Synthesis S. Saranya et al. Paper

A Facile Access to *trans*-3-Styryl-4-hydrazinocyclopentenes via Palladium-Catalyzed Ring Opening of Diazanorbornenes with (*Z*)-β-Bromostyrenes/2,3-Dibromohydrocinnamic Acids

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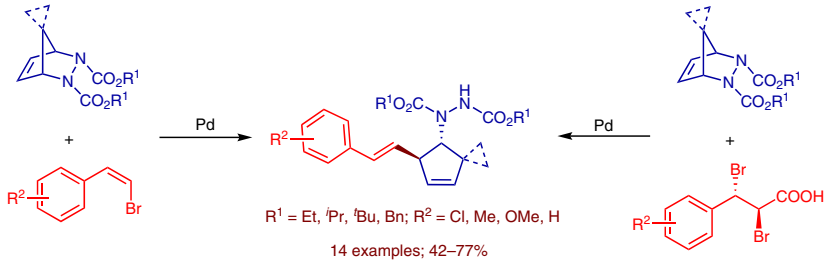

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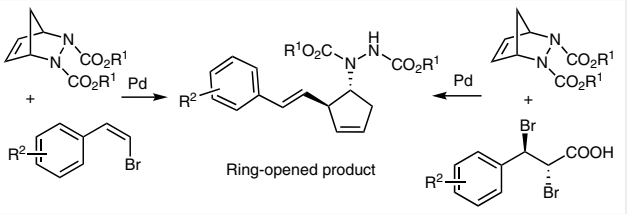
Abstract *trans*-3-Styryl-4-hydrazinocyclopentenes have been synthesized via palladium-catalyzed desymmetrization of diazanorbornenes with (*Z*)-β-bromostyrenes. The reaction also works well with (*Z*)-β-bromostyrenes generated in situ from 2,3-dibromohydrocinnamic acids. The synthesized hydrazinocyclopentenes provide an easy route towards synthetic intermediates of many scaffolds of biological potential.

Key words diazanorbornenes, palladium catalysis, (*Z*)-β-bromostyrenes, 2,3-dibromohydrocinnamic acids, functionalized cyclopentanoids, hydrazinocyclopentenes

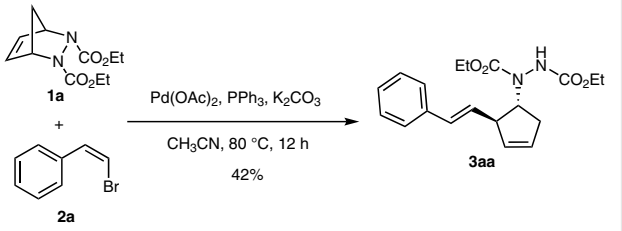
The synthesis of five-membered carbocycles has fascinated organic chemists for several years, as such compounds can serve as potent synthetic intermediates, particularly in the construction of highly functionalized and structurally complex molecules with sufficient stability.[1] These cyclopentanoid rings are one of the attractive and versatile synthons in pharmaceuticals and are the key structural unit in various natural products, such as terpenes, steroids and prostaglandins. Among various cyclopentenes, the disubstituted hydrazinocyclopentenes have gained much attention in synthetic organic chemistry due to their attractive synthetic applications,[2] and we have developed methodologies for the stereoselective synthesis of 3,4-disubstituted cyclopentenes via one-step ring opening of diazanorbornenes with several monocentered nucleophiles.[2e,3,4] The desymmetrization of diazanorbornenes with bicentered reactive species provided cyclopentene-fused carbocycles[5] and heterocycles.[4c,6,7] However, the reactivity of many other nucleophiles remains unexplored and the design of new strategies for the desymmetrization of diazanorbornenes is a challenging task.

Palladium-catalyzed Heck-type reactions of bromovinylarenes with norbornenes have been well explored since the report by Catellani and co-workers on the synthesis of 'condensed cyclopentanes'.[8] Recently, Mao and Bao reported the palladium(0)-catalyzed C–H bond activation of (*E*)- and (*Z*)-β-bromostyrenes with norbornenes, affording cyclopropane derivatives via [2 + 1] cycloaddition[9] and cyclobutanes via [2+1+1] annulation.[10] As expected, the robust bicyclic skeleton of norbornene remained unaffected in all the above cases. Hence, we were interested to investigate the effect of replacing norbornene with diazanorbornene, foreseeing the formation of more functionalized products by the ring fragmentation of these strained alkenes. The reactivity of diazanorbornenes with various nucleophiles under palladium catalysis has been explored in detail in our laboratory[3,4c,5,7] and also by others.[11,12] To the best of our knowledge, there is only a single report on the palladium-catalyzed coupling of diazanorbornene with (*E*)-β-bromostyrene, and this reaction mainly afforded the bicyclic hydroarylated product along with disubstituted cyclopentenes as a side product in a negligible amount.[11a,13] This prompted us to investigate the palladium-catalyzed desymmetrization of diazanorbornenes with (*Z*)-β-bromostyrene, the results of which are discussed in this paper (Scheme 1).



Scheme 1 Palladium-catalyzed reaction of diazanorbornenes with (*Z*)-β-bromostyrenes/2,3-dibromohydrocinnamic acids

We initiated our investigation with the reaction of 1 equivalent of diazanorbornene **1a** and 1 equivalent of (*Z*)-β-bromostyrene (**2a**) in the presence of 10 mol% $Pd(OAc)_2$ as catalyst, 20 mol% PPh_3 as ligand and 2 equivalents of K_2CO_3 as base, in acetonitrile at 80 °C for 12 hours. The ring-opened product, the *trans*-3-styryl-4-hydrazinocyclopentene **3aa**, was formed in 42% yield (Scheme 2).



Scheme 2 Ring opening of diazanorbornene **1a** with (*Z*)-β-bromostyrene (**2a**)

Further, we carried out detailed optimization studies in order to find the best catalyst system for the reaction; the results are summarized in Table 1.

Of the various palladium catalysts screened, $Pd(OAc)_2$ furnished the product **3aa** in highest yield (Table 1, entry 1 vs entries 2–5). 1,1-Bis(diphenylphosphino)methane (dppm) was found to be most proficient among the different phosphine ligands examined (Table 1, entries 1, 9–11). The role of inorganic bases (Cs_2CO_3, K_2CO_3, NaOAc) as well as an organic base (Et_3N) was checked; 2 equivalents of K_2CO_3 provided the best yield. Solvents other than acetonitrile were tested (THF, DCE, DMF), with no yield improvement. The addition of tetrabutylammonium chloride (phase-transfer catalyst) resulted in a reduced reaction yield, while the yield improved to 67% when 5 mol% scandium(III) triflate was added (Table 1, entries 15 and 16). Thus, the best conditions for the reaction proved to be the combination of 10 mol% $Pd(OAc)_2$, 20 mol% dppm, 2 equivalents of K_2CO_3 and 5 mol% $Sc(OTf)_3$ in acetonitrile at 80 °C for 12 hours.

With the optimal conditions in hand, diazanorbornenes derived from different dialkyl azodicarboxylates were reacted with (*Z*)-β-bromostyrene (**2a**). Differently substituted cyclopentenes were formed in moderate to good yields (Table 2, entries 1–4). Substituted (*Z*)-β-bromostyrenes were also good substrates for this reaction. Thus, the reaction of various diazanorbornenes with (*Z*)-β-bromostyrenes **2b–d** with a chloro, methyl or methoxy substituent at the *para* position furnished the corresponding *trans*-3-styryl-4-hydrazinocyclopentenes in moderate to good yields (Table 3). The scope of the reaction was also extended to spirotricyclic olefins (Table 2, entries 5 and 6).

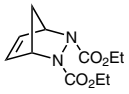
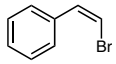
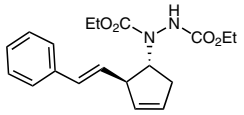
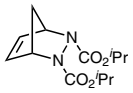
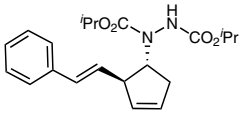
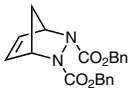
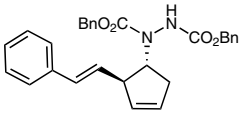
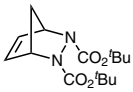
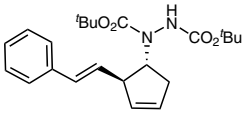
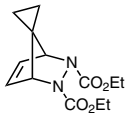
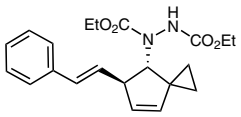
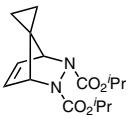
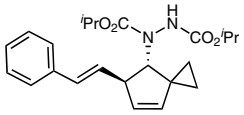
The geometry of the styryl double bond was resolved from the ^1H NMR spectrum of compound **3da**. Compound **3da** gave a clear doublet for one of the olefinic protons with a coupling constant of 16 Hz corresponding to *trans* geome-

Table 1 Optimization Studies for the Palladium-Catalyzed Ring Opening of Diazanorbornenes with (*Z*)-β-Bromostyrenes[a]

Entry	Catalyst	Ligand	Base	Solvent	Temp (°C)	Yield[b] (%) of **3aa**
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	CH_3CN	80	42
2	$PdCl_2$	PPh_3	K_2CO_3	CH_3CN	80	25
3	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	K_2CO_3	CH_3CN	80	26
4	$Pd(PPh_3)_2Cl_2$	PPh_3	K_2CO_3	CH_3CN	80	40
5	$[Pd(allyl)Cl]_2$	PPh_3	K_2CO_3	CH_3CN	80	21
6	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF	65	18
7	$Pd(OAc)_2$	PPh_3	K_2CO_3	DCE	80	22
8	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	100	32
9	$Pd(OAc)_2$	dppm	K_2CO_3	CH_3CN	80	52
10	$Pd(OAc)_2$	dppe	K_2CO_3	CH_3CN	80	42
11	$Pd(OAc)_2$	dppf	K_2CO_3	CH_3CN	80	38
12	$Pd(OAc)_2$	dppm	Cs_2CO_3	CH_3CN	80	33
13	$Pd(OAc)_2$	dppm	Et_3N	CH_3CN	80	28
14	$Pd(OAc)_2$	dppm	NaOAc	CH_3CN	80	24
15[c]	$Pd(OAc)_2$	dppm	K_2CO_3	CH_3CN	80	40
16[d]	**$Pd(OAc)_2$**	**dppm**	**K_2CO_3**	**CH_3CN**	**80**	**67**

[a] Reaction conditions: **1a** (1 equiv), **2a** (1 equiv), catalyst (10 mol%), base (2 equiv), ligand (20 mol%), solvent (3 mL), 12 h.
[b] Isolated yield.
[c] TBACl (1 equiv) was added.
[d] $Sc(OTf)_3$ (5 mol%) was added.

Table 2 Reaction of Diazanorbornenes and Spirotricyclic Olefins with (*Z*)-β-Bromostyrene[a]

Entry	Olefin	(*Z*)-β-Bromostyrene	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **3aa**	67
2	 **1b**	**2a**	 **3ba**	70
3	 **1c**	**2a**	 **3ca**	49
4	 **1d**	**2a**	 **3da**	52
5	 **1e**	**2a**	 **3ea**	50
6	 **1f**	**2a**	 **3fa**	53

[a] Reaction conditions: olefin (1 equiv), (*Z*)-β-bromostyrene (1 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), dppm (20 mol%), $Sc(OTf)_3$ (5 mol%), CH_3CN (3 mL), 80 °C, 12 h.
[b] Isolated yield.

try which can be attributed to the feasible *cis–trans* isomerization of double bonds in the presence of a palladium catalyst.[14]

Our success in the ring opening of bicyclic hydrazines with (*Z*)-β-bromostyrenes encouraged us to check the reaction with the styrene precursor 2,3-dibromohydrocinnamic acid (**4a**). Since a base is used in our reaction conditions, the in situ generation of (*Z*)-β-bromostyrene (**2a**) from 2,3-dibromohydrocinnamic acid (**4a**) via base-assisted debrominative decarboxylation[15] was envisaged. The 2,3-dibromohydrocinnamic acid was expected to be the substrate for competition between oxidative addition of palladium(0) to the C–Br bond and the base-assisted debrominative decarboxylation. The 3,4-disubstituted cyclopentene derivative **3aa** itself was formed in 23% yield when diazanorbornene **1a** was reacted with 2,3-dibromohydrocinnamic acid (**4a**) in the presence of $Pd(OAc)_2$, PPh_3 and K_2CO_3 in acetonitrile at 80 °C for 12 hours, thereby opening the chance to reduce our synthetic strategy by one step (Scheme 3).

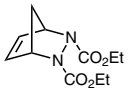
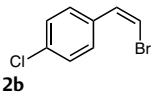
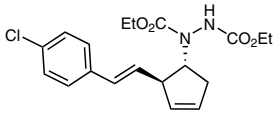
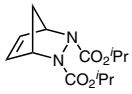
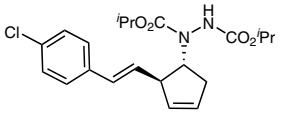
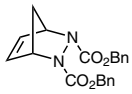
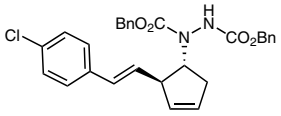
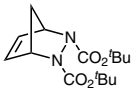
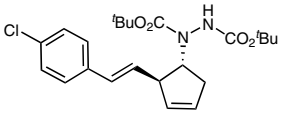
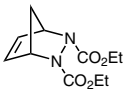
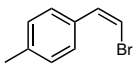
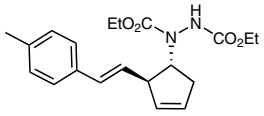
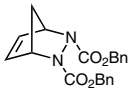
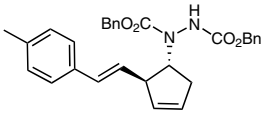
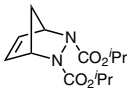
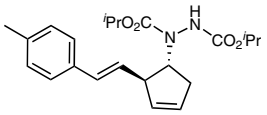
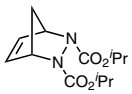
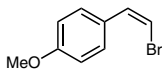
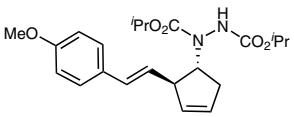
Detailed optimization studies were carried out to obtain the best conditions for this transformation. Screening of a range of palladium catalysts, phosphine ligands and bases in different solvents proved that the best combination was $Pd(PPh_3)_2Cl_2$, PPh_3 and K_2CO_3 in acetonitrile at 80 °C for 12 hours (Table 4). Addition of a catalytic amount of Lewis acid did not result in a significant yield improvement (Table 4, entry 10).

The highest yield of **3aa** was obtained when the amount of 2,3-dibromohydrocinnamic acid (**4a**) and base was increased to 2 equivalents and 4 equivalents, respectively (Table 4, entry 11). Thus, 1 equivalent of diazanorbornene **1a** and 2 equivalents of **4a** in the presence of 10 mol%

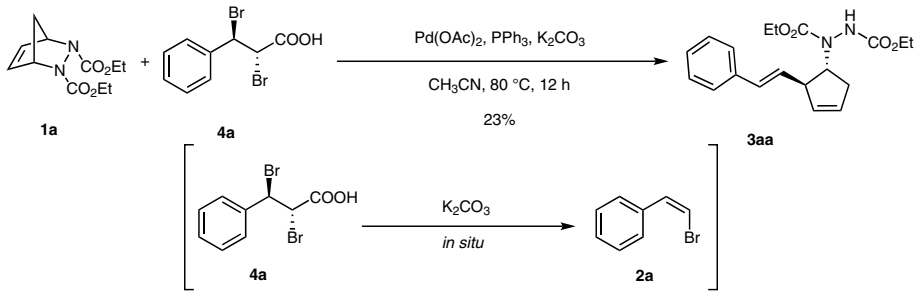
$Pd(PPh_3)_2Cl_2$, 20 mol% PPh_3 and 4 equivalents of K_2CO_3 in acetonitrile at 80 °C for 12 hours furnished the product **3aa** in 63% yield. The reaction was general to a number of diazanorbornenes and 2,3-dibromohydrocinnamic acids, with yields comparable to those of the reactions with the corresponding (*Z*)-β-bromostyrenes (Table 5).

A mechanism similar to that in our previous reports on the palladium-catalyzed ring opening of diazanorbornenes with different nucleophiles can be proposed.[2e] The first step

Table 3 Reaction of Diazanorbornenes with Substituted (*Z*)-β-Bromostyrenes[a]

Entry	Diazanorbornene	(*Z*)-β-Bromostyrene	Product	Yield[b] (%)
1	 **1a**	 **2b**	 **3ab**	61
2	 **1b**	**2b**	 **3bb**	70
3	 **1c**	**2b**	 **3cb**	53
4	 **1d**	**2b**	 **3db**	51
5	 **1a**	 **2c**	 **3ac**	67
6	 **1c**	**2c**	 **3cc**	58
7	 **1b**	**2c**	 **3bc**	71
8	 **1b**	 **2d**	 **3bd**	77

[a] Reaction conditions: diazanorbornene (1 equiv), (*Z*)-β-bromostyrene (1 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), dppm (20 mol%), $Sc(OTf)_3$ (5 mol%), CH_3CN (3 mL), 80 °C, 12 h.
[b] Isolated yield.



Scheme 3 Reaction of diazanorbornene **1a** with 2,3-dibromohydrocinnamic acid (**4a**)

Table 4 Optimization Studies for the Palladium-Catalyzed Ring Opening of Diazanorbornenes with 2,3-Dibromohydrocinnamic Acids[a]

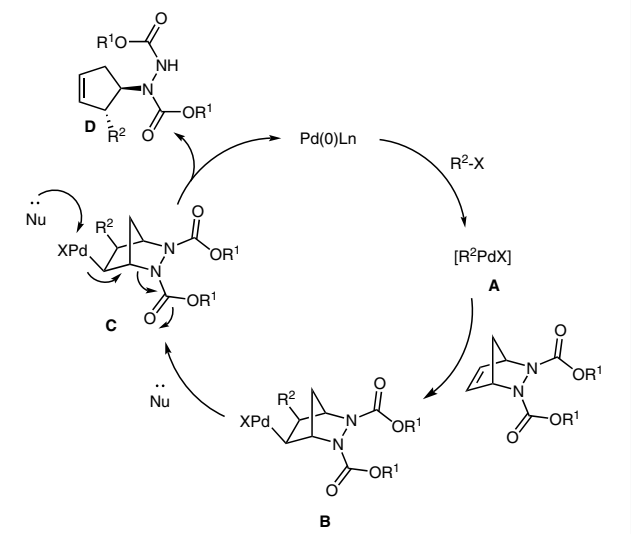
Entry	Catalyst	Ligand	Base	Solvent	Temp (°C)	Yield[b] (%) of **3aa**
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	CH_3CN	80	23
2	$PdCl_2$	PPh_3	K_2CO_3	CH_3CN	80	15
3	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	K_2CO_3	CH_3CN	80	20
4	$Pd(PPh_3)_2Cl_2$	PPh_3	K_2CO_3	CH_3CN	80	41
5	$[Pd(allyl)Cl]_2$	PPh_3	K_2CO_3	CH_3CN	80	27
6	$Pd(PPh_3)_2Cl_2$	PPh_3	Cs_2CO_3	CH_3CN	80	30
7	$Pd(PPh_3)_2Cl_2$	PPh_3	Et_3N	CH_3CN	80	31
8	$Pd(PPh_3)_2Cl_2$	PPh_3	NaOAc	CH_3CN	80	25
9	$Pd(PPh_3)_2Cl_2$	PPh_3	NaOAc	DMF	100	36
10[c]	$Pd(PPh_3)_2Cl_2$	PPh_3	K_2CO_3	CH_3CN	80	43
11[d]	$Pd(PPh_3)_2Cl_2$	PPh_3	K_2CO_3	CH_3CN	80	63
12[d]	**$Pd(PPh_3)_2Cl_2$**	**dppm**	**K_2CO_3**	**CH_3CN**	**80**	**47**
13[d]	$Pd(PPh_3)_2Cl_2$	dppe	K_2CO_3	CH_3CN	80	49
14[d]	$Pd(PPh_3)_2Cl_2$	dppf	K_2CO_3	CH_3CN	80	58

[a] Reaction conditions: **1a** (1 equiv), **4a** (1 equiv), catalyst (10 mol%), base (2 equiv), ligand (20 mol%), solvent (3 mL), 12 h.
[b] Isolated yield.
[c] 5 mol% $Sc(OTf)_3$ was added.
[d] **4a** (2 equiv) and base (4 equiv) were used.

of the catalytic cycle involves oxidative addition of palladium(0) to the C–Br bond of (*Z*)-β-bromostyrene to form the organopalladium complex **A**. Addition of **A** to the olefinic bond of the diazanorbornene results in **B**. Attack of the nucleophile and successive elimination of L_nPdNu opens the bicyclic ring, eliminating the product **D** from the catalytic cycle (Scheme 4). The Lewis acid can assist the C–N bond cleavage by coordinating to the carbonyl oxygen.

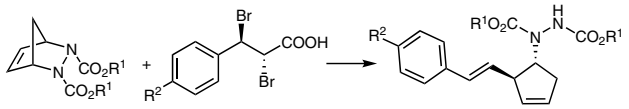
In conclusion, we have developed a mild, simple and efficient strategy for the exclusive synthesis of *trans*-3-styryl-4-hydrazinocyclopentenes. The generality of the method was established by carrying out the reactions of various bicyclic hydrazines with unsubstituted and substituted bromostyrenes. The reaction can also be carried out via in situ generation of the (*Z*)-β-bromostyrene from the respective 2,3-dibromohydrocinnamic acid, using a different catalytic combination. The scope of the reaction can be extended towards the synthesis of cyclopentylamines, which are the potential intermediates of many biologically relevant molecules.

All chemicals were of the best grade, commercially available and were used without further purification. All solvents were purified according to standard procedures; anhydrous solvents were obtained according to literature methods and were stored over molecular sieves. Analytical TLC was performed with Merck aluminum TLC sheets coated with silica gel F_{254}. Gravity column chromatography was performed using silica gel and mixtures of hexane/EtOAc for elution. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AMX 500 spectrometer [$CDCl_3$ or $CDCl_3/CCl_4$ (7:3 mixture) as solvent]; chemical shifts are reported as δ values in units of parts per million downfield from TMS (δ = 0.0) and relative to the signal of chloroform-*d* (δ = 7.25, singlet). Multiplicities are given as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), m (multiplet). Coupling con-



Scheme 4 Plausible mechanism

Table 5 Reaction of Diazanorbornenes and Spirotricyclic Olefins with 2,3-Dibromohydrocinnamic Acids[a]



1 4 3

Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	**3aa**	63	8	**3bb**	62
2	**3ba**	63	9	**3cb**	46
3	**3ca**	48	10	**3db**	44
4	**3da**	42	11	**3ac**	62
5	**3ea**	47	12	**3cc**	58
6	**3fa**	53	13	**3bc**	67
7	**3ab**	54	14	**3bd**	75

[a] Reaction conditions: diazanorbornene (1 equiv), 2,3-dibromohydrocinnamic acid (2 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (4 equiv), CH_3CN (3 mL), 80 °C, 12 h.

stants are reported as *J* values in Hz. ^{13}C NMR spectra are reported as δ values in units of parts per million downfield from TMS (δ = 0.0) and relative to the signal of chloroform-*d* (δ = 77.03, triplet). Mass spectra were recorded under ESI/HRMS conditions (60000 resolution) using a Thermo Scientific Exactive mass spectrometer. IR spectra were recorded on a Bruker FT-IR spectrophotometer.

Diazanorbornenes 1 Derived from Cyclopentadienes; General Procedure

A dialkyl azodicarboxylate (1 equiv) was dissolved in Et_2O and the solution was cooled to 0 °C. Then, the cyclopentadiene (2 equiv) was added and the reaction mixture was stirred for 12 h. Excess cyclopentadiene was added if a yellow color persisted in the reaction mixture. Completion of the reaction was monitored by TLC, and the solvent was removed by evaporation. The crude sample was purified by column chromatography (silica gel 100–200 mesh, EtOAc/hexane) to afford the corresponding diazanorbornene.

2,3-Dibromohydrocinnamic Acids 4 and (*Z*)-β-Bromostyrenes 2; General Procedure[16]

Aldehyde (1 equiv), malonic acid (1 equiv), pyridine (3 equiv) and a few drops of piperidine were taken into a 50-mL three-neck flask equipped with a reflux condenser, and the reaction mixture was stirred at 100 °C for 8 h and 120 °C for 2 h. It was then transferred to a beaker containing concentrated hydrochloric acid (10 mL) and ice–water (30 mL). The resultant precipitate was filtered, washed with ice–water (3 ×) and recrystallized (EtOH) to give the pure *trans*-cinnamic acid.

The *trans*-cinnamic acid (1 equiv) was dissolved in $CHCl_3$ and the solution was cooled to 0 °C. Bromine (3 equiv) was added dropwise and the resulting solution was stirred at this temperature for 20 min. The solution was stored in a refrigerator overnight, then filtered and washed with cold $CHCl_3$ (2 ×) to give the crude 2,3-dibromohydrocinnamic acid **4** which was used in the next step without further purification.

To a mixture of 2,3-dibromohydrocinnamic acid **4** (1 equiv) and anhyd DMF at 0 °C, triethylamine (2 equiv) was added dropwise. The solution was stirred at 0 °C for 30 min and then at room temperature for 6 h. Water (20 mL) was added and the mixture was extracted with Et_2O. The organic layers were combined, washed with saturated potassium carbonate and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane) to afford respective (*Z*)-β-bromostyrene **2**.

Palladium-Catalyzed Ring Opening of Diazanorbornenes 1 with (*Z*)-β-Bromostyrenes 2; General Procedure

The diazanorbornene **1** (50 mg, 1 equiv) and (*Z*)-β-bromostyrene **2** (1 equiv) were taken into a Schlenk tube to which $Pd(OAc)_2$ (10 mol%), dppm (20 mol%), K_2CO_3 (2 equiv) and $Sc(OTf)_3$ (5 mol%) were added. After degassing the mixture for 10 min, anhyd CH_3CN (3 mL) was added. The reaction mixture was purged with argon and stirred mechanically at 80 °C for 12 h. The reaction mixture was first subjected to filtration through Celite in order to remove metal residues, and then the solvent was evaporated in vacuo. The residue was subjected to silica gel (100–200 mesh) column chromatography to yield the respective *trans*-3-styryl-4-hydrazinocyclopentene **3**.

Palladium-Catalyzed Ring Opening of Diazanorbornenes 1 with 2,3-Dibromohydrocinnamic Acids 4; General Procedure

The diazanorbornene **1** (50 mg, 1 equiv) was treated with the 2,3-dibromohydrocinnamic acid **4** (2 equiv) along with $Pd(PPh_3)_2Cl_2$ (10 mol%), PPh_3 (20 mol%) and K_2CO_3 (4 equiv) in a Schlenk tube, and the mixture was evacuated for 10 min. Then, anhyd CH_3CN (3 mL) was added. After the reaction mixture was purged with argon, it was stirred at 80 °C for 12 h. Palladium residues were removed by filtration using Celite, and the filtrate was concentrated. The respective *trans*-3-styryl-4-hydrazinocyclopentene **3** was isolated by silica gel column chromatography of the residue.

Diethyl 1-(2-Styrylcyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3aa)

Yield: Method A: 48 mg (67%); Method B: 45 mg (63%); pale yellow, viscous liquid.

R_f = 0.36 (EtOAc/hexane, 3:7).

IR (neat): 3299, 3057, 2984, 2928, 2362, 2334, 1709, 1471, 1413, 1378, 1306, 1235, 1173, 1128, 1099, 1059, 862, 759, 700, 658, 614, 537 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 7.5 Hz, 2 H), 7.28–7.25 (m, 2 H), 7.19–7.16 (m, 1 H), 6.47–6.41 (m, 2 H), 6.22–6.18 (m, 1 H), 5.77–5.74 (m, 1 H), 5.63 (dd, J_1 = 4 Hz, J_2 = 2 Hz, 1 H), 4.71–4.70 (m, 1 H), 4.23–4.14 (m, 4 H), 3.58 (br s, 1 H), 2.67–2.62 (m, 1 H), 2.53–2.50 (m, 1 H), 1.30–1.20 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 156.2, 137.3, 134.4, 131.9, 131.2, 130.3, 129.8, 128.5, 127.1, 126.2, 125.6, 64.8, 62.6, 62.2, 51.4, 35.1, 14.5.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{19}H_{24}N_2NaO_4$: 367.16338; found: 367.16383.

Diisopropyl 1-(2-Styrylcyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3ba)

Yield: Method A: 48 mg (70%); Method B: 44 mg (63%); pale yellow, viscous liquid.

R_f = 0.48 (EtOAc/hexane, 3:7).

IR (neat): 3299, 3059, 2982, 2933, 1712, 1495, 1460, 1407, 1381, 1307, 1250, 1179, 1141, 1107, 1039, 965, 918, 841, 761, 700, 649 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7. 33 (d, J = 7.5 Hz, 2 H), 7.30–7.26 (m, 2 H), 7.20–7.17 (m, 1 H), 6.44–6.41 (m, 1 H), 6.28 (m, 1 H), 6.21 (br s, 1 H), 5.77–5.75 (m, 1 H), 5.64–5.63 (m, 1 H), 4.99–4.89 (m, 2 H), 4.70 (br s, 1 H), 3.58 (br s, 1 H), 2.63 (m, 1 H), 2.53–2.50 (m, 1 H), 1.29–1.20 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 154.1, 138.9, 135.2, 134.3, 134.0, 130.6, 130.3, 128.8, 128.5, 128.4, 128.1, 126.1, 70.0, 69.2, 65.1, 47.9, 35.1, 22.1, 22.0, 21.9.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{28}N_2NaO_4$: 395.19468; found: 395.19540.

Dibenzyl 1-(2-Styrylcyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3ca)

Yield: Method A: 32 mg (49%); Method B: 31 mg (48%); pale yellow, viscous liquid.

R_f = 0.46 (EtOAc/hexane, 3:7).

IR (neat): 3296, 3061, 3032, 2958, 2926, 2854, 1955, 1714, 1606, 1496, 1452, 1406, 1303, 1262, 1215, 1162, 1125, 1050, 970, 912, 849, 823, 748, 697, 594 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 10 H), 7.24–7.18 (m, 5 H), 6.50–6.40 (m, 2 H), 6.18 (br s, 1 H), 5.74 (s, 1 H), 5.62 (s, 1 H), 5.20–5.08 (m, 4 H), 4.75 (br s, 1 H), 3.58 (br s, 1 H), 2.65 (m, 1 H), 2.35 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5, 155.8, 137.2, 136.4, 135.8, 135.5, 134.5, 132.0, 130.9, 130.5, 128.5, 128.4, 128.4, 128.4, 128.1, 128.0, 127.8, 127.1, 126.2, 126.0, 123.4, 68.1, 67.8, 63.0, 51.4, 35.0.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{29}H_{28}N_2NaO_4$: 491.19468; found: 491.19562.

Di-*tert*-butyl 1-(2-Styrylcyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3da)

Yield: Method A: 35 mg (52%); Method B: 28 mg (42%); pale yellow, viscous liquid.

R_f = 0.58 (EtOAc/hexane, 3:7).

IR (neat): 3410, 3065, 2978, 2925, 2854, 1705, 1613, 1479, 1455, 1395, 1368, 1334, 1252, 1158, 1051, 1023, 850, 757, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 4 H), 7.26–7.17 (m, 1 H), 6.41 (d, J = 16 Hz, 1 H), 6.20 (m, 1 H), 5.92 (br s, 1 H), 5.76 (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, 1 H), 5.63 (m, 1 H), 4.65 (br s, 1 H), 3.55 (br s, 1 H), 2.65–2.61 (m, 1 H), 2.52–2.49 (m, 1 H), 1.48–1.41 (m, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 155.0, 135.4, 132.8, 130.5, 130.0, 128.5, 128.3, 128.2, 127.7, 126.1, 121.5, 81.4, 80.3, 53.2, 49.8, 31.2, 28.2, 28.1, 28.1.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{32}N_2NaO_4$: 423.22598; found: 423.20526.

Diethyl 1-(5-Styrylspiro[2.4]hept-6-en-4-yl)hydrazine-1,2-dicarboxylate (3ea)

Yield: Method A: 35 mg (50%); Method B: 33 mg (47%); pale yellow, viscous liquid.

R_f = 0.44 (EtOAc/hexane, 3:7).

IR (neat): 3293, 3058, 2982, 2927, 2854, 1711, 1602, 1517, 1467, 1447, 1411, 1380, 1301, 1230, 1173, 1129, 1097, 1061, 1023, 970, 924, 873, 759, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, J = 7.5 Hz, 2 H), 7.31–7.28 (m, 2 H), 7.22–7.20 (m, 1 H), 6.49–6.46 (m, 1 H), 6.32–6.28 (m, 1 H), 6.15 (br s, 1 H), 5.66 (s, 1 H), 5.31 (d, J = 5.5 Hz, 1 H), 4.50 (br s, 1 H), 4.24–4.18 (m, 4 H), 3.82 (m, 1 H), 1.31–1.24 (m, 6 H), 0.89–0.87 (m, 1 H), 0.81–0.79 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 154.2, 136.3, 131.2, 129.9, 129.0, 128.8, 128.6, 128.4, 128.2, 127.1, 126.2, 68.4, 62.4, 61.9, 52.7, 29.7, 14.5, 14.2, 9.0, 8.9.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{26}N_2NaO_4$: 393.17903; found: 393.17748.

Diisopropyl 1-(5-Styrylspiro[2.4]hept-6-en-4-yl)hydrazine-1,2-dicarboxylate (3fa)

Yield: Method A: 36 mg (53%); Method B: 36 mg (53%); pale yellow, viscous liquid.

R_f = 0.53 (EtOAc/hexane, 3:7).

IR (neat): 3289, 3058, 3025, 2982, 2852, 1710, 1600, 1572, 1494, 1467, 1451, 1404, 1382, 1299, 1235, 1180, 1144, 1108, 1035, 966, 835, 758, 696, 604, 564 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 3 H), 7.21–7.19 (m, 2 H), 6.48–6.44 (m, 1 H), 6.31 (br s, 1 H), 6.21 (s, 1 H), 5.65 (s, 1 H), 5.29 (d, J = 5 Hz, 1 H), 4.97–4.89 (m, 2 H), 4.49–4.30 (m, 1 H), 3.81–3.74 (m, 1 H), 1.28–1.22 (m, 12 H), 0.90–0.87 (m, 1 H), 0.79–0.78 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2, 155.8, 137.4, 136.3, 131.3, 129.7, 128.8, 128.5, 128.4, 127.0, 126.2, 117.9, 70.2, 70.0, 69.4, 52.3, 29.6, 22.0, 21.9, 14.1, 13.9.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_4$: 421.21033; found: 421.20918.

Diethyl 1-(2-(4-Chlorostyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3ab)

Yield: Method A: 48 mg (61%); Method B: 43 mg (54%); pale yellow, viscous liquid.

R_f = 0.38 (EtOAc/hexane, 3:7).

IR (neat): 3296, 2983, 2935, 1712, 1594, 1489, 1411, 1378, 1310, 1261, 1176, 1095, 1060, 1019, 892, 840, 764, 647 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 4 H), 6.47–6.37 (m, 2 H), 6.21–6.17 (m, 1 H), 5.76 (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, 1 H), 5.62 (d, J = 4 Hz, 1 H), 4.70 (br s, 1 H), 4.22–4.14 (m, 4 H), 3.58 (br s, 1 H), 2.66–2.61 (m, 1 H), 2.52–2.49 (m, 1 H), 1.30–1.20 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 155.2, 139.2, 135.9, 132.7, 132.0, 131.8, 129.1, 128.8, 128.7, 127.4, 65.1, 62.4, 62.1, 51.3, 35.1, 14.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{23}ClN_2NaO_4$: 401.12440; found: 401.12216.

Diisopropyl 1-(2-(4-Chlorostyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3bb)

Yield: Method A: 52 mg (70%); Method B: 46 mg (62%); pale yellow, viscous liquid.

R_f = 0.50 (EtOAc/hexane, 3:7).

IR (neat): 3297, 3056, 2982, 2935, 1709, 1594, 1491, 1465, 1407, 1381, 1304, 1244, 1179, 1140, 1107, 1039, 1016, 965, 829, 764, 727, 649 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 4 H), 6.40–6.37 (m, 1 H), 6.31 (br s, 1 H), 6.22–6.14 (m, 1 H), 5.76 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1 H), 5.62 (d, J = 4 Hz, 1 H), 4.99–4.88 (m, 2 H), 4.69 (br s, 1 H), 3.57 (br s, 1 H), 2.62–2.60 (m, 1 H), 2.53–2.49 (m, 1 H), 1.28–1.22 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1, 155.5, 135.9, 135.3, 132.7, 132.1, 131.8, 131.0, 129.0, 128.6, 127.3, 70.0, 69.9, 64.4, 51.3, 35.0, 22.1, 22.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{27}ClN_2NaO_4$: 429.15570; found: 429.15652.

Dibenzyl 1-(2-(4-Chlorostyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3cb)

Yield: Method A: 37 mg (53%); Method B: 32 mg (46%); pale yellow, viscous liquid.

R_f = 0.52 (EtOAc/hexane, 3:7).

IR (neat): 3294, 3063, 3034, 2954, 2856, 1956, 1713, 1591, 1494, 1452, 1407, 1304, 1219, 1173, 1094, 1051, 1019, 974, 913, 828, 745, 699, 595 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 14 H), 6.43–6.35 (m, 2 H), 6.14–6.06 (m, 1 H), 5.73 (s, 1 H), 5.60 (m, 1 H), 5.16 (m, 4 H), 4.73 (br s, 1 H), 3.58 (s, 1 H), 2.62 (m, 1 H), 2.52 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 155.9, 135.9, 135.8, 135.5, 132.7, 131.8, 129.2, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.4, 119.7, 117.8, 68.2, 68.0, 65.4, 48.1, 35.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{27}ClN_2NaO_4$: 525.15570; found: 525.15783.

Di-*tert*-butyl 1-(2-(4-Chlorostyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3db)

Yield: Method A: 37 mg (51%); Method B: 32 mg (44%); pale yellow solid; mp 77–79 °C.

R_f = 0.62 (EtOAc/hexane, 3:7).

IR (neat): 3319, 3057, 2979, 2932, 1709, 1593, 1488, 1456, 1394, 1367, 1334, 1253, 1159, 1094, 1052, 1016, 969, 896, 852, 761, 529 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 4 H), 6.39–6.36 (m, 1 H), 6.20–6.15 (m, 2 H), 5.76 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1 H), 5.62 (m, 1 H), 4.65–4.47 (m, 1 H), 3.54 (br s, 1 H), 2.60 (m, 1 H), 2.51 (m, 1 H), 1.52–1.41 (m, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6, 154.6, 134.2, 132.6, 131.4, 130.8, 129.4, 128.7, 128.6, 128.5, 127.3, 121.3, 81.7, 81.3, 64.0, 53.2, 31.2, 28.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{31}ClN_2NaO_4$: 457.18700; found: 457.18826.

Diethyl 1-(2-(4-Methylstyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3ac)

Yield: Method A: 50 mg (67%); Method B: 46 mg (62%); pale viscous liquid.

R_f = 0.40 (EtOAc/hexane, 3:7).

IR (neat): 3304, 2983, 2931, 2873, 1745, 1715, 1515, 1468, 1451, 1414, 1374, 1334, 1175, 1109, 1059, 971, 892, 866, 802, 765, 516 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, J = 8 Hz, 2 H), 7.07 (d, J = 8 Hz, 2 H), 6.40–6.34 (m, 2 H), 6.16–6.11 (m 1 H), 5.75 (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, 1 H), 5.63 (dd, J_1 = 6 Hz, J_2 = 1.5 Hz, 1 H), 4.69 (br s, 1 H), 4.23–4.14 (m, 4 H), 3.55 (br s, 1 H), 2.66–2.62 (m, 1 H), 2.54–2.49 (m, 1 H), 2.32 (s, 3 H), 1.31–1.28 (m, 3 H), 1.22 (t, J = 7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 155.9, 136.5, 134.6, 132.1, 130.1, 129.3, 129.2, 129.1, 128.5, 126.6, 65.2, 62.3, 61.8, 47.9, 35.0, 21.1, 14.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2NaO_4$: 381.17903; found: 381.17786.

Dibenzyl 1-(2-(4-Methylstyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3cc)

Yield: Method A: 38 mg (58%); Method B: 38 mg (58%); pale yellow, viscous liquid.

R_f = 0.56 (EtOAc/hexane, 3:7).

IR (neat): 3291, 3088, 3022, 2923, 2856, 2732, 1953, 1716, 1700, 1609, 1511, 1454, 1408, 1333, 1273, 1218, 1127, 1049, 972, 912, 847, 755, 697, 600 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 6 H), 7.23–7.18 (m, 6 H), 7.07 (d, J = 7.5 Hz, 2 H), 6.50 (s, 1 H), 6.38–6.35 (m, 1 H), 6.11 (br s, 1 H), 5.73 (s, 1 H), 5.62–5.58 (m, 1 H), 5.15–5.07 (m, 4 H), 4.74–4.69 (m, 1 H), 3.56 (s, 1 H), 2.63 (br s, 1 H), 2.53–2.50 (m, 1 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5, 155.5, 141.0, 136.7, 135.8, 135.6, 134.5, 132.2, 129.9, 129.1, 129.0, 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 126.9, 126.2, 68.2, 67.8, 65.3, 51.4, 35.1, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{30}N_2NaO_4$: 505.21033; found: 505.20949.

Diisopropyl 1-(2-(4-Methylstyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3bc)

Yield: Method A: 51 mg (71%); Method B: 48 mg (67%); pale yellow, viscous liquid.

R_f = 0.56 (EtOAc/hexane, 3:7).

IR (neat): 3291, 2979, 2922, 2873, 2854, 1742, 1698, 1676, 1514, 1466, 1407, 1371, 1311, 1178, 1145, 1109, 1038, 911, 888, 843, 670 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, J = 8 Hz, 2 H), 7.07 (d, J = 7.5 Hz, 2 H), 6.38 (d, J = 16 Hz, 1 H), 6.26 (s, 1 H), 6.14 (br s, 1 H), 5.75 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1 H), 5.63 (d, J = 4 Hz, 1 H), 4.99–4.88 (m, 2 H), 4.68 (s, 1 H), 3.55 (s, 1 H), 2.62–2.53 (m, 1 H), 2.52–2.48 (m, 1 H), 2.32 (s, 3 H), 1.28–1.22 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7, 155.4, 137.4, 136.6, 134.6, 134.2, 132.1, 130.2, 129.2, 129.1, 126.1, 122.7, 70.0, 69.6, 65.0, 47.9, 35.1, 22.1, 22.0.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{30}N_2NaO_4$: 409.21033; found: 409.20856.

Diisopropyl 1-(2-(4-Methoxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3bd)

Yield: Method A: 58 mg (77%); Method B: 56 mg (75%); pale yellow, viscous liquid.

R_f = 0.37 (EtOAc/hexane, 3:7).

IR (neat): 3301, 3055, 2981, 2935, 2851, 1705, 1599, 1498, 1466, 1406, 1375, 1282, 1258, 1180, 1145, 1108, 1052, 964, 909, 886, 785, 764, 725, 677 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.54 (m, 1 H), 7.21 (d, J = 8 Hz, 1 H), 6.80 (d, J = 8.5 Hz, 2 H), 6.32–6.29 (m, 2 H), 6.08 (br s, 1 H), 5.75 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1 H), 5.61 (d, J = 4 Hz, 1 H), 4.98–4.90 (m, 2 H), 4.68 (br s, 1 H), 3.88 (s, 3 H), 3.55 (br s, 1 H), 2.62 (m, 1 H), 2.52–2.48 (m, 1 H), 1.29–1.22 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5, 154.9, 136.4, 132.0, 131.7, 130.8, 130.7, 129.2, 129.0, 128.4, 126.3, 111.7, 70.0, 69.6, 65.1, 56.1, 51.2, 35.0, 22.1, 22.0.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{30}N_2NaO_5$: 425.20524; found: 425.20414.

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Supporting Information

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