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A study on the regio- and stereoselectivity in palladium-catalyzed cyclizations of alkenes and alkynes bearing bromoaryl and nucleophilic groups

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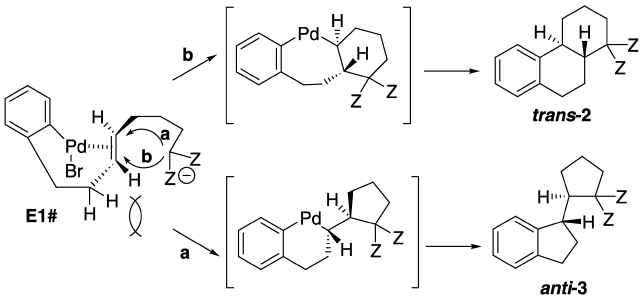
Abstract—We have studied the remarkable dependence of the stereochemistry of the cyclization on the double bond geometry and of the effect of the bulkiness of the nucleophile on the regiochemistry of the palladium mediated cyclization of alkenes bearing aryl bromides and nucleophiles. In contrast, the cyclization of the acetylenic homologous substrates is not dependent on the nature of the nucleophile.

1. Introduction

Control of regio- and stereochemistry during the simultaneous creation of consecutive stereogenic centers continue to offer considerable challenge to organic chemists.[1] Transition metal-mediated tandem or cascade reactions have recently emerged as new and powerful methods, which are aimed at achieving this goal. The scope and limitations of such reactions have been the subject of recent reviews.[2] Following this trend, we have developed a new palladium-mediated cyclization reaction of unsaturated substrates bearing a nucleophilic substituent.[3] By using the intramolecular version of this strategy, we have already achieved the stereocontrolled synthesis of fused tricyclopentanoid[4] and linearly condensed hexahydro-1*H*-benz[*f*]indenes.[5] It is noteworthy that these cyclizations proceed in a completely *trans*-stereoselective manner since they involve attack of the carbon nucleophile onto the double bond which is electrophilically activated by the organopalladium species.

It was envisioned that application of the same concept to linear substrates having an internal *trans* double bond such as **E1** would either proceed via a 5-*exo* or a 6-*endo*-trig process leading to tricyclic compounds **2** and **3**, respectively (Scheme 1). We thought that the syntheses of these two tricyclic compounds would occur with concomitant stereocontrol of the two newly formed adjacent carbon centers since the nucleophile and the organopalladium species add in a *trans* fashion across the unsaturated linkage. This means



Scheme 1.

that, due to the stereochemistry of the initial double bond substrate, the ring fusion in compound **2** must be *trans*. The relative configuration of **3** would be fixed for the same reason. Moreover, examination of molecular models led us to believe that the bulkiness of the nucleophile would be a determining factor controlling the selectivity (5-*exo*- versus 6-*endo-trig*) of the reaction. In general, *exo*-cyclization is kinetically more favorable than the *endo* mode of attack. In the particular case of a substrate of type **1**, the geometric requirement for the intramolecular palladium-mediated cyclization in the 6-*endo-trig* process seems to induce less strain in the transition state relative to attack according to 5-*exo-trig* process. However, severe steric interactions between a bulky nucleophile and one of the allylic hydrogens of the linear substrate could be anticipated in the *endo*-cyclization mode. We were therefore interested to see if these steric interactions could be used as stereocontrolling elements during the cyclization. Indeed, a thin nucleophile would favor 5-*exo* pathway, while the 6-*endo-trig* would be preferred in the presence of a bulky nucleophile (Scheme 1). We also wanted to examine the

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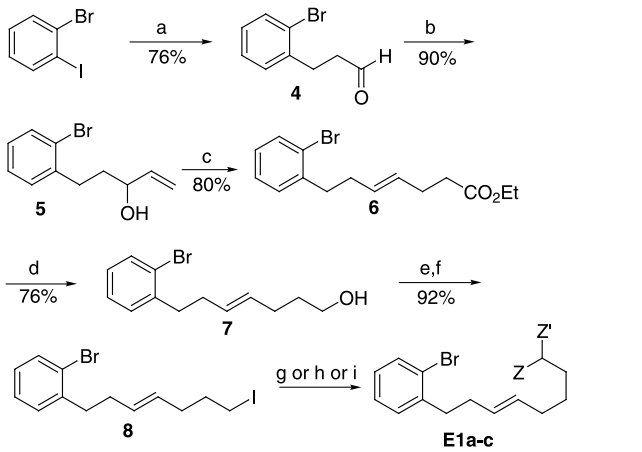
importance of olefin geometry on the stereochemical course of the cyclization.

In this paper, we report details of our work[6] and show that the cyclization proceeds with virtually complete regio- and stereocontrol. Moreover, the reaction is shown to be stereospecific with the stereochemical outcome depending on the geometry of the internal alkene.

2. Results and discussion

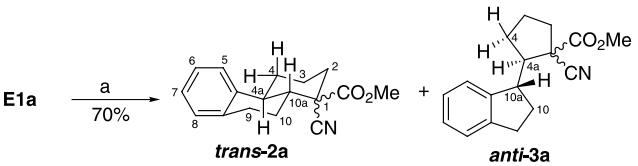
2.1. Cyclization of linear *trans*-alkenes E1a–c

In order to validate the feasibility of our strategy, the palladium catalyzed cyclization reactions of linear *trans* alkenes of type **E1a–c** differing in the bulkiness of the nucleophilic moiety were investigated. The cyclization substrates **E1a–c** were prepared via the route outlined in Scheme 2, in a seven-step sequence from commercially available 1-bromo-2-iodobenzene. Thus treatment of this dihalide with allylic alcohol, in DMF, at 50 °C, according to the procedure published by Jeffery[7] [$Pd(OAc)_2$, benzyltriethylammonium chloride, $NaHCO_3$] afforded the single aldehyde **4** in 92% yield. Treatment of **4** with vinylmagnesium bromide led to allylic alcohol **5** in 90% yield. The orthoester Claisen rearrangement of **5** proceeded in triethylorthoacetate at reflux to give 80% of the ester **6**. Reduction of **6** with lithium aluminium hydride in diethyl ether cleanly provided the alcohol **7** which was transformed to the iodide **8** via the corresponding mesylate. Substitution of the iodide group by the sodium salts of methyl cyanoacetate, dimethyl malonate and malononitrile, respectively, furnished the corresponding precursors **E1a–c**.



Scheme 2. Reagents and conditions: (a) allyl alcohol, $Pd(OAc)_2$ 5%, $NaHCO_3$, TEBA, DMF, 50 °C; (b) vinylmagnesium bromide, THF, −30–25 °C, 2 h; (c) $CH_3-C(OEt)_3$, propionic acid, reflux, 12 h; (d) $LiAlH_4$, ether, 25 °C, 30 min; (e) MsCl, TEA, CH_2Cl_2, 0 °C, 2 h;(f) NaI, acetone, reflux, 12 h; ((g) NaH, dimethylmalonate, DMF/THF 1/1, reflux, 18 h; (h) NaH, malononitrile, THF, reflux, 12 h; (i) NaH, methylcyanoacetate, DMF/THF 1/1, reflux, 12 h.

Initial experiments to cyclize the *trans* alkene **1a** using previously developed methodology in our group failed.[4] Therefore, when a solution of **1a** in THF was treated with 1.1 equiv. of *t*BuOK, followed by addition of 5 mol% of Pd(dppe),[8] no reaction was observed and starting material was recovered even after prolonged reflux times. Optimum conditions of our tandem biscyclization reaction performed on the substrate **E1a** involved formation of the enolate with *t*BuOK, in presence of 5 mol% of Pd(dppe), in dry 1-methyl-2-pyrrolidinone (NMP) at 50 °C. After 24 h, the starting material was consumed and a 1:1 mixture of two tricyclic compounds was obtained in 70% combined yield. The ^1H NMR of the crude reaction product revealed no traces of bicyclic products resulting from the competing Heck reaction (Scheme 3).



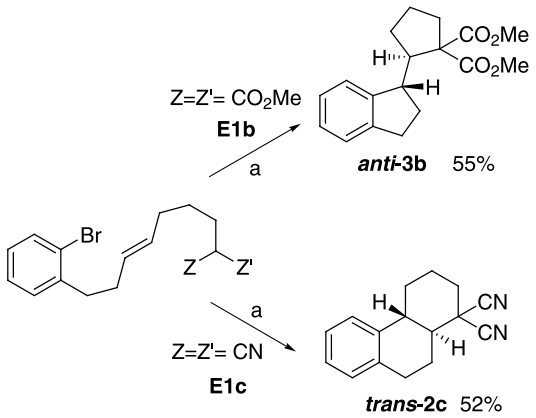
Scheme 3. Reaction conditions: (a) $Pd(OAc)_2$ 5%, dppe 10%, 1-heptene 10%, 18-C-6 crown ether 20%, *t*BuOK, NMP, 50 °C.

These two tricyclic compounds were separated by careful medium pressure liquid chromatography and their structures were confirmed by ^1H and ^{13}C NMR data. The solid less polar product was identified as one epimer of *trans*-**2a** by a 400 MHz two dimensional DQF COSY spectrum and a $^1H-^{13}C$ HMQC experiment (heteronuclear multiple quantum coherence) recorded in the phase-sensitive mode that permit identification of most of the hydrogens and carbons.[9] Thus, H_{4a} resonates at δ=2.12 ppm as doublet of a doublet of a doublet. The J_{4a-10a}, $J_{4a-4a\ ax}$ and $J_{4a-4a\ eq}$ constants were 12.1, 11.3, 3.9 Hz, respectively, and were consistent with the expected two large coupling constants J_{ax-ax} and one J_{ax-eq} of a *trans*-octahydrophenanthrene.[10]

The structure assigned to the liquid more polar product was one epimer of *anti*-**3a** by arguments analogous to those made for the assignment of *trans*-**2a**. In the ^1H NMR, the double doublet of doublets at 3.4 ppm is assigned to the H_{10a} angular proton. It is coupled to the adjacent H_{10} and $H_{10'}$ protons by coupling constants J_{10a-10}=8.3 Hz, $J_{10a-10'}$=7.1 Hz typical of a five-membered ring. The splitting of the H_{10a} signal is due to its coupling with the adjacent angular proton H_{4a} (J_{10a-4a}=11.5 Hz) and this confirms the expected *anti* relationship between them.

As expected, the palladium induced cyclization of **E1a** bearing a medium size nucleophile proceeded via both *exo* and *endo*-pathway, but surprisingly, only one diastereomer of *trans*-**2a** and *anti*-**3a** were formed at the carbon bearing the nitrile and the ester. The configuration of the quaternary center was not determined. Next, we attempted the cyclization of substrate **E1b** bearing a bulky nucleophile. This was carried out under the usual reaction conditions used for **E1a**. After 5 h at 60 °C, the reaction provided exclusively compound *anti*-**3b** which was isolated in 55% yield after chromatographic purification. No traces of the other regioisomer or of classical Heck reaction product were observed within the limits of ^1H NMR and capillary GC

sensitivities. The stereostructural assignments for the tricyclic compound were verified by comparison of its characteristic ^{1}H NMR data with those of *anti*-**3a**. In particular, the *trans* relationship between H_{10a} and H_{4a} was readily deduced from the coupling constant J_{10a-4a}=11 Hz (Scheme 4).



Scheme 4. Reaction conditions: (a) $Pd(OAc)_2$ 5%, dppe 10%, 1-heptene 10%, 18-C-6 crown ether 20%, *t*BuOK, NMP, 50 °C.

This result clearly indicates that the 5-*exo*-cyclization can be controlled by judicious choice of the nucleophile substituent. Finally, we turned our attention to the cyclization of the substrate **E1c** bearing a thin nucleophile. In contrast to the facile cyclization of substrates **E1a** and **E1b**, **E1c** appeared to be more resistant since using the procedure mentioned above, all the starting material was only consumed after 65 h at 60 °C.[11] A colorless solid was isolated in 52% yield after flash-chromatography and characterized as the regioisomer *trans*-**2c**, resulting from the 6-*endo-trig* cyclization process on the basis of spectroscopic correlation with *trans*-**2a** (Scheme 4). The *trans* junction of the ring was confirmed by its ^{1}H NMR spectrum in C_6D_6 in which the H_{10a} proton resonates at δ=1.50 ppm and its coupling pattern as a doublet (J=4.3 Hz) of triplet (J=12 Hz) consistent with a small J_{ax-eq} and two large J_{ax-ax} couplings. In addition, a single crystal X-ray diffraction analysis confirmed the stereochemical assignment of this diastereomer (Fig. 1).

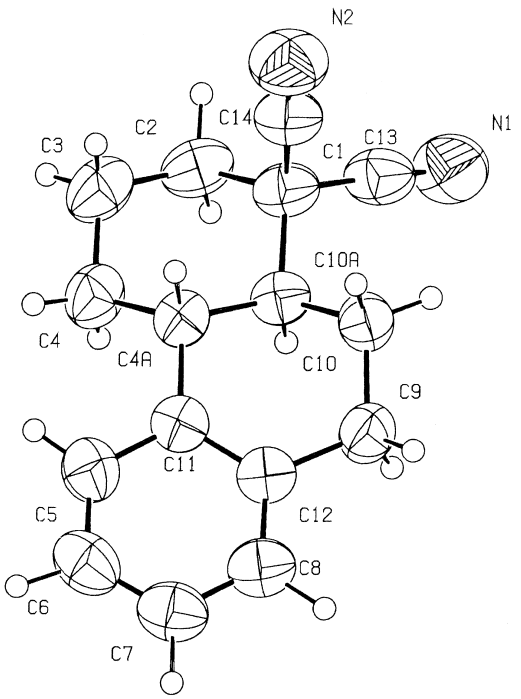
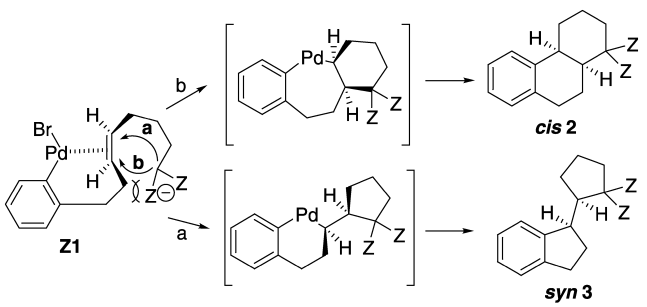


Figure 1. X-ray crystallographic structure of compound *trans*-**2c**: ORTEP view.

This last result shows that, in this case, the tandem carbopalladation–cyclization sequence proceeds with complete regio- and stereoselectivity leading to the *trans* perhydrophenanthrene ring. This system is very common in natural products, particularly in the carbon framework of steroids and many triterpenoids.[12]

2.2. Cyclization of linear *cis*-alkenes Z1a–c

Since the ring junction stereochemistry is governed by alkene geometry, a question which is raised by these successful preliminary results is the stereospecificity of this tandem carbopalladation–cyclization sequence. In order to gain further insight into this problem, we investigated the cyclization of *Z* linear substrates of type **1** (Scheme 5).

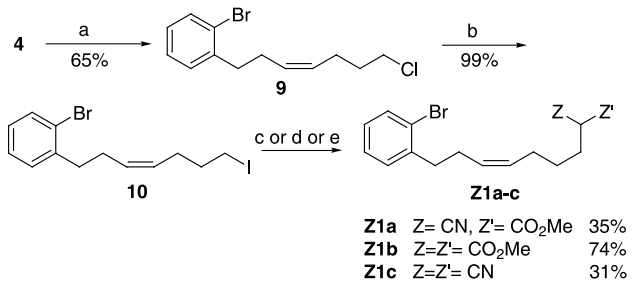


Scheme 5.

Using molecular model, we speculated as previously described for the cyclization of *trans* isomers, that the regioselectivity would depend again upon steric factors. Indeed, in the approach of the nucleophile to the internal double bond, a strong interaction was observed between one of the allylic hydrogens and the nucleophile. Bulky ones would therefore favor the 5-*exo* cyclization while smaller ones would shift the reaction to the expected 6-*endo* pathway. The success of such a reaction would lead to the synthesis of the *cis*-octahydrophenanthrene skeleton. It is noteworthy that a few synthetic methodologies have been developed to construct this core structure which is of current interest.[13]

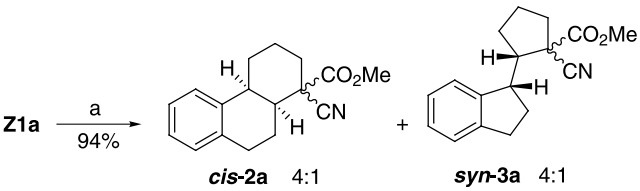
Access to the required starting material **Z1a–c** proved to be straightforward with the key step being a Wittig condensation of the known phosphonium salt[14] with the aldehyde **4** giving the *Z*-alkene **9** with complete stereoselectivity. Conversion of the chloride to the iodide **10** followed by reaction with the sodium salts of methyl cyanoacetate, dimethyl malonate and malononitrile, respectively, produced the corresponding precursors **Z1a**, **Z1b**, **Z1c** (Scheme 6).

Treatment of **Z1a** with Pd(dppe) (5 mol%) and *t*BuOK (1.1 equiv.) in NMP at 50 °C afforded an inseparable



Scheme 6. Reagents and conditions: (a) (4-chlorobutyl)-triphenylphosphonium bromide, KHMDS, THF, 0 °C; (b) NaI, acetone, reflux, 12 h; (c) NaH, methylcyanoacetate, DMF/THF 1/1, reflux, 12 h; (d) NAH, dimethylmalonate, DMF/THF 1/1 reflux, 18 h; (e) NaH, malononitrile, THF, reflux, 12 h.

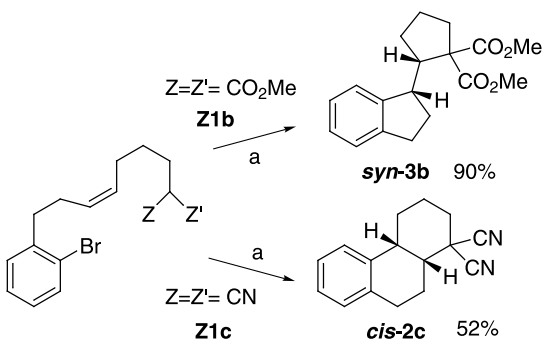
mixture of four isomeric tricyclic compounds in a ratio of about 4:4:1:1 after only 1.5 h (according to GC) and in 94% yield. We suspected that these four substrates were two couples of diastereomers for each of the regioisomers, *cis*-**2a** and *syn*-**3a**. The ^{1}H and ^{13}C NMR spectra of the mixture were significantly different from those reported for *trans*-**2a** and *anti*-**3a** and no traces of compounds resulting from a Heck reaction were observed. Because of the low regio- and diastereoselectivity (referred to C_1 carbon) exerted in this cyclization, we decided not to investigate which of the four isomers were predominant (Scheme 7).



Scheme 7. Reaction conditions: (a) $Pd(OAc)_2$ 5%, dppe 10%, 1-heptene 10%, 18-C-6 crown ether 20%, *t*BuOK, NMP, 50 °C.

Interestingly, treatment of **Z1b** under the same conditions gave *syn*-**3b** as a single diastereomer in 90% yield after 12 h at 50 °C (Scheme 8). Spectral data clearly indicated the five-membered ring: in particular, the C_{10} axial proton at δ 2–2.5 ppm has the expected coupling pattern (ddd, J=7.1, 8.8, 13.8 Hz). The *cis* relationship between H_{4a} and H_{10a} was established by the coupling constant (J=3 Hz) in the homonuclear decoupling spectrum (Scheme 8).

This result indicates that the pallado-catalyzed cyclization of linear compounds **1b** is stereospecific and that the



Scheme 8. Reaction conditions: (a) $Pd(OAc)_2$ 5%, dppe 10%, 1-heptene 10%, 18-C-6 crown ether 20%, *t*BuOK, NMP, 50 °C.

dimethylmalonate group again exerts a profound influence upon the regiochemistry of cyclization process by virtue of its steric bulk.

Finally, we have investigated the cyclization of **Z1c** bearing a smaller nucleophile. This reaction was performed at 50 °C for 48 h to afford the single crystalline *cis* octahydrophenanthrene **2c** in 52% yield (Scheme 8). The small ^{1}H NMR coupling (J=3.7 Hz) observed between the angular hydrogens confirmed the expected *cis* ring fusion of **2c**. The ^{13}C NMR spectrum displays two methine carbons (36.8 and 40 ppm) showing that the carbons of the ring junction in *cis*-**2c** are more shielded than those of *trans*-**2c** (38.8 and 44.5 ppm). This is in accordance with the fact that the ^{13}C NMR shift values for a *cis* ring junction of perhydrophenanthrenes are smaller than those for a *trans* junction.[15] Single X-ray diffraction analysis unambiguously established the expected stereochemistry as shown in Figure 2.

The remarkable influence of the double bond geometry of the starting material on the stereochemistry of the product was here also demonstrated. Furthermore, the regiochemistry of the cyclization could be controlled by the size of the nucleophile.

2.3. Cyclization of the acetylenic substrates 14a–b

It was of interest to examine the behavior of the corresponding acetylenic substrates under our standard conditions of cyclization. We wanted to know if the bulkiness of the nucleophile could also exert a beneficial directing effect on the regioselectivity during the palladium mediated cyclization leading either to cyclopentylidenindane **15** or to hexahydrophenanthrene **16** (Scheme 9).

To this end, syntheses of the two required acetylenic substrates were each accomplished in a four step sequence starting from the commercially available 2-bromobenzyl bromide as illustrated in Scheme 10. The required Grignard reagent was generated in situ in diethyl ether, from propargyl bromide and magnesium turnings and then added to 2-bromobenzyl bromide to provide **11** in 75% yield. Deprotonation of the resulting acetylenic product by lithium diisopropylamide (LDA) followed by addition of an excess of 1-bromo-3-chloropropane afforded chloride **12** in 60% yield. Halide exchange (NaI, acetone) gave the desired iodide **13** in excellent yield. This iodide was treated with the sodium salts of dimethylmalonate and malonitrile to respectively produce the corresponding acetylenic precursors **14a** and **14b**.

The cyclization of substrate **14a** under the conditions previously used for alkenyl compounds gave, after 24 h at 60 °C, an inseparable mixture of two products in a 3:2 ratio (as determined by ^{1}H NMR). In the ^{1}H NMR spectrum of the product mixture, the minor compound appeared to be **17** resulting from the competing Heck reaction with a proton triplet centered at 3.38 ppm characteristic of proton at the α position of a malonate function, and a vinylic proton at 4.6 ppm. For the major product, the absence of these two protons strongly suggested the biscyclization had taken place but the regiochemistry of the cyclization (6-*endo* versus 5-*exo*) could not be ascertained. In order to improve

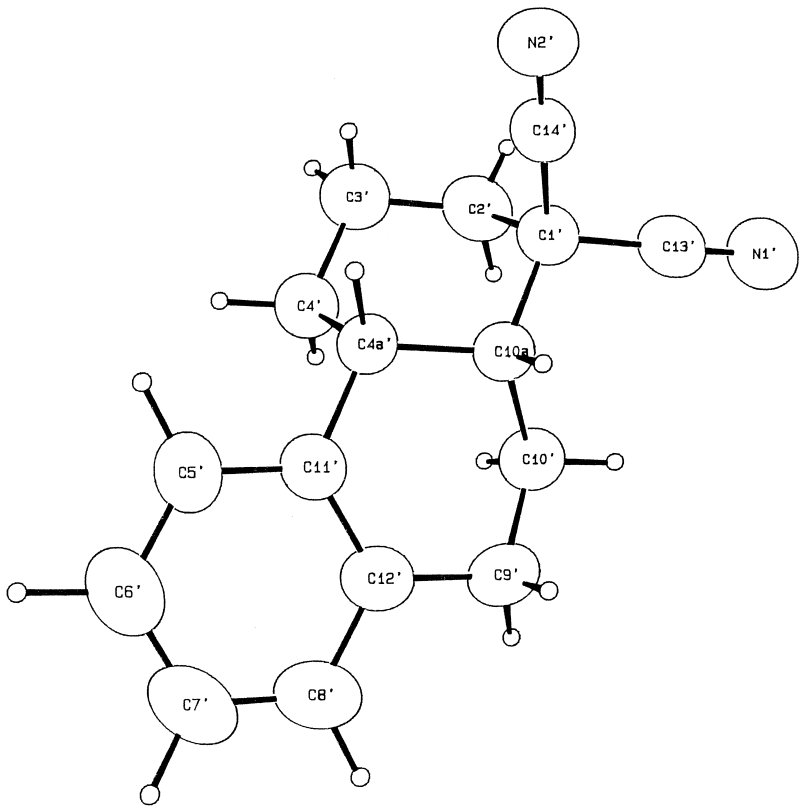
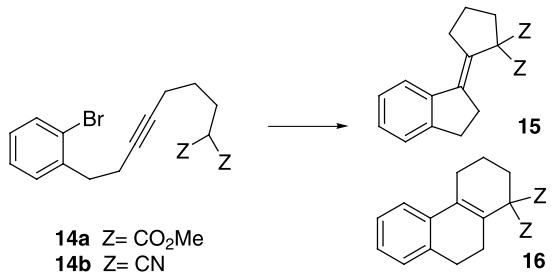
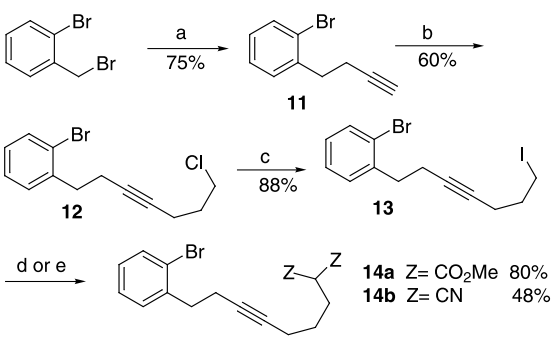


Figure 2. X-ray crystallographic structure of compound *cis*-**2c**: ORTEP view.



Scheme 9.



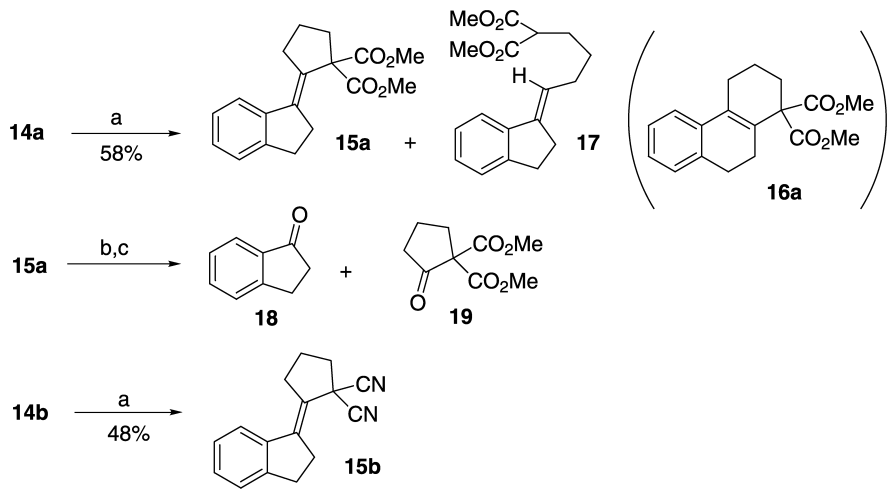
Scheme 10. Reagents and conditions: (a) propargyl bromide, Mg, $HgCl_2$ cat., ether THF, 0 °C; (b) LDA, −78 °C, 1 h then 1-bromo-3-chioro-propane, −60 °C to reflux, 12 h; (c) Nal, acetone, reflux, 12 h; (d) NaH, dimethylmalonate, DMF/THF 1:1, reflux, 18 h; (e) NaH, malononitrile, THF, reflux, 12 h.

the selectivity in favor of the biscyclized product, we decided to test the reaction in DMSO. In this solvent, the reaction was complete after 2 h at 90 °C leading to the previously obtained tricyclic compound (**15a** or **16a**) in 58% yield as the only isolable product. To determine the structure of this unsaturated substrate, the alkene was oxidatively cleaved by treatment with ozone[16] followed by addition of dimethylsulfide leading to two products. The mixture was analyzed by GC–MS proving the presence of 1-indanone **18** by comparison with an authentic sample. The second product shown an ion peak at M^+=200 according to the structure of **19**. This result clearly demonstrated the cyclopentylindanylidene structure **15a** and not **16a** for the biscyclization product (Scheme 11).

Same conditions were applied to **14b** leading after 2 h to a unique crystalline product in 48% yield. The regiochemistry of this compound was derived from a single X-ray diffraction analysis and revealed the cyclopentylindanylidene structure **15b** (Fig. 3). Contrary to the ethylenic substrates, the regioselectivity of the biscyclization process of the acetylenic homologs is independent of the bulkiness of the nucleophile.

3. Conclusion

In summary, we have demonstrated that the simple tandem palladium-catalyzed cyclization of linear compound of type *Z* or *E* proceeds with complete retention of the stereochemistry in a stereocontroled mode. Moreover, it was possible to effect either 5-*exo* or 6-*endo*-cyclization



Scheme 11. Reagents and conditions: (a) $Pd(OAc)_2$ 5%, dppe 10%, 1-heptene 10%, 18-C-6 crown ether 20%, *t*BuOK, DMSO, 90 °C, 2 h; (b) O_3, CH_2Cl_2, −78 °C; (c) DMS, −78 °C to 25 °C.

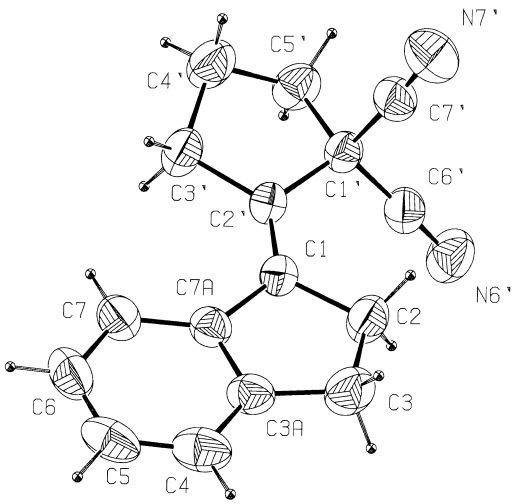


Figure 3. X-ray crystallographic structure of compound **15b**: ORTEP view.

selectively by appropriate choice of the electron withdrawing substituents of the nucleophile. *exo*-Cyclizations are observed when a sterically hindered nucleophile is employed. *endo*-Cyclizations leading to octahydrophenanthrene is the only reaction observed with a less sterically demanding nucleophile. Notably, these cyclizations proceed in a completely stereoselective *trans* manner. The reaction is then stereospecific, the stereochemistry is defined by that of the double bond in the initial substrate, the relative configuration of the indane substrates are hereby controlled. The biscyclization of acetylenic homologs could also be performed leading exclusively to cyclopentylidenindane structure, in that case the bulkiness of the nucleophile has no effect on the course of the reaction.

4. Experimental

4.1. General

All reactions were carried out under a nitrogen atmosphere using standard syringe, cannula and septa techniques. All reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel plates (60 F-254, Merck) or by gas chromatography on a DB 1 capillary column 30 m. Column chromatographies were performed on a silica gel Si 60 (40–63 mesh, Merck). Melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 337 instrument. Nuclear magnetic resonance spectra were obtained on a Brucker AC 200 spectrometer (^{1}H: 200 MHz or ^{13}C: 50 MHz) or on a Brucker AC 300 spectrometer (^{1}H: 300 MHz or ^{13}C: 75 MHz) using TMS as an internal standard. Chemical shifts were expressed in ppm downfield from TMS and coupling constants (*J*) in Hertz. Microanalysis were performed by Service Central d'Analyse du CNRS, Solaize, France. THF was distilled from Na/benzophenone, *N*-methyl pyrrolidone (NMP) and DMSO (dimethyl sulfoxide) were distilled under N_2 from CaH_2, DMF was distilled from P_2O_5 and Et_2O was distilled from LAH prior to use.

4.1.1. 3-(*o*-Bromophenyl)propan-1-al (4). To a solution of $Pd(OAc)_2$ (60 mg, 0.27 mmol), allylic alcohol (1.2 mL, 17.7 mmol), triethylbenzylammonium chloride (1.6 g, 7.1 mmol) and $NaHCO_3$ (1.48 g, 17.7 mmol) in 50 mL of DMF was added 1-bromo-2-iodobenzene (2.2 g, 7.9 mmol). The black solution was heated at 50 °C for 24 h. The mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The organic phase was extracted with Et_2O (3×100 mL), washed with brine (2×100 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography (PE/Et_2O=95:5) to give **4** as a yellow oil (1.15 g, 76%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.8 (2H, m), 3.1 (2H, m), 7.1 (1H, m), 7.25 (2H, m), 7.55 (1H, d, J=7.9 Hz), 9.85 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.7, 43.6, 124.2, 127.6, 128.0, 130.5, 132.9, 139.7, 201.1. IR (neat): 3060, 2960, 2850, 2720, 1720, 1590, 1470, 1440, 1180, 1020, 750 cm^{-1}.

4.1.2. 5-(*o*-Bromophenyl)pent-1-en-3-ol (5). A solution of vinylmagnesium bromide 1 M in THF (11.1 mL) was added dropwise to a stirred solution of **4** (1.57 g, 7.37 mmol) in THF (20 mL) maintained at −30 °C. The solution was allowed to warm to room temperature. After stirring for 2 h,

the reaction was quenched with saturated aqueous NH_4Cl solution. The alcohol was extracted with Et_2O (3×50 mL), washed with brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography (PE/Et_2O=70:30) to give **5** as a yellow liquid (1.71 g, 90%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 (1H, s), 1.75 (2H, m), 2.85 (2H, m), 4.15 (1H, m), 5.2 (2H, m), 5.95 (1H, ddd, J=17.2, 10.4, 6 Hz), 7.1 (1H, m), 7.25 (2H, m), 7.55 (1H, d, J=7.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.2, 37.1, 72.6, 115.7, 124.6, 127.6, 127.8, 130.6, 133.0, 141.0, 141.3. IR (neat): 3400, 3060, 2920, 2860, 1640, 1570, 1470, 1020, 990, 920, 900 cm^{-1}. Anal. calcd for $C_{11}H_{13}OBr$: C, 54.79; H, 5.43. Found: C, 55.20; H, 5.31.

4.1.3. Ethyl (*E*)-7-(*o*-bromophenyl)hept-4-enoate (6). The allylic alcohol **5** (1.71 g, 7.10 mmol) was refluxed with freshly distilled triethyl orthoacetate (39 mL, 214 mmol) and propionic acid (47 μl, 0.63 mmol) for 15 h. After removal of triethyl orthoacetate under vacuum, the residual oil was purified by flash chromatography (PE/Et_2O=70:30) to give ester **6** as a yellow oil (1.76 g, 80%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7.2 Hz), 2.34 (6H, m), 2.78 (2H, m), 4.15 (2H, q, J=7.2 Hz), 5.44 (1H, dt, J=15.4, 6.3 Hz), 5.54 (1H, dt, J=15.4, 6.3 Hz), 7.08 (1H, m), 7.25 (2H, m), 7.55 (1H, d, J=7.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 27.9, 32.6, 34.2, 36.1, 60.2, 124.4, 128.3, 127.5, 129.1, 130.2, 130.4, 132.7, 141.1, 173.1. IR (neat): 3060, 2980, 2860, 1740, 1570, 1470, 1440, 1370, 1180, 1020, 970, 750, 660 cm^{-1}. Anal. calcd for $C_{15}H_{19}O_2Br$: C, 57.81; H, 6.15; O, 10.28. Found: C, 57.96; H, 6.02; O, 10.41.

4.1.4. (*E*)-7-(*o*-Bromophenyl)hept-4-en-1-ol (7). A solution of ester **6** (1.88 g, 6.04 mmol) in dry Et_2O (20 mL) was added dropwise to a cold (0 °C) stirred suspension of LAH (230 mg, 6.04 mmol) in dry Et_2O (50 mL). The mixture was stirred at room temperature for 1 h. Water (0.230 mL), 1 N NaOH (0.230 mL) then 3 mL of water were successively added until a precipitate appeared. The slurry was filtered through a pad of celite and the filtrate was dried over Na_2SO_4 and concentrated. The residual oil was purified by flash chromatography using (PE/AcOEt=90:10) to give alcohol **7** as a yellow oil (1.24 g, 76%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (1H, s), 1.58 (2H, qn, J=6.9 Hz), 2.06 (2H, m), 2.3 (2H, m), 2.79 (2H, m), 3.61 (2H, t, J=6.4 Hz), 5.44 (1H, dt, J=15.4, 5.5 Hz), 5.53 (1H, dt, J=15.4, 5.4 Hz), 7.08 (1H, m), 7.25 (2H, m), 7.55 (1H, d, J=7.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.0, 32.4, 32.9, 36.4, 62.6, 124.6, 127.4, 127.7, 129.8, 130.60, 130.7, 132.9, 141.3. IR (neat): 3320, 3060, 2920, 2860, 1590, 1570, 1470, 1440, 1020, 970, 750, 660 cm^{-1}. Anal. calcd for $C_{13}H_{17}OBr$: C, 58.01; H, 6.37; O, 5.94. Found: C, 57.79; H, 6.26; O, 5.53.

4.1.5. (*E*)-2-[7-(2-Bromophenyl)-hept-4-enyl] malonic acid dimethyl ester (E1b). Methane sulfonyl chloride (0.76 mL, 9.82 mmol) was added dropwise to a stirred solution of alcohol **7** (2.00 g, 7.43 mmol) in a mixture of CH_2Cl_2 (60 mL) and triethylamine (1.41 mL, 9.66 mmol). After stirring for 2 h at 0 °C and 3 h at room temperature, the reaction mixture was diluted with diethyl ether (150 mL) and the mixture was washed with a saturated aqueous NH_4Cl solution (70 mL), dried and concentrated in vacuo. The residue was dissolved in acetone and sodium iodide (2.20 g, 14.7 mmol) was added. The mixture was refluxed for 12 h and cooled to room temperature. Et_2O (200 mL) was added and the mixture was washed with a saturated aqueous $Na_2S_2O_3$ solution (2×100 mL), brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography using pure petroleum ether as eluent to give the iodide **8** as a yellow oil (2.6 g, 92%).

A dispersion of 60% NaH in mineral oil (90.0 mg, 2.24 mmol) was suspended in a mixture of THF (5 mL) and DMF (5 mL), and dimethylmalonate (282 μL, 2.47 mmol) was added dropwise. The resulting solution of sodium malonate was added dropwise to a stirred solution of the iodide derivative **8** (447 mg, 1.18 mmol) in THF (7.5 mL) and DMF (7.5 mL) and the mixture was heated overnight at 70 °C. The reaction was quenched with 5% HCl. The malonate was extracted with Et_2O (3×50 mL) and the organic phase washed with brine (50 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography (PE/Et_2O=80:20) to afford **E1b** as a colorless oil (370 mg, 80%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.4 (2H, m), 1.95 (2H, m), 2.03 (2H, m), 2.3 (2H, m), 2.75 (2H, m), 3.36 (1H, t, J=7 Hz), 3.75 (6H, s), 5.3–5.4 (2H, dt, J=15.1, 7 Hz), 7.19 (1H, m), 7.22 (2H, m), 7.53 (1H, d, J=7.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28, 32.2, 32.9, 36.4, 52.0, 52.6, 124.6, 127.4, 127.6, 129.9, 130.4, 130.6, 132.9, 141.0, 170.0. IR (neat): 3060, 2960, 2920, 2840, 1735 (broad), 1570, 1470, 1440, 1150, 1020, 970, 750 cm^{-1}. Anal. calcd for $C_{18}H_{23}O_4Br$: C, 56.41; H, 6.05; O, 16.7. Found: C, 56.62; H, 5.99; O, 16.9.

4.1.6. (*E*)-9-(2-Bromophenyl)-2-cyano-non-6-enoic acid methyl ester (E1a). Prepared as above for compound **E1b**. Colorless oil (42%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (2H, m), 1.59 (2H, m), 1.88 (2H, m), 2.12 (2H, m), 2.79 (2H, t, J=22 Hz), 3.49 (1H, m), 3.82 (3H, s), 5.45 (2H, m), 7.09 (1H, m), 7.20 (2H, m), 7.51 (1H, d, J=8.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.5, 29.2, 31.5, 32.7, 36.1, 38.8, 53.4, 116.4, 124.5, 127.3, 127.6, 129.5, 130.43, 130.45, 132.7, 141.1, 166.0. IR (neat): 3060, 2960, 2860, 2240, 1700, 1565, 1470, 1440, 1260, 1120, 1020, 970, 750, 650.

4.1.7. (*E*)-2-[7-(2-Bromophenyl)-hept-4-enyl] malononitrile (E1c). A dispersion of 60% NaH in mineral oil (74.0 mg, 1.84 mmol) was suspended in THF (10 mL) and cooled at 0 °C. Malononitrile (130 mg, 1.98 mmol) in THF (10 mL) was added dropwise. The resulting solution of sodium malononitrile was added at room temperature to a solution of the iodide **8** (400 mg, 1.06 mmol) in THF (10 mL). The resulting mixture was refluxed overnight in THF. The reaction was quenched with a saturated aqueous NH_4Cl solution (20 mL). The dinitrile was extracted with Et_2O (3×50 mL) and the organic phase was washed with brine (50 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography (PE/Et_2O=80:20) to afford **E1c** as a colorless oil (172 mg, 50%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (2H, m), 1.89 (2H, m), 2.08 (2H, m), 2.42 (2H, m), 2.8 (2H, m), 3.66 (1H, t, J=7 Hz), 5.35 (1H, dt, J=15.1, 7 Hz), 5.54 (1H, dt, J=15.1, 7 Hz), 7–7.4 (3H, m), 7.52 (1H, d, J=7.5 Hz). ^{13}C (75 MHz, $CDCl_3$) δ 22.5, 26.1, 30.0, 31.0, 32.6, 35.9, 112.6, 124.4, 127.4, 127.6, 128.9, 130.5, 131.1, 132.8, 140.9. IR (neat): 3060, 2920, 2870, 2260, 1620, 1590, 1570, 1470, 1440, 1140, 1020, 970,

750 cm^{-1}. Anal. calcd for $C_{16}H_{17}N_2Br$: C, 60.58; H, 5.40. Found: C, 60.80; H, 5.51.

4.2. General procedure for the preformation of the palladium (0) complex and formation of 2-indan-1-ylcyclopentane-1,1-dicarboxylic acid dimethyl ester (*anti*-3b)

The Pd (0) complex was preformed using the same experimental procedure for all cyclizations. Under N_2, a mixture of 5 mol% of $Pd(OAc)_2$, 10 mol% of dppe (1,2-bis(diphenylphosphino)ethane) and 10 mol% of 1-heptene in NMP (*N*-methyl pyrrolidone) was stirred and heated with a hairdrier until the mixture turned brick-red. On the one hand, a solution of *t*BuOK (49 mg, 0.43 mmol) and 18-crown-6 (21 mg, 0.08 mmol) in NMP (1 mL) was added to a solution of malonate **E1b** (150 mg, 0.39 mmol) in NMP (2 mL). The mixture was stirred at room temperature for 30 min. On the other hand, the palladium (0) complex was preformed in NMP (2 mL) by reaction of 1-heptene (0.56 mL, 0.04 mmol) with $Pd(OAc)_2$ (4.50 mg, 0.02 mmol) and dppe (15.9 mg, 0.04 mmol). The addition of the brick-red Pd(0) solution was made via a cannula to the malonate solution prepared above. The mixture was stirred at 50 °C for 3 h. The solution was directly purified by flash chromatography (PE/Et_2O=80:20) to afford *anti*-**3b** as a pure white solid (65 mg, 55%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (1H, ddd, J=3.6, 8.7, 13.5 Hz), 1.65 (1H, ddd, J=7.9, 11.2, 14.2 Hz), 1.85 (2H, m), 2.10 (3H, m), 2.56 (1H, dt, J=8.1, 13.6 Hz), 2.75 (2H, m), 3.0 (1H, dt, J=2.8, 10 Hz), 3.10 (1H, ddd, J=7.1, 9.7, 13.8 Hz), 3.75 (6H, s), 7.10–7,53 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 30.9, 31.6, 31.9, 37.3, 47.6, 49.9, 52.2, 52.6, 63.0, 124.6, 125.5, 125.6, 126.6, 144.7, 146.6, 172.3, 174.0. IR (KBr): 3060, 2940, 2840, 1740. Anal. calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.29; H, 7.68. Mp 50–52 °C.

4.2.1. *trans*-2-Cyano-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-carboxylic acid methyl ester (*trans*-2a) and 1-cyano-2-indan-1-yl-cyclopentanecarboxylic acid methyl ester (*anti*-3a).

Same experimental procedure as for **E1b**. The mixture was stirred at 50 °C for 24 h. The solution was directly purified by flash chromatography (PE/Et_2O=80:20) to give *trans*-**2a** and *anti*-**3a** (combined yield: 70%).

trans-**2a**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.15–1.30 (1H, m), 1.65–1.82 (2H, m), 1.83–1.98 (4H, m), 2.12 (1H, ddd, J=12.1, 11.3, 3.9 Hz), 2.5 (1H, m), 2.81 (3H, m), 3.8 (3H, s), 7–7.25 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 26.0, 29.3, 30.1, 34.4, 38.8, 44.5, 52.1, 53.5, 117.8, 125.7, 126.1, 126.2, 129.0, 135.9, 138.2, 170.0.

anti-**3a**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.72–2.10 (3H, m), 2.17–2.38 (4H, m), 2.50 (1H, m), 2.70 (1H, m), 2.79–3.01 (2H, m), 3.4 (1H, ddd, J=11.5, 8.3, 7.1 Hz), 3.90 (3H, s), 7.14–7.35 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 31.0, 31.1, 31.3, 39.7, 48.3, 52.6, 53.0, 53.6, 118.8, 124.7, 124.8, 125.9, 126.9, 144.1, 145.3, 171.1.

4.2.2. *trans*-3,4,4a,9,10,10a-Hexahydro-2*H*-phenanthrene-1,1-dicarbonitrile (*trans*-2c).

Same experimental procedure as for **E1b**. Scale: 234 mg, 0.74 mmol of **E1c**.The mixture was stirred at 50 °C for 65 h. The solution was directly purified by flash chromatography (PE/Et_2O=90:10) to give *trans*-**2c** as a pure white solid (90 mg, 52%). IR (KBr): 3060, 2940, 2215, 1600. ^1H NMR (300 MHz, C_6D_6) δ 0.6 (1H, tdt, J=12.5, 12.5, 3.9 Hz), 1.1–1.4 (4H, m), 1.50 (1H, dt, J=4.3, 12 Hz), 1.70 (1H, dt, J=12.7, 3.4 Hz), 1.8 (1H, dd, J=13.3, 3 Hz), 1.95 (1H, ddt, J=12.6, 5.4 Hz), 2.35 (1H, m), 2.35 (2H, m), 6.8–7.2 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 26.3, 28.9, 29.3, 34.8, 38.6, 39.3, 45.7, 116.0, 126.3, 126.6, 126.8, 129.3, 135.6, 137.2. Anal. calcd for $C_{16}H_{16}N_2$: C, 81.35; H, 6.82. Found: C, 81.14; H, 6.72. Mp 174–176 °C.

4.2.3. X-ray crystal structure analysis.

Crystal data for *trans*-**2c** at 295 K collected on a Nonius CAD 4. $C_{16}H_{16}N_2$, M=236.31, monoclinic, $C2/c$, a=26.332(4), b=7.4772(7), c=17.345(3) Å, α=90, β=130.648(12), γ=90°, V=2591.2(6) $Å^3$, Z=8, λ(Cu Kα)=1.54056 Å, D_c=1.212 g cm^{-3}, 2585 reflections, 211 parameters, R=0.0615 and Rw=0.1800 for 2264 reflections with $I>2\sigma(I)$. CCDC registration number 221276.

4.2.4. (*Z*)-2-[7-(2-Bromophenyl)-hept-4-enyl] malonic acid dimethyl ester (Z1b).

8.16 g (18.8 mmol) of phosphonium salt of 1-bromo-4-chlorobutane and 3.83 g (19.2 mmol) of potassium hexamethyldisilazane (KHMDS) were placed in a round bottomed flask flushed with N_2. At 0 °C, 77 mL of dry THF were added dropwise, the mixture turning to orange solution. After 15 min at 0 °C, aldehyde **4** (2.0 g, 9.4 mmol) in THF (17 mL) was added dropwise to the ylide solution and the resulting betaine-ylide solution was stirred at 0 °C for 3 h. The solvent was partially removed in vacuo and 20 mL of pentane were added in order to precipitate triphenylphosphine oxide. Filtration through a pad of silica gel and removal of solvent under reduced pressure gave a crude oil. Chromatography on silica gel using PE as eluent gave the compound **9** (1.76 g, 65%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (2H, qn, J=6.7 Hz), 2.14 (2H, m), 2.40 (2H, m); 2.70 (2H, t, J=7.5 Hz); 3.47 (2H, t, J=7 Hz), 5.38 (1H, dt, J=11, 7 Hz), 5.49 (1H, dt, J=11, 7 Hz), 7.1 (1H, m), 7.2 (2H, m), 7.55 (1H, d, J=7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.4, 27.5, 32.4, 36.2, 44.4, 124.4, 127.2, 127.6, 128.9, 129.8, 130.5, 132.8, 141.0. IR (neat): 3050, 2960, 2870, 1570, 1470, 1440, 1200, 1120, 1050, 1025, 920, 750, 700 cm^{-1}.

Following the same experimental procedure as for **E1b**, using iodide **10** as intermediate, the residue was purified by flash chromatography (PE/Et_2O=80:20) to afford **Z1b** as an oil (292 mg, 74%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.4 ppm (2H, m), 1.87 (2H, q, J=7.7 Hz), 2.00 (2H, q, J=7.1 Hz); 2.30 (2H, q, J=7.7 Hz), 2.76 (2H, t, J=7.7 Hz), 3.33 (1H, t, J=7.7 Hz), 3.75 (6H, s); 5.3–5.6 (2H, dt, J=10.7, 7 Hz), 7.05 (1H, m), 7.25 (2H, m), 7.5 (1H, d, J=8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.7, 27.3, 27.6, 28.2, 36.2, 51.2, 52.4, 124.4, 127.3, 127.6, 129.0, 129.9, 130.6, 132.7, 141.0, 169.8. IR (neat): 3010, 2960, 2930, 2860, 1750 (broad), 1570, 1470, 1440, 1350, 1150, 1020, 750, 660 cm^{-1}. Anal. calcd for $C_{18}H_{23}O_4Br$: C, 56.41; H, 6.05. Found: C, 56.81; H, 6.25.

4.2.5. (*Z*)-9-(2-Bromophenyl)-2-cyano-non-6-enoic acid methyl ester (Z1a).

Same experimental procedure as for **E1b**. Colorless oil (35%). ^1H NMR (200 MHz, $CDCl_3$) δ

1.40–1.60 (2H, m), 1.80–1.92 (2H, m), 1.98–2.08 (2H, m), 2.29–2.40 (2H, m), 2.76 (2H, t, J=7 Hz), 3.46 (1H, t, J=7 Hz), 3.81 (3H, s), 5.28–5.55 (2H, m), 7.0–7.09 (1H, m), 7.19–7.25 (2H, m), 7.51 (1H, d, J=7.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.2, 26.6, 27.6, 29.3, 36.1, 37.3, 53.4, 116.4, 124.4, 127.3, 127.6, 129.2, 129.5, 130.7, 132.7, 140.9, 166.6. IR (neat): 3060, 3010, 2940, 2870, 2250, 1760, 1570, 1470, 1260, 1210, 1020, 970 cm^{-1}.

4.2.6. (*Z*)-2-[7-(2-Bromophenyl)-hept-4-enyl] malononitrile (Z1c). Same experimental procedure as for **E1c**. Scale: 500 mg, 1.32 mmol of iodide **10**. The residue was purified by flash chromatography (PE/Et_2O=70:30) to afford **Z1c** as an oil (180 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 (2H, m), 1.8 (2H, m), 2.2 (2H, m), 2.35 (2H, m), 2.8 (2H, m), 3.66 (1H, t, J=7 Hz), 5.36 (1H, dt, J=10.7, 7 Hz), 5.52 (1H, dt, J=10.7, 7 Hz), 7.1 (1H, m), 7.2 (2H, m), 7.5 (1H, d, J=7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 25.8, 26.4, 27.7, 30.2, 36.1, 112.6, 125, 127.5, 127.9, 128.6, 130.4, 130.9, 132.4, 141. IR (neat): 3060, 3010, 2980, 2925, 2860, 2260, 1570, 1470, 1440, 1030, 970, 750, 660 cm^{-1}. Anal. calcd for $C_{16}H_{17}N_2Br$: C, 60.58; H, 5.40. Found: C, 60.81; H, 5.53.

4.2.7. 2-Indan-1-ylcyclopentane-1,1-dicarboxylic acid dimethylester (*syn*-3b). Same experimental procedure as for **E1b**. Scale: 120 mg, 0.3 mmol of **Z1b**. The mixture was stirred at 50 °C for 15 h. The solution was directly purified by flash chromatography (PE/Et_2O=80:20) to give (82 mg, 90%) of *syn*-**3b** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 (3H, m), 1.75 (2H, m), 2.0 (2H, m), 2.5 (1H, ddd, J=7.1, 8.5, 13.6 Hz), 2.85 (2H, m), 3.2 (1H, dt, J=2.9, 7.2 Hz), 3.6 (1H, dt, J=2.9, 10 Hz), 3.75 (6H, s), 7.1–7.34 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 26.4, 29.9, 32.2, 34.8, 44.7, 50.1, 52.6, 62.9, 123.9, 124.3, 126.4, 126.6, 143.7, 146.9, 173.0. IR (neat): 3060, 2940, 2840, 1740. Anal. calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.45; H, 7.54.

4.2.8. *cis*-3,4,4a,9,10,10a-Hexahydro-2*H*-phenanthrene-1,1-dicarbonitrile (*cis*-2c). For dicarbonitrile compound, the experimental procedure was identical as previously. Scale: 210 mg, 0.66 mmol of **Z1c**. The mixture was stirred at 50 °C for 48 h. The solution was directly purified by flash chromatography (PE/Et_2O=90:10) to give *cis*-**2c** in 58% yield (90 mg) as a pure white solid. ^{1}H NMR (300 MHz, C_6D_6) δ 0.7–1.5 (7H, M), 1.6 (1H, ddt, J=13, 3, 1.5 Hz), 1.8 (1H, dt, J=13.2, 3.7 Hz), 2.25 (1H, ddd, J=17, 12, 6 Hz), 2.45 (1H, dd, J=17, 6 Hz), 2.8 (1H, dt, J=12.6, 3.7 Hz), 7.2 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 21.8, 28.0, 29.0, 29.5, 36.8, 37.0, 40.0, 116.0, 126.3, 126.7, 129.0, 129.2, 134.4, 139.0. IR (KBr): 3060, 2940, 2215. Anal. calcd for $C_{16}H_{16}N_2$: C, 81.30; H, 6.82. Found: C, 81.03; H, 6.80. Mp 113–115 °C.

4.2.9. X-ray crystal structure analysis. Crystal data for *cis*-**2c** at 293 K collected on a Nonius CAD 4. $C_{16}H_{16}N_2$, M=236.32, triclinic, $P-1$, a=9.218(1), b=9.596(1), c=16.064(2) Å, α=75.50(1), β=74.89(1), γ=75.01(1)°, V=1299.3(3) Å^3, Z=4, λ(CuKα)=1.54056 Å, D_c=1.209 g cm^{-3}, 5202 reflections, 421 parameters, R=0.072 and Rw=0.127 for 4496 reflections with $I>3\sigma(I)$. CCDC registration number 221277.

4.3. Alkyne series

4.3.1. 4-(*o*-Bromophenyl)-but-1-yne (11). In a round bottom flask flushed with N_2 were placed magnesium turnings (1.42 g, 58.3 mmol) and $HgCl_2$ (48 mg, 0.18 mmol) in diethyl ether (10 mL). At room temperature, few drops of pure propargyl bromide were added. After some minutes an exothermic reaction started and the mixture was cooled to 0 °C. When the exothermic reaction has subsided, the remainder of the propargyl bromide (3.6 mL, 48 mmol) in diethyl ether (20 mL) was added dropwise over a period of 1 h, while the temperature was maintained at 0 °C. After completion of the addition, the mixture was stirred for 1 h at 0 °C. Then the Grignard solution was allowed to warm to room temperature and was added via a cannula to a solution of 2-bromobenzyl bromide (10 g, 40 mmol) in THF (50 mL). After stirring at room temperature for 3 h the mixture was quenched with water (100 mL) and extracted with diethyl ether (3×100 mL). The organic layer was washed with brine (100 mL), dried and concentrated. To eliminate the excess of 2-bromobenzyl bromide the crude oil was dissolved in DMSO and sodium cyanide (6 g) was added (3 g/100 mL DMSO). After stirring for 12 h at room temperature the formation of polar 2-bromobenzyl cyanide was occurred. The mixture was quenched with water (200 mL), extracted with Et_2O (2×150 mL) and washed with brine (150 mL). The organic layer was dried, concentrated and purified by chromatography (PE/Et_2O=90:10) to afford **11** as a colorless oil (6.23 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0 (1H, t, J=2.5 Hz), 2.54 (2H, td, J=2.5, 7.5 Hz), 3.0 (2H, t, J=7.5 Hz); 7.1 (1H, m), 7.2 (2H, m), 7.56 (1H, d, J=7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 35.1, 69.1, 83.3, 124.0, 127.4, 128.2, 130.5, 130.8, 132.8.

4.3.2. 2-[7-(2-Bromophenyl)-hept-4-ynyl] malonic acid dimethyl ester (14a). At −20 °C, *n*BuLi (2.5 M in hexane) (2.11 mL, 5.28 mmol) was added dropwise to a solution of diisopropylamine (0.88 mL, 6.22 mmol) in THF (2 mL). The LDA solution was stirred for 1 h at −20 °C and was cooled to −78 °C. A solution of **11** (1.0 g, 4.8 mmol) in THF (2 mL) was added via a canula to the LDA solution. The mixture was stirred for 1 h at −78 °C. Finally, 1-bromo-3-chloropropane (0.71 mL, 7.2 mmol) was added via a syringe. The solution was allowed to warm at RT and was refluxed overnight. The mixture was cooled to RT, quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O (3×50 mL). The organic layer was washed with brine (50 mL), dried and concentrated. The excess of 1-bromo-3-chloropropane was eliminated by distillation under atmospheric pressure. The starting material **11** was trapped in Et_2O (12 h, RT) by an aqueous solution of silver nitrate (14% in weight). The formation of water insoluble silver acetylide occurred. The mixture was diluted with Et_2O (20 mL), washed with water (10 mL) and brine (10 mL). The organic layer was dried, concentrated and purified by chromatography using PE as eluent to afford **12** as an yellow oil (1.48 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.9 ppm (2H, t, J=7.3 Hz), 2.33 (2H, m), 2.48 (2H, m); 2.93 (2H, t, J=7.4 Hz), 3.58 (2H, t, J=6.6 Hz), 7.10 (1H, m), 7.25 (2H, m), 7.5 (1H, d, J=7.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.1, 19.6, 32.2, 35.6, 44.4, 71.0, 80.0, 124.0, 127.2, 128.1, 130.7, 132.8, 141.0. IR (neat):

3060, 2960, 2920, 2860, 1570, 1470, 1440, 1290, 1120, 1020, 750 cm^{-1}.

12 (433 mg, 1.52 mmol) and sodium iodide (0.5 g, 3.3 mmol) were dissolved in acetone (10 mL) The solution was refluxed overnight and cooled to room temperature. The mixture was diluted in Et_2O (50 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (10 mL). The organic layer was dried, concentrated and purified by chromatography using PE to afford **13** as a pale yellow oil (507 mg, 88%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (2H, m), 2.27 (2H, m), 2.48 (2H, m), 2.93 (2H, t, J=7.4 Hz), 3.23 (2H, t, J=6.6 Hz), 7.1 (1H, m), 7.25 (2H, m), 7.52 (1H, d, J=7.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.3, 19.1, 19.7, 32.3, 35.5, 70, 80, 124, 127.3, 128, 130.7, 132.7, 141. IR (neat): 3060, 2960, 2920, 2860, 1570, 1470, 1440, 1220, 1020, 750, cm^{-1}.

At room temperature, NaH (90.5 mg, 3.77 mmol) washed in pentane was suspended in THF (25 mL) and dimethylmalonate (0.48 mL, 4.17 mmol) was added dropwise. The sodium enolate solution was stirred for 30 min at RT and was added dropwise to a solution of **13** (750 mg, 1.99 mmol) in DMF (15 mL). The resulting mixture was refluxed overnight and cooled to RT. The mixture was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O (3×50 mL) and washed with brine (50 mL). The organic layer was dried, concentrated and purified by chromatography (PE/Et_2O=90:10) to afford **14a** as a colorless oil (593 mg, 80%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (2H, m), 1.98 (2H, td, J=7.5 Hz), 2.19 (2H, tt, J=2.2, 7.5 Hz), 2.48 (2H, tt, J=2.2, 7.5 Hz), 2.91 (2H, t, J=7.5 Hz), 3.38 (1H, t, J=7.5 Hz), 3.75 (6H, s), 7.1–7.3 (3H, m), 7.51 (1H, d, J=8.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.5, 19.2, 26.6, 28.0, 35.7, 51.3, 52.5, 79.7, 80.1, 124.4, 127.3, 128.0, 130.8, 132.7, 140.0, 169.7. IR (neat): 3000, 2950, 1750 (br), 1440, 1390, 1200, 1150, 1030, 850, 755 cm^{-1}. Anal. calcd for $C_{18}H_{21}O_4Br$: C, 56.70; H, 5.56. Found: C, 56.54; H, 5.65.

4.3.3. 2-[7-(2-Bromophenyl)-hept-4-ynyl] malononitrile (14b). Under N_2 at 0 °C malononitrile (131 mg, 1.98 mmol) in THF (1 mL) was added dropwise to a solution of NaH washed in pentane (44 mg, 1.84 mmol) in THF (3.5 mL). After stirring at RT for 30 min, the sodium enolate solution was added dropwise to a solution of **13** (500 mg, 1.32 mmol) in THF (1 mL). The resulting mixture was refluxed overnight and cooled to RT. The solution was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O (3×50 mL) and washed with brine (50 mL). The organic layer was dried, concentrated and purified by chromatography (PE/Et_2O=85:15) to afford **14b** as an yellow oil (186 mg, 45%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.78 (2H, m), 2.07 (2H, m), 2.28 (2H, m), 2.51 (2H, m), 2.94 (2H, t, J=7.3 Hz), 3.74 (1H, t, J=7 Hz), 7.05 (1H, m), 7.2 (2H,m), 7.51 (1H, d, J=8.1 Hz). ^{13}C NMR (50 MHz,$CDCl_3$): δ 17.7, 19.1, 22.3, 25.4. 29.9, 35.4, 78.7, 81.2, 112.5, 124.5, 127.4, 128.2, 130.7, 132.1, 139.8. IR (neat): 3060, 2950, 2860, 2260, 1440, 1030, 750 cm^{-1}. Anal. calcd for $C_{16}H_{15}N_2Br$: C, 60.96; H, 4.80. Found: C, 61.37; H, 5.1.

4.3.4. 2-Indan-1-ylidenecyclopentane-1,1-dicarboxylic acid dimethylester (15a). The palladium zero complex was preformed using the same procedure as the olefinic compound (concentration 0.05 M in DMSO). *t*BuOK (41 mg, 0.36 mmol) and 18-C-6 crown ether in DMSO (0.33 mL) were added to a solution of **14a** (125 mg, 0.33 mmol) in DMSO (0.66 mL). The sodium enolate solution was stirred for 30 min at RT. The palladium zero solution was added via a cannula to the sodium enolate solution and the mixture was stirred at 90 °C for 2 h. The mixture was cooled to RT, quenched with water, extracted with Et_2O (2×10 mL) and the organic layer was washed with brine (10 mL), dried, concentrated and purified by chromatography (PE/Et_2O=90:10) to afford **15a** as an yellow oil (57 mg, 58%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (2H, t, J=7.2 Hz), 2.47 (2H, t, J=7.2 Hz), 2.72 (2H, m), 2.82 (2H, t, J=6.3 Hz), 2.97 (2H, t, J=6.3 Hz), 3.70 (6H, s), 7.22 (3H, m), 7.53 (1H, d, J=6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 30.68, 30.73, 33.2, 38.8, 52.7, 60.7, 124.9, 125.1, 126.2, 127.4, 132.7, 140.2, 142.3, 147.6, 171.9. MS *m*/*z*: 300.05 (16), 236 (12), 210.15 (16), 209.05 (100), 208.05 (54), 207.05 (12), 181.15 (14), 165.05 (13). IR (neat): 3060, 2940, 1750, 1430, 1250.

4.3.5. 1-Cyano-2-indan-1-ylidene cyclopentanecarboxylic acid methyl ester (15b). For dicarbonitrile compound **14b** (93 mg, 0.32 mmol) the experimental procedure was identical as previously, the mixture was stirred at 90 °C for 2 h and cooled to RT. The mixture was filtered through silica gel (PE/Et_2O=90:10) and was concentrated to afford **15b** as a transparent crystalline solid (34 mg, 50%). ^1H NMR (300 MHz, $CDCl_3$): δ 2.12 (2H, q, J=6.9 Hz), 2.64 (2H, t, J=7 Hz), 2.89 (2H, t, J=7 Hz), 3.15 (4H, s), 7.1–7.4 (3H, m), 7.5 (1H, d, J=7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 30.6, 30.7, 31.9, 37.8, 41.0, 115.0, 124.6, 125.3, 125.6, 126.7, 129.2, 140.1, 144.5, 148.8. MS *m*/*z*: 234 (74), 206 (35), 205 (20), 178 (10), 156 (100), 155 (27), 116 (21), 115 (32). IR (neat): 3080, 2940, 2860, 2220. Mp 137–139 °C.

4.3.6. X-ray crystal structure analysis. Crystal data for **15b** at 295 K collected on a Nonius Kappa CCD. $C_{16}H_{14}N_2$, M=234.3, triclinic, $P-1$, a=7.546(2), b=10.267(2), c=17.602(4) Å, α=100.67(3), β=96.03(3), γ=108.85(3)°, V=1248.3(4) $Å^3$, Z=4, λ (Mo Kα)=0.71073 Å, D_c= 1.247 g cm^{-3}, 5664 reflections, 325 parameters, R=0.0502 and Rw=0.1072 for 1776 reflections with $I>4\sigma(I)$. CCDC registration number 221278.

4.4. X-ray diffraction studies

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (see registration numbers in experimental). Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

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