromatography (Petroleum ether/EtOAc 80:20) to give *N*-[2-(1-phenyl-cyclohexa-2,5-dienyl)-ethyl]-methanesulfonamide **3c** as a white solid (737 mg, 98%). Mp = 94-96 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 3288, 1314, 1153, 1060, 728, 703, 595, 525, 514. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.10-2.15 (2H, m, C<u>H</u>$_2$CH$_2$N), 2.68-2.74 (2H, m, bis allylic CH_2), 2.94 (3H, s, NSO_2CH_3), 3.15-3.22 (2H, m, CH_2N), 4.83 (1H, broad s, NH), 5.61-5.66 (2H, m, CH x 2 olefinic), 5.92 (2H, dt*a*, $^3J_{HH}$ 10.5, $^4J_{HH}$ 3.4 and 3.4 Hz, CH x 2 olefinic), 7.17-7.23 (1H, m, CH aromatic), 7.29-7.36 (4H, m, 4CH aromatic). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ_C 26.0 (CH_2 bis-allylic), 39.8 (<u>C</u>H$_2$CH$_2$N), 40.1 (NSO_2CH_3), 40.8 (CH_2N), 43.0 (C aliphatic), 124.7 (CH x 2, olefinic), 126.4 (CH aromatic), 126.4, 128.5 (2CH x 2 aromatic), 131.7 (CH x 2 olefinic), 147.1 (C aromatic). Anal. calcd for $C_{15}H_{19}NO_2S$ (277.11): C, 64.95; H, 6.90; N, 5.05; S, 11.56. Found: C, 65.17; H, 7.18; N, 4.88; S, 11.79.

***N*-{2-[1-(3,5-Dimethoxy-phenyl)-cyclohexa-2,5-dienyl]-ethyl}-methanesulfonamide (3d).**
To a solution of 2-[1-(3,5-dimethoxyphenyl)-cyclohexa-2,5-dienyl]-ethylamine[20,21] (298 mg, 1.15 mmol) in DCM (11 mL) were added triethylamine (480 µL, 3.45 mmol) and methanesulfonyl chloride (90 µL, 2.30 mmol). After stirring for 2 hours, the organic layer was washed with water, dried over sodium sulfate, filtrated, and the solvents were evaporated. The crude mixture was purified through silica gel chromatography (Petroleum ether/EtOAc 65:35) to give **3d** as a colorless viscous oil (328 mg, 85%). IR (film, NaCl, $\nu_{max,}$ cm^{-1}): 3307, 2937, 1614, 1455, 1316, 1203, 1149, 1062, 975, 839, 797. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.06 (2H, t, $^3J_{HH}$ 5.3 Hz, C<u>H</u>$_2$CH$_2$N), 2.69 (2H, broad s, CH_2 bis-allylic), 2.92 (3H, s, NSO_2CH_3), 3.11-3.19 (2H, m, CH_2N), 3.76 (6H, s, OCH_3 x 2), 4.64 (1H, broad s, NH), 5.59-5.63 (2H, m, CH x 2 olefinic), 5.87-5.93 (2H, m, CH x 2 olefinic), 6.30 (1H, s, CH aromatic), 6.48 (2H, s, CH x 2 aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 26.0 (CH_2 bis-allylic), 40.1 (<u>C</u>H$_2$CH$_2$N), 40.3 (NSO_2CH_3), 40.7 (CH_2N), 43.2 (C aliphatic), 55.4 (OCH_3 x 2), 97.8 (CH aromatic), 105.1 (CH x 2, aromatic), 124.9 (CH x 2, olefinic), 131.5 (CH x 2, olefinic), 149.7 (C aromatic), 160.9 (C x 2, aromatic). MS(ESI) *m*/*z* (%): 360 (M+Na, 100). HRMS calcd for (M+Na) $C_{17}H_{23}NNaO_4S$: 360.1245; found 360.1232 (3.6 ppm).

***N*-[2-(4,6-Diphenyl-bicyclo[3.1.0]hex-2-en-6-yl)-ethyl]-4-methyl-benzenesulfonamide (5a).**
In a dry two necked flask were introduced **3a** (211 mg, 0.60 mmol), silver carbonate (247 mg, 0.90 mmol), triphenylphosphine (23 mg, 0.09 mmol), palladium acetate (7 mg, 0.03 mmol) and acetonitrile (30 mL). Phenyl iodide **4a** (100 µL, 0.9 mmol) was added and the mixture was warmed to 85 °C and stirred overnight. The mixture was filtered through celite, which was then washed with ethyl acetate. Evaporation of the solvents led to a paste, which was purified through silica gel chromatography (Petroleum ether/EtOAc 85:15), affording **5a** as a viscous oil (198 mg, 77%). IR (film, KBr, $\nu_{max,}$ cm^{-1}): 3286, 3024, 2923, 1599, 1494, 1444, 1325, 1160, 1094, 703, 664. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.41-1.51 (1H, m, C<u>H</u>*a*H*x*CH$_2$N), 1.78-1.88 (2H, m, CH*a*<u>H</u>*x*CH$_2$N and CH cyclopropane), 2.29 (1H, dt*a*, J_{HH} 6.0, 2.6 and 2.6 Hz, CH cyclopropane), 2.43 (3H, s, CH_3), 2.94-2.87 (2H, m, CH_2N), 3.23 (1H, broad s, CH cyclopropane), 4.59 (1H, t,

$^3J_{HH}$ 6.0 Hz, NH), 5.15 (1H, ddd, J_{HH} 5.3, 2.2 and 0.8 Hz, olefinic H), 5.87 (1H, dt*a*, J_{HH} 5.3, 2.3 and 2.3 Hz, olefinic H), 7.07-7.33 (12H, 10 CH aromatic + 2 CH tosyl), 7.65 (2H, d, $^3J_{HH}$ 8.3 Hz, 2 CH tosyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 21.6 (CH_3 tosyl), 37.0 (CH cyclopropane), 37.5 (C aliphatic), 38.0 (CH cyclopropane), 41.1, 41.2 ($2CH_2$, CH_2CH_2N), 51.1 (CH allylic), 126.5, 126.6 (2CH, phenyl), 127.1, 127.9, 128.1, 128.6, 129.7 (5CH x 2 aromatic), 131.4 (CH olefinic), 131.7 (CH x 2, aromatic), 134.3 (CH, olefinic), 137.0, 137.5, 143.4, 144.2 (4C aromatic). MS(SIMS) *m*/*z* (%): 452 (M+Na, 100), 429 (M), 274 (33), 259 (47), 245 (77). HRMS calcd for (M) $C_{27}H_{27}NO_2S$: 429.1763; found 429.1758 (1.2 ppm).

***N*-{2-[4,6-Bis-(3,5-dimethoxyphenyl)-bicyclo[3.1.0]hex-2-en-6-yl]-ethyl}-4-methylbenzene-sulfonamide (5b).** In a dry two necked flask were introduced *N*-{2-[1-(3,5-dimethoxyphenyl)-cyclohexa-2,5-dienyl]-ethyl}-4-methyl-benzenesulfonamide **3b** (66 mg, 0.168 mmol), silver carbonate (93 mg, 0.336 mmol), triphenylphosphine (6.6 mg, 0.025 mmol), 3,5-dimethoxy-iodobenzene **4b** (89 mg, 0.336), palladium acetate (1.9 mg, 0.008 mmol) and acetonitrile (8.5 mL). The mixture was warmed to 85 °C and stirred for 20 hours. The mixture was filtered through celite, which was then washed with ethyl acetate. Evaporation of the solvents led to a paste, which was purified through silica gel chromatography (Petroleum ether/EtOAc 80:20), affording **5b** as a viscous oil (48 mg, 52%). IR (film, KBr, $\nu_{max,}$ cm^{-1}): 2937, 1594, 1458, 1425, 1325, 1204, 1155, 1064, 839, 732. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.38-1.50 (1H, m, C<u>H</u>*a*H*x*CH_2N), 1.72-1.84 (2H, m, CH*a*<u>H</u>*x*CH_2N and CH cyclopropane), 2.21-2.26 (1H, m, CH cyclopropane), 2.41 (3H, s, CH_3 tosyl), 2.91 (2H, q*a*, $^3J_{HH}$ 7.3 Hz, CH_2N), 3.28 (1H, broad s, CH cyclopropane), 3.77 (12H, $2OCH_3$ x 2), 4.46 (1H, broad s, NH), 5.20 (1H, d, $^3J_{HH}$ 5.3 Hz, CH olefinic), 5.82-5.84 (1H, m, CH olefinic), 6.22 (2H, s, 2CH aromatic) 6.32 (4H, s, 2CH x 2 aromatic), 7.25 (2H, d, $^3J_{HH}$ 8.3 Hz, CH x 2 tosyl), 7.63 (2H, d, $^3J_{HH}$ 8.3 Hz, CH x 2 tosyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 21.6 (CH_3 tosyl), 37.1, 38.0 (2CH cyclopropane), 38.1 (C aliphatic), 41.2, 41.3 ($2CH_2$, CH_2CH_2N), 51.2 (CH allylic), 55.4, 55.5 ($2OCH_3$ x 2), 98.2, 98.5 (2CH aromatic), 105.9, 110.0 (2CH x 2 aromatic), 127.1, 129.8 (2CH x 2 tosyl), 131.6, 134.2 (2CH olefinic), 137.0, 140.0, 143.4, 146.7 (4C aromatic), 160.5, 161.0 (2C x 2 aromatic). MS(ESI) *m*/*z* (%): 1121 (2M+Na, 22), 588 (M+K, 13), 572 (M+Na, 100). HRMS calcd for $[M+Na]^+$ $C_{31}H_{35}NNaO_6S$: 572.2083; found 572.2082 (0 ppm).

***N*-{2-[4-(3,5-Dimethoxy-phenyl)-6-phenyl-bicyclo[3.1.0]hex-2-en-6-yl]-ethyl}-methane-sulfonamide (5c).** In a dry two necked flask were introduced *N*-[2-(1-Phenyl-cyclohexa-2,5-dienyl)-ethyl]-methanesulfonamide **3c** (169 mg, 0.610 mmol), silver carbonate (336 mg, 1.22 mmol), triphenylphosphine (24 mg, 0.092 mmol), 3,5-dimethoxy-iodobenzene **4b** (322 mg, 1.22 mmol), palladium acetate (6.8 mg, 0.030 mmol) and acetonitrile (24.5 mL). The mixture was warmed to 85 °C and stirred for 16 hours. The mixture was filtered through celite, which was then washed with ethyl acetate. Evaporation of the solvents led to a paste, which was purified through silica gel chromatography (Petroleum ether/EtOAc 70:30), affording **5c** as a white solid (98 mg, 39%). Mp = 123-125 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 3295, 2936, 2255, 1606, 1454,

1316, 1203, 1149, 1064, 973, 910, 777, 735, 710. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.53-1.63 (1H, m, C<u>H</u>*a*H*x*CH_2N), 1.90 (1H, d, $^3J_{HH}$ 6.0 Hz, CH cyclopropane), 1.93-2.00 (1H, m, CH*a*<u>H</u>*x*CH_2N), 2.36 (1H, dt*a*, J_{HH} 6.0, 2.5 and 2.5 Hz, CH cyclopropane), 2.82 (3H, s, NSO_2CH_3), 3.00-3.10 (2H, m, CH_2N), 3.19-3.23 (1H, m, CH cyclopropane), 3.78 (6H, s, OCH_3 x 2), 4.43 (1H, broad s, NH), 5.16 (1H, ddd, J_{HH} 5.3, 2.2 and 1.5 Hz, CH olefinic), 5.91 (1H, dt*a*, *J* = 5.3, 2.0 and 2.0 Hz, CH olefinic), 6.33 (1H, t, $^4J_{HH}$ 2.3 Hz, CH aromatic), 6.36 (1H, t, $^4J_{HH}$ 2.3 Hz, CH x 2 aromatic), 7.17-7.35 (5H, m, 5CH aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$): 36.9 (CH cyclopropane), 37.7 (C aliphatic), 37.9 (CH cyclopropane), 40.0 (NSO_2CH_3), (CH_2N), 41.7 (<u>C</u>H_2CH_2N), 51.3 (CH allylic), 55.4 (OCH_3 x 2), 98.5 (CH aromatic), 105.8 (CH x 2 aromatic), 126.6 (CH aromatic), 128.2 (CH x 2 aromatic), 131.6 (CH olefinic), 131.7 (CH x 2 aromatic), 134.1 (CH olefinic), 137.5, 146.6 (2C aromatic), 160.9 (C x 2 aromatic). MS(SIMS) *m*/*z* (%): 436 (M+Na, 35), 414 (M+H, 100), 305 (35). HRMS calcd for (M+H) $C_{23}H_{28}NO_4S$ 413.1661; found 413.1655 (1.5 ppm).

DFT computed ^{13}C NMR spectrum of 5c

Gaussian09 was used with B3LYP/6-311+G(2d,p)-SCRF//B3LYP/6-311+G(2d,p) basis set. The solvent (chloroform) effect has been accounted with SCRF=(smd,solvent=chloroform).

The following equation is used to produce scaled chemical shifts (δ) from computed isotropic shielding constants (σ). Scaling factors from ref. 23 were used.

$$\delta = \frac{intercept - \sigma}{-slope}$$

With slope = -1.0451 and intercept = 182.3835 (R^2 = 0.9986).

Computed δ_C (experimental δ_C) 36.9 (36.9), 37.1 (37.7), 39.8 (41.2), 40.0 (37.9), 42.1 (41.7), 44.3 (40.0), 54.3 (51.3), 52.9 (55.4), 95.0 (98.5), 102.5 (105.8), 125.0 (126.6), 126.9 (128.2), 131.0 (131.6), 133.8 (131.7), 134.5 (134.1), 138.5 (137.5), 147.2 (146.6), 161.4 (160.9).

***N*-{2-[4,6-Bis-(3,5-dimethoxy-phenyl)-bicyclo[3.1.0]hex-2-en-6-yl]-ethyl}-methanesulfonamide (5d).** In a dry two necked flask equipped with a condenser were introduced iodo-3,5-dimethoxybenzene **4b** (517 mg, 1.96 mmol), silver carbonate (538 mg, 1.96 mmol), palladium acetate (7.3 mg, 0.033 mmol), triphenylphosphine (26 mg, 0.098 mmol) then a solution of (N-{2-[1-(3,5-dimethoxy-phenyl)-cyclohexa-2,5-dienyl]-ethyl}-methanesulfonamide **3d** (220 mg, 0.653 mmol) in acetonitrile (26 mL). The mixture was warmed to 85 °C for 14 hours. The mixture was filtered through celite, which was then washed with ethyl acetate. Evaporation of the solvents led to a paste, which was purified through silica gel chromatography (25 g, Petroleum ether/EtOAc 70:30), affording, first, starting material **3d** (48 mg, 22%) then **5d** as a viscous oil ($\Delta Rf \leq 0.1$) (117 mg, 38%). IR (film, NaCl, $\nu_{max,}$ cm^{-1}): 3298 cm^{-1}, 2937, 1594, 1456, 1320, 1204, 1154, 1064, 839, 777, 735. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.53-1.62 (1H, m, C<u>H</u>*a*H*x*CH_2N), 1.85-1.98 (2H, m, CH*a*<u>H</u>*x*CH_2N and CH cyclopropane), 2.31-2.35 (1H, m, CH cyclopropane), 2.85 (3H, s, NSO_2CH_3), 3.05-3.11 (2H, q*a*, $^3J_{HH}$ 6.6 Hz, CH_2N), 3.34 (1H, broad

s, CH cyclopropane), 3.78 (6H, s, OCH_3 x 2), 3.79 (6H, s, OCH_3 x 2), 4.33 (1H, broad s, NH), 5.22-5.25 (1H, m, CH olefinic), 5.86-5.89 (1H, m, CH olefinic), 6.31-6.35 (6H, m, CH aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 37.2 (CH cyclopropane), 38.0 (C aliphatic), 38.1 (CH cyclopropane), 40.2 (NSO_2CH_3), 41.4 (CH_2N), 41.7 ($\underline{C}H_2CH_2N$), 51.2 (CH allylic), 55.4 ($2OCH_3$ x 2), 98.1, 98.5 (2CH aromatic), 105.9, 110.1 (2CH x 2 aromatic), 131.5, 134.3 (2CH olefinic), 140.0, 146.7 (2C aromatic), 160.6, 161.0 (2C x 2 aromatic). MS(ESI) *m*/*z* (%): 496 (M+Na, 100). HRMS calcd for (M+Na) $C_{25}H_{31}NNaO_6S$ 496.1770; found 496.1786 (-3.3 ppm).

***N*-{2-[4-(4-Methoxy-phenyl)-6-phenyl-bicyclo[3.1.0]hex-2-en-6-yl]-ethyl}-4-methyl-benzenesulfonamide (5e).** In a dry two-necked flask were introduced 4-methyl-*N*-[2-(1-phenyl-cyclohexa-2,5-dienyl)-ethyl]-benzenesulfonamide **3a** (71 mg, 0.200 mmol), silver carbonate (55 mg, 0.20 mmol), triphenylphosphine (10 mg, 0.04 mmol), palladium acetate (2.3 mg, 0.01 mmol) in acetonitrile (8 mL). 4-Methoxyphenyl iodide **4c** (47 mg, 0.20 mmol) was added and the mixture was warmed to 85 °C and stirred overnight. The mixture was filtered through celite, which was then washed with ethyl acetate. Evaporation of the solvents led to a paste, which was purified through silica gel chromatography (Petroleum ether/EtOAc 90:10), affording **5e** as a viscous oil (34 mg, 37%). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.38-1.50 (1H, m, C$\underline{H}a$H$x$$CH_2$N), 1.72-1.87 (2H, m, CH$a\underline{H}x$$CH_2$N and CH cyclopropane), 2.26 (1H, dt$a$, J_{HH} 6.1, 2.4 and 2.4 Hz, CH cyclopropane), 2.42 (3H, s, CH_3 tosyl), 2.89 (2H, qa, $^3J_{HH}$ 7.6 Hz, CH_2N), 3.17 (1H, broad s, CH cyclopropane), 3.79 (3H, s, OCH_3), 4.45 (1H, t, $^3J_{HH}$ 6.1 Hz, NH), 5.12 (1H, ddd, J_{HH} 5.5, 2.1 and 1.2 Hz, CH olefinic), 5.83 (1H, dt$a$, J_{HH} 5.5, 2.1 and 2.1 Hz, CH olefinic), 6.83 (2H, d, $^3J_{HH}$ 8.6 Hz, CH x 2 aromatic), 7.04-7.09 (4H, m, CH x 2 aromatic and 2 CH tosyl), 7.21-7.29 (5H, m, CH aromatic), 7.63 (2H, $^3J_{HH}$ 8.3 Hz, 2 CH tosyl). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 21.6 (CH_3 tosyl), 36.8 (CH cyclopropane), 37.7 (C aliphatic), 38.2 (CH cyclopropane), 41.1, 41.2 ($2CH_2$, CH_2CH_2N), 50.2 (CH allylic), 55.4 (OCH_3), 113.9 (CH x 2 aromatic), 126.5 (CH aromatic), 127.1, 128.1, 128.8, 129.8 (4CH x 2 aromatic), 131.0 (CH olefinic), 131.7 (CH x 2 aromatic), 134.5 (CH olefinic), 136.3, 136.9, 137.6, 143.4, 158.3 (5C aromatic).

Acknowledgements

This work was supported by the MNERT through a PhD grant to RL. We also thank the CNRS for its help.

References

1. Abd Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369 and references therein. http://dx.doi.org/10.2174/1385272023373347

2. Studer, A.; Schleth, F. *Synlett* **2005**, 3033 and references therein.
http://dx.doi.org/10.1055/s-2005-921899
3. Nakahara, K.; Fujioka, H. *Symmetry* **2010**, *2*, 437 and references therein.
http://dx.doi.org/10.3390/sym2020437
4. Walton, J. C.; Studer, A. *Acc. Chem. Res*. **2005**, *38*, 794 and references therein.
http://dx.doi.org/10.1021/ar050089j
PMid:16231875
5. Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755.
http://dx.doi.org/10.1021/ol0618353
PMid:17020295
6. Rousseau, G.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2008**, *10*, 4441.
http://dx.doi.org/10.1021/ol8016885
PMid:18783229
7. Zeni, G.; Larock, R. C. *Chem. Rev*. **2004**, *104*, 2285.
http://dx.doi.org/10.1021/cr020085h
PMid:15137792
8. Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400.
http://dx.doi.org/10.1002/anie.200300630
PMid:15221827
9. McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* **2011**, *13*, 2830.
http://dx.doi.org/10.1021/ol200784y
PMid:21534607 PMCid:PMC3103601
10. Beniazza, R.; Dunet, J.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2007**, *9*, 3913.
http://dx.doi.org/10.1021/ol701493k
PMid:17824704
11. Guram, A. S.; Bei, X.; Turner, H. W. *Org. Lett.* **2003**, *5*, 2485.
http://dx.doi.org/10.1021/ol0347287
PMid:12841761
12. Bouquillon, S.; Hénin, F.; Muzart, J. *Organometallics* **2000**, *19*, 1434.
http://dx.doi.org/10.1021/om990961q
13. Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620.
http://dx.doi.org/10.1021/ja0394838
PMid:14871078
14. Hay, M. B.; Wolfe, J. P. *Tetrahedron Lett.* **2006**, *47*, 2793.
http://dx.doi.org/10.1016/j.tetlet.2006.02.066
PMid:19789723 PMCid:PMC2752900
15. Ney, J. E.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3605.
http://dx.doi.org/10.1002/anie.200460060
PMid:15293259

16. Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447.
http://dx.doi.org/10.1016/j.tet.2005.03.110
17. Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851.
http://dx.doi.org/10.1021/jo801631v
PMid:18942792 PMCid:PMC2633938
18. Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468.
http://dx.doi.org/10.1021/ja054754v
PMid:16305233 PMCid:PMC2750864
19. Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351.
http://dx.doi.org/10.1055/s-0031-1289668
PMid:23243321 PMCid:PMC3521566
20. Lebeuf, R.; Dunet, J.; Beniazza, R.; Ibrahim, D.; Bose, G.; Robert, F.; Landais, Y. *J. Org. Chem.* **2009**, *74*, 6469.
http://dx.doi.org/10.1021/jo901395m
PMid:19655764
21. Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557.
http://dx.doi.org/10.1021/ol051377i
PMid:16209478
22. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.
http://dx.doi.org/10.1021/cr020039h
PMid:12914487
23. Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. *J. Chem. Rev.* **2012**, *112*, 1839. Scaling factors and methods were taken from the tables in the supporting information.
http://dx.doi.org/10.1021/cr200106v
PMid:22091891
24. Grigg, R.; Rasul, R.; Redpath, J.; Wilson, D. *Tetrahedron Lett.* **1996**, *37*, 4609.
http://dx.doi.org/10.1016/0040-4039(96)00889-1
25. Celik, M.; Alp, C.; Coskun, B.; Gültekin, M. S.; Balci, M. *Tetrahedron Lett.* **2006**, *47*, 3659.
http://dx.doi.org/10.1016/j.tetlet.2006.03.137

