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Stereoselective Heck arylation of a functionalized cyclopentenyl ether using (*S*)-*N*-methyl-pyrrolidine as the stereochemical controller

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ABSTRACT

The study of a series of palladium(0)-catalyzed *C*2-arylations of a 1-cyclopentenyl ether equipped with a chiral (*S*)-*N*-methyl-pyrrolidine auxiliary is reported. Stereoselective Heck monoarylations were performed using aryl iodides under classical heating conditions for 1.7–3.0 h at 80 °C and in one case using 30 min of microwave irradiation at 110 °C. To further explore the scope and nature of this stereoselective methodology, aryl bromides were also utilized as arylating agents, using 20 min of microwave processing at 120–130 °C. High to excellent diastereopurities (90–98% de) were obtained according to ^{1}H NMR and GC–MS analyses. The prolinol fragment apparently controlled the diastereoselectivity of the Heck reaction by presenting the arylpalladium species from the preferred side of the double bond. By X-ray structure diffraction analysis of an *N*-quaternized Heck product, the absolute configuration of the new stereocenter was established as (*R*), supporting a *Si*-face migratory insertion.

1. Introduction

Palladium-catalyzed Heck reactions have gained importance because of their unique capability of forming carbon–carbon bonds in an atom- and step-economical fashion with high selectivities.[1–4] Among the alternative ways to induce stereodifferentiation by Heck methodology, the most elegant is by means of a chiral catalyst.[5–7] Regrettably, in the area of intermolecular Pd(0)-catalyzed Heck arylations, only a few truly efficient enantioselective examples have been described.[8–11] An alternative strategy relies on the usage of a chiral palladium(II)-directing auxiliary (chelation-control).[12–15] In this case, the vinyl substrate is equipped with a functionality designed to establish an initial metal pre-coordination, followed by a pseudo-intramolecular presentation of the organopalladium complex for the most favored diastereotopic face of a cyclic olefin. By choosing the appropriate position, connection, tether length, geometry, and palladium(II)-coordinating strength of the auxiliary, it has been possible to control both the stereoselectivity of the migratory insertion and the regioselectivity of the following β-elimination to afford highly diastereoselective intermolecular Heck reactions.[15]

In 2003, we published a chelation-controlled Heck method for stereoselective generation of (*R*)-2-aryl-2-methylcyclopentanones in 90–98% ee and 45–78% overall yield by a Heck arylation of prolinol vinyl ether **1** with aryl iodides **2** and aryl bromides **6**, followed by subsequent hydrolysis of the Heck product (*S*,*R*)-**3** (Scheme 1).[16] In this transformation, (*S*)-*N*-methyl-pyrrolidine acted as the organopalladium-directing group and the formed quaternary carbon center was inert to racemization during the final acidic hydrolysis.[16,17] However, although the optical purities of the isolated (*R*)-2-aryl-2-methylcyclopentanones were very satisfying, we were unable to identify the stereocontrolling reaction step. Was the transition-state barrier for the migratory insertion determining the *C*2-chirality, or alternatively, would the most stable (and most abundant) π-complex stereoisomer intermediate undergo insertion and subsequent β-elimination to provide the product (*S*,*R*)-**3** in diastereomeric excess? At this stage we initiated a computational investigation[18] to clarify the mechanistic features governing the stereochemical outcome. The work proved difficult and computationally demanding due to the complexity and number of putative intermediates. Before finalizing the calculations, a DFT study on the Heck arylation of **1** with aryl halides was published by Ming et al.[19] Pleasingly, the results from theoretical calculations by this research group supported the experimental outcome, yielding the (*S*,*R*)-**3** product. They concluded that the insertion barrier, and not the difference in π-complex stability, was the prime factor for the stereoselection in the directed Heck arylation.

The intriguing features of this class of auxiliary-controlled Heck reactions encouraged us to investigate non-*C*2-methylated olefin **4** as a simplified derivative of **1**, using the same chiral pyrrolidine auxiliary (Scheme 2). The double bond of vinyl ether **4** is only trisubstituted and we reasoned that both the π-complex formation

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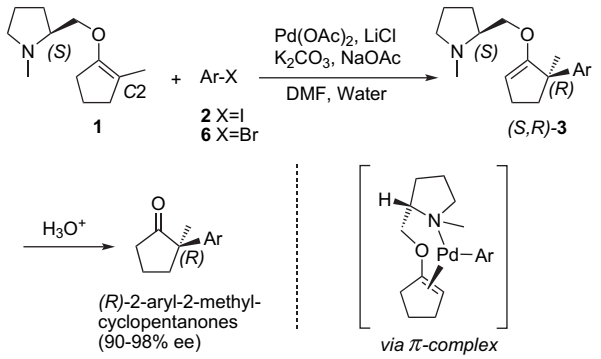
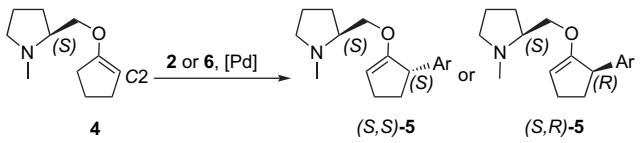


Scheme 1. Heck arylation of tetrasubstituted (*S*)-*N*-methyl-pyrrolidine-functionalized vinyl ether **1** and subsequent hydrolysis.

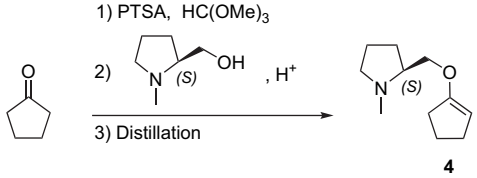


Scheme 2. Possible diastereomeric outcomes in Heck arylation of trisubstituted vinyl ether **4**.

and the insertion rate should increase using **4**. Since theoretical DFT calculations were found problematic, we decided to experimentally investigate the Heck arylation of olefin **4**. In this paper we hereby report: (1) the synthesis of vinyl ether **4**, (2) the identification of classical and microwave-assisted reaction conditions for mono-arylation of **4** using either aryl iodides **2** or aryl bromides **6**, and (3) an unambiguous establishment of a *Si*-insertion process by X-ray crystallographic analysis of an isolated salt of the (*S*,*R*)-**5** product.

2. Results and discussion

An acid-catalyzed transacetalization–elimination process was utilized in the preparation of vinyl ether **4** from cyclopentanone and (*S*)-*N*-methyl prolinol (Scheme 3). The reaction was found to be highly moisture sensitive and reversible, cleaving the product and reforming cyclopentanone if dry conditions were not established. Continuous azeotropic distillation with toluene and subsequent addition of small amounts of chloroform to remove formed methanol provided a residue, which was purified by silica-chromatography, yielding 45% of pure product **4**.

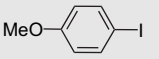
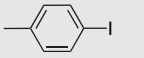
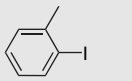
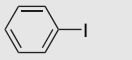
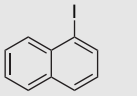
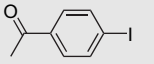
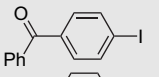
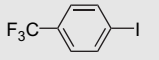
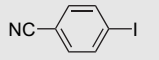


Scheme 3. Synthesis of vinyl ether **4**.

2.1. Aryl iodides as coupling partners

Utilizing previous experiences on Heck arylations of non-cyclic vinyl ethers,[12] straightforward phosphine-free conditions[20,21] were selected for arylation of **4** using $Pd(OAc)_2$ (2 mg, 9 μmol) as pre-catalyst, aryl iodides **2a**–**i** (0.30 mmol), **4** (60 mg, 0.33 mmol), NaOAc (31 mg, 0.38 mmol), LiCl (25 mg, 0.60 mmol), K_2CO_3 (50 mg, 0.36 mmol), H_2O (0.1 mL), and DMF (1.0 mL). The reactions were performed in a sealed vessel using a heating-block set at 80 °C. After full conversion of yield-determining **2a**–**i** (1.7–3.0 h), arylated products (*S*,*R*)-**5a**–**i** were isolated (>95% purity) using column chromatography on silica. As depicted in Table 1, most aryl iodides performed well, producing moderate to good isolated yields. A slightly lower yield was experienced with hindered **2c** (29%, entry 3). This was probably due to a slower insertion rate allowing more pronounced dehalogenation and competing reactions, mainly homocoupling but also diarylation. Importantly, GC–MS and ^1H NMR analyses of the crude products proved a diastereomeric excess of more than 96% for all reactions with classical heating regardless of the electronic properties of the aryl group (Table 1). The high stereoselectivity elucidates the excellent capability of the pyrrolidine auxiliary to control the stereochemical outcome of the reaction. Despite the possibility for further arylation of the in situ generated trisubstituted double bond of monoarylated **5**, no or very small amounts of diarylated products (≤4%) were detected using this protocol. In order to improve the outcome with *ortho*-substituted **2c**, the reaction was also carried out in sealed vessels under controlled microwave irradiation[22–24] using an identical reaction system. Full conversion of **2c** and an improved yield of 42% was obtained after merely 30 min of heating at 110 °C (Table 1, entry 4). Under these conditions, the diastereomeric excess was reduced to 94%.

Table 1
Diastereoselective (*S*)-*N*-methyl-pyrrolidine-controlled Heck synthesis of **5** using aryl iodides

Entry	Aryl iodide		Time [h]	Isolated yield[a] [%]		de[b] [%]	$[\alpha]_D$
1		**2a**	2.0	57	**5a**	98	−97°
2		**2b**	2.7	60	**5b**	>98	−82°
3		**2c**	3.0	29	**5c**	96	−44°
4[c]		**2c**	0.5	42	**5c**	94	−43°
5		**2d**	3.0	54	**5d**	98	−73°
6		**2e**	2.2	58	**5e**	96	+10°
7		**2f**	1.7	51	**5f**	>98	−78°
8		**2g**	3.0	45	**5g**	>98	−73°
9		**2h**	2.5	50	**5h**	>98	−76°
10		**2i**	3.0	57	**5i**	>98	−94°

[a] Reaction conditions: **2a**–**i** (0.30 mmol), **4** (0.33 mmol), $Pd(OAc)_2$ (9 μmol), NaOAc (0.36 mmol), LiCl (0.60 mmol), K_2CO_3 (0.36 mmol), H_2O (0.1 mL) in DMF (1.0 mL) at 80 °C; >95% purity according to GC–MS.
[b] Determined by GC–MS and ^1H NMR of the crude product.
[c] Performed with controlled microwave heating at 110 °C.

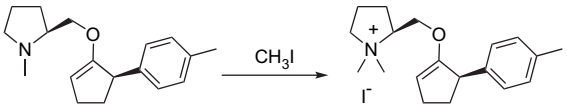
2.2. Aryl bromides as coupling partners

The productive reaction conditions for aryl iodides were found to be insufficient for activation of the cheaper but more sluggish aryl bromides (**6a**–**i**). In addition, hydrolysis of the starting vinyl ether, competing diarylation, and dehalogenation of starting material complicated both product generation and isolation of the desired product. These difficulties were solved using controlled microwave heating and *trans*-di-μ-acetatobis[2-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (Herrmann's palladacycle)[25–27]/2-(di-*tert*-butylphosphino)biphenyl (JohnPhos)[28] as a thermostable

catalytic system, resulting in both faster reactions and higher yields of products **5a–i**.[29,30] All the microwave reactions were performed under an atmosphere of air in septum sealed reaction vials charged with **6a–i** (0.30 mmol), **4** (60 mg, 0.33 mmol), Herrmann's palladacycle (8 mg, 9.0 μmol), JohnPhos (8 mg, 27.0 μmol), NaOAc (29 mg, 0.36 mmol), LiCl (25 mg, 0.60 mmol), K_2CO_3 (50 mg, 0.36 mmol), H_2O (0.1 mL), and DMF (1.0 mL). The reaction mixtures were irradiated for 20 min at 120 °C or 130 °C using a single-mode reactor with temperature control. At higher reaction temperature, the diarylation process becomes more competitive, partly due to reduced steric requirements of the ArPdBr complex, set against the alternative ArPdI intemediate.[12] In comparison, reactions using aryl iodides **2a** and **2c** at 120 °C did not provide the diarylated product at all. The preparative results with aryl bromides using our optimized conditions are summarized in Table 2, showing identical or slightly improved yields compared with the corresponding reactions with aryl iodides **2a–i**, except for the case of electron-rich 4-bromoanisole **6a**. In this case, rapid homocoupling of **6a**, producing the bianisyl side-product and rapid diarylation of **4**, competed with the formation of the desired monoarylated product **5a**. Despite the higher reaction temperature, the diastereomeric selectivity remained virtually intact (90–98% de), although diarylation was slightly more pronounced using aryl bromides instead of the iodo counterparts. Thus, the efficiency of the catalyst-presenting (*S*)-*N*-methyl-pyrrolidine remained high also in the presence of the Pd(II)-coordinating phosphine ligand JohnPhos.

2.3. X-ray diffraction analysis

To determine the absolute configuration of the Heck arylation products, (*S*,*R*)-**5b** (27 mg, 0.10 mmol) was selected and *N*-methylated by stirring the compound in methyl iodide (2 mL) for 2 h at 40 °C (Scheme 4).



Scheme 4. Synthesis of the quarternary ammonium salt (*S*,*R*)-**7b**.

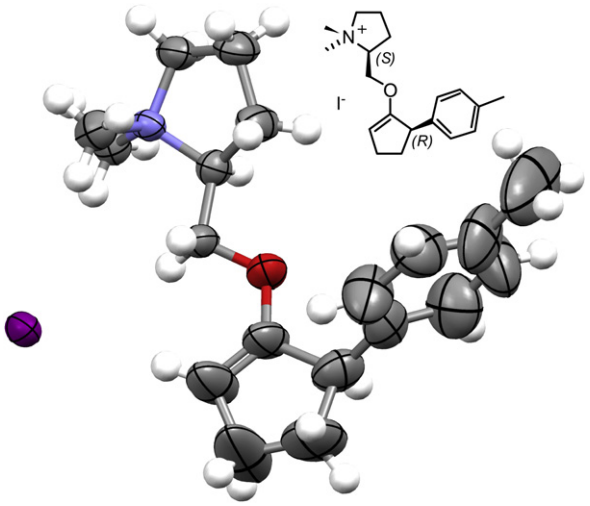
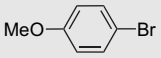
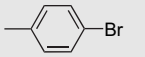
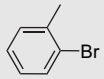
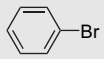
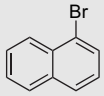
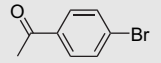
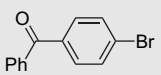
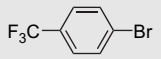
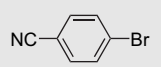


Figure 1. Ortep plot of *C*2-arylated *N*,*N*-dimethyl vinyl ether ammonium iodide salt (*S*,*R*)-**7b**. Probability level 40%. Hydrogens are fixed with a radius of 0.30 Å. Please note that the cyclopentenyl ring is slightly disordered with large thermal displacements at C2 and C4.

The resulting quaternary ammonium salt **7b** was thereafter recrystallized in *i*-PrOH. X-ray crystallography analysis based on the known (*S*)-stereocenter of the prolinol moiety revealed that the (*S*,*R*)-*C*2-isomer was formed, confirming a *Si*-face insertion to the cyclopentene π-system (Fig. 1).

Table 2
Diastereoselective (*S*)-*N*-methyl-pyrrolidine-controlled Heck synthesis of **5** using aryl bromides

Entry	Aryl bromide		Temperature [°C]	Isolated yield[a] [%]		de[b] [%]	$[\alpha]_D$
1		**6a**	130	35	**5a**	98	−97°
2		**6b**	120	68	**5b**	94	−79°
3		**6c**	130	56	**5c**	90	−42°
4		**6d**	120	65	**5d**	92	−70°
5		**6e**	120	46	**5e**	92	+9°
6		**6f**	120	44	**5f**	98	−78°
7		**6g**	120	56	**5g**	>98	−73°
8		**6h**	130	57	**5h**	>98	−76°
9		**6i**	120	57	**5i**	98	−94°

[a] Reaction conditions: **6a–i** (0.30 mmol), **4** (0.33 mmol), Herrmann's palladacycle (9 μmol), JohnPhos (27 μmol), NaOAc (0.36 mmol), LiCl (0.60 mmol), K_2CO_3 (0.36 mmol), H_2O (0.1 mL), and DMF (1.0 mL). Microwave heating in a sealed vessel for 20 min; >95% purity according to GC–MS.
[b] Determined by GC–MS and ^1H NMR of the crude product.

3. Conclusion

In summary, palladium(0)-catalyzed Heck methods for highly diastereoselective syntheses of monoarylated cyclopentenyl ethers (*S*,*R*)-**5a–i** have been developed by the use of a palladium-presenting pyrrolidine auxiliary. Chelation-controlled *C*2-arylations proceeded smoothly and with high to excellent diastereoselectivities (90–98% de) using nine different aryl iodides and the corresponding aryl bromides as arylating agents. Best results with aryl bromides were obtained under controlled microwave heating using a phosphine ligand based catalytic system. Investigated (*S*)-*N*-methyl-pyrrolidine-functionalized 1-cyclopentenyl ether undergoes *Si*-face insertion, providing (*R*)-configuration of the arylated *C*2-carbon. The absolute configuration was unambiguously established using X-ray crystallographic analysis of a quaternary ammonium salt prepared from the corresponding isolated Heck product (*S*,*R*)-**5b**.

4. Experimental

4.1. General comments

^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solution at 400 MHz and 100 MHz, respectively. Chemical shifts for ^1H and ^{13}C

are referenced to TMS via the solvent signals (^{1}H, $CHCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.0 ppm). Low resolution mass spectra were recorded on a GC–MS instrument equipped with a Varian Chrompack Capillary column CP-SIL 8 CB Low Bleed/MS (30 m×0.22 mm, 0.25 μm) and utilizing an ion generation potential of 70 eV. The oven temperature was 40–300 °C (gradient 30 °C/min), 70–320 °C (gradient 16 °C/min), or 90–300 °C (gradient 8 °C/min). Diastereomeric excess was measured by GC–MS and ^{1}H NMR of the crude product; the different diastereomers were assumed to give equal response factor on GC–MS. HRMS experiment was performed on a 7-tesla hybrid ion trap (LTQ) FT mass spectrometer modified with a nanospray ion source. Elemental analyses were performed by MikroKemi AB, Uppsala, Sweden or Analytische Laboratorien, Lindlar, Germany. Conventionally heated reactions were performed in thick-walled tubes fitted with Teflon-lined screw caps. Optical rotations were obtained on a Perkin–Elmer 241 polarimeter using dichloromethane as solvent (c=10 mg/mL) at ambient temperature (20–22 °C). Microwave heating was carried out using an automatic Smith single-mode synthesizer from Biotage, Sweden, producing a radiation frequency of 2450 MHz. Microwave reaction vessels in Pyrex (5 mL, code no 351520, Smith process vial) with silicon septum were also supplied by Biotage. Analytical TLC was performed using Merck glass-backed 0.2 mm silica-gel 60 F-254 plates. Visualization was performed by ultraviolet light and/or by staining with phosphomolybdic acid (12 g) in ethanol (250 mL). Flash column chromatography was performed using commercially available silica (Merck grade 9385, 230–400 mesh, 60 Å) or aluminum oxide (Aldrich, activated, neutral, STD grade, 150 mesh, 58 Å).

4.2. Materials

Palladium(II)acetate and Herrmann's precatalyst (*trans*-di-μ-acetatobis[2-(di-*o*-tolylphosphino)benzyl]dipalladium(II)) were obtained from Strem Chemicals. 2-(Di-*tert*-butylphosphino)biphenyl, cyclopentanone, trimethylorthoformate and (*S*)-(−)-1-methyl-2-pyrrolidine-methanol were purchased from Sigma–Aldrich and used as received. All other reagents obtained from commercial sources were used as received. Spectral and analytical properties of all products synthesized using method A are summarized below. All products were obtained as colorless viscous oils. Compounds **4**, **5a–i**, and **7b** are all novel structures.

4.3. Preparation of (*S*)-2-(cyclopent-1-enyloxymethyl)-1-methyl-pyrrolidine (4)

1,1-Dimethoxy-cyclopentane (1.6 g, 13.0 mmol), prepared as described by Nilsson et al.,[16] and (*S*)-(−)-1-methyl-2-pyrrolidine-methanol (1.5 g, 13.0 mmol) were dissolved in 4 mL toluene. HCl/ether was slowly added until all amine was precipitated. Subsequently, chloroform (4 mL) was added to increase the solubility. The slurry was transferred to a distillation device and heated at 100 °C overnight. The oil-bath temperature was raised to 115 °C and chloroform (4 mL) was added twice a day. The distillation was interrupted when GC–MS analysis of the residue showed complete consumption of 1,1-dimethoxy-cyclopentane. Addition of sodium hydroxide (0.1 M, 25 mL) and subsequent extraction with diethyl ether (3×25 mL) provided a red-brown crude product after drying (K_2CO_3(s)) and concentration of the combined etheral phases. Purification by column chromatography on silica-gel using 96:4 *iso*-hexane/triethylamine provided pure **4** (1.0 g, 45%). ^{1}H NMR δ 4.44–4.41 (m, 1H), 3.74 (dd, J=5.0, 9.7 Hz, 1H), 3.63 (dd, J=6.0, 9.7 Hz, 1H), 3.08–3.03 (m, 1H), 2.52–2.45 (m, 1H), 2.40 (s, 3H), 2.37–2.18 (m, 5H), 2.02–1.57 (m, 5H); ^{13}C NMR δ 160.1, 93.9, 71.8, 64.4, 57.7, 41.5, 31.9, 29.0, 28.7, 22.9, 21.3; MS (70 eV) m/z (relative intensity) 181 (M^+, 2), 98 (5), 84 (100), 42 (8). Anal. Calcd for $C_{11}H_{18}NO$: C, 72.88; H, 10.56. Found: C, 72.85; H, 10.55.

4.4. General procedure for Heck arylation using aryl iodides, Table 1, entries 1–3, 5–9

The reactants were added to a reaction vial in the following order: aryl iodide **2** (0.30 mmol), **4** (60 mg, 0.33 mmol), $Pd(OAc)_2$ (2 mg, 9 μmol), NaOAc (29 mg, 0.36 mmol), LiCl (25 mg, 0.60 mmol), K_2CO_3 (50 mg, 0.36 mmol), DMF (1 mL), and water (0.1 mL). The tube was closed and the contents were magnetically stirred and heated for 1.7–3 h at 80 °C. The reaction was stopped when GC–MS analysis showed complete conversion of **2**. The reaction mixture was diluted with dichloromethane and thereafter filtered through a plug of Celite. The filtrate was washed using 0.1 M NaOH (aq) (25 mL). The aqueous layer was thereafter extracted with dichloromethane (3×25 mL). The organic phases were combined, dried with K_2CO_3 (s), concentrated, and purified by column chromatography on silica-gel affording pure products (*S*,*R*)-**5a–i**.

4.5. Microwave procedure for Heck arylation using 2-iodo-toluene, Table 1, entry 4

The reactants were added to a 0.5–2.0 mL process vial in the following order: 2-iodo-toluene (65 mg, 0.30 mmol), **4** (60 mg, 0.33 mmol), $Pd(OAc)_2$ (2 mg, 9 μmol), NaOAc (29 mg, 0.36 mmol), LiCl (25 mg, 0.60 mmol), K_2CO_3 (50 mg, 0.36 mmol), DMF (1 mL), and water (0.1 mL). The vial was sealed and the contents were magnetically stirred and microwave-heated for 30 min at 110 °C. The reaction mixture was diluted with dichloromethane and thereafter filtered through a plug of Celite. The filtrate was washed using 0.1 M NaOH (aq) (25 mL). The aqueous layer was thereafter extracted with dichloromethane (3×25 mL). The organic phases were combined, dried with K_2CO_3 (s), concentrated, and purified by column chromatography on silica-gel affording pure product (*S*,*R*)-**5c**.

4.6. General procedure for Heck arylation using aryl bromides, Table 2, entries 1–9

The reactants were added to a 0.5–2.0 mL process vial in the following order: aryl bromide **2** (0.30 mmol), **4** (60 mg, 0.33 mmol), Herrmann's palladacycle (8.4 mg, 9 μmol), 2-(di-*tert*-butylphosphino)biphenyl (8.1 mg, 27 μmol), NaOAc (29 mg, 0.36 mmol), LiCl (25 mg, 0.60 mmol), K_2CO_3 (50 mg, 0.36 mmol), DMF (1 mL), and water (0.1 mL). The vial was sealed and the contents were magnetically stirred and microwave-heated for 20 min at 120–130 °C. The reaction mixture was diluted with dichloromethane and thereafter filtered through a plug of Celite. The filtrate was washed using 0.1 M NaOH (aq) (25 mL). The aqueous layer was thereafter extracted with dichloromethane (3×25 mL). The organic phases were combined, dried with K_2CO_3 (s), concentrated, and purified by column chromatography on silica-gel affording pure products (*S*,*R*)-**5a–i**.

4.7. Experimental data and characterization of compounds 4 and (*S*,*R*)-5a–i

*4.7.1. (S)-2-[(R)-5-(4-Methoxy-phenyl)-cyclopent-1-enyloxy-methyl]-1-methyl-pyrrolidine (**5a**)*

Using method A, compound **5a** was obtained in 98% de and 57% yield after purification by column chromatography on silica-gel (*iso*-hexane/diethyl ether/triethylamine, 70:25:5). Using method C, compound **5a** was obtained in 98% de and 35% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethyl-acetate/triethylamine, 80:16:4). ^{1}H NMR δ 7.11 (dd, J=2.1, 6.6 Hz, 2H), 6.82 (dd, J=2.1, 6.6 Hz, 2H), 4.65 (dt, J=1.5, 2.3 Hz, 1H), 3.81 (dd, J=5.7, 9.5 Hz, 1H), 3.79 (s, 3H), 3.75–3.68 (m, 1H), 3.56 (dd, J=6.8, 9.5 Hz, 1H), 2.99 (ddd, J=2.2, 7.0, 9.1 Hz, 1H), 2.50–2.25 (m, 4H), 2.33

(s, 3H), 2.19 (ddd, *J*=7.1, 9.1, 9.9 Hz, 1H), 1.88–1.60 (m, 4H), 1.46–1.36 (m, 1H); ^{13}C NMR δ 161.2, 158.1, 136.8, 128.5, 113.8, 95.5, 73.4, 63.9, 57.8, 55.4, 49.5, 41.9, 32.7, 29.2, 27.6, 23.41; MS (70 eV) *m*/*z* (relative intensity) 287 (M^+, 2), 98 (50), 84 (100). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.10; H, 8.79; N, 4.80. $[\alpha]_D^{22}$ −97°.

4.7.2. (S)-1-Methyl-2-((R)-5-p-tolyl-cyclopent-1-enyloxymethyl)-pyrrolidine (**5b**)

Using method A, compound **5b** was obtained in >98% de and 60% yield after purification by column chromatography on silica-gel (*iso*-hexane/triethylamine, 96:4). Using method C, compound **5b** was obtained in 94% de and 68% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 80:16:4). ^{1}H NMR δ 7.08 (s, 4H), 4.66 (dt, *J*=2.3, 1.4 Hz, 1H), 3.83 (dd, *J*=5.7, 9.6 Hz, 1H), 3.77–3.70 (m, 1H), 3.58 (dd, *J*=6.6, 9.6 Hz, 1H), 3.00 (m, 1H), 2.56–2.35 (m, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 2.26–2.14 (m, 1H),1.92–1.59 (m, 5H), 1.51–1.40 (m, 1H); ^{13}C NMR δ 161.1, 141.5, 135.6, 129.1, 127.5, 95.7, 73.2, 63.9, 57.8, 49.9, 41.8, 32.7, 29.2, 27.6, 23.1, 21.2; MS (70 eV) *m*/*z* (relative intensity) 271 (M^+, 2), 98 (12), 84 (100). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.39; H, 9.09; N, 5.08. $[\alpha]_D^{22}$ −82°.

4.7.3. (S)-1-Methyl-2-((R)-5-o-tolyl-cyclopent-1-enyloxymethyl)-pyrrolidine (**5c**)

Using method A, compound **5c** was obtained in 96% de and 29% yield after purification by column chromatography on silica-gel (*iso*-hexane/diethyl ether/triethylamine, 70:25:5). Using method B, compound **5c** was obtained in 94% de and 42% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 90:6:4). Using method C, compound **5c** was obtained in 90% de and 56% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 90:6:4). ^{1}H NMR δ 7.16–7.06 (m, 4H), 4.73 (dt, *J*=1.4, 2.4 Hz, 1H), 3.99 (dddd, *J*=1.4, 2.7, 5.0, 10.3 Hz, 1H), 3.85 (dd, *J*=5.5, 9.4 Hz, 1H), 3.60 (dd, *J*=6.9, 9.5 Hz, 1H), 3.00 (dd, *J*=2.3, 6.9 Hz, 1H), 2.49–2.30 (m, 4H), 2.35 (s, 3H), 2.34 (s, 3H), 2.27–2.16 (m, 1H), 1.91–1.60 (m, 4H), 1.51–1.43 (m, 1H); ^{13}C NMR δ 160.7, 142.6, 136.1, 130.2, 126.5, 126.0, 125.9, 96.4, 73.3, 64.0, 57.8, 46.7, 41.9, 31.4, 29.4, 27.4, 23.1, 19.7; MS (70 eV) *m*/*z* (relative intensity) 271 (M^+, 3), 98 (30), 84 (100). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.21; H, 9.41; N, 5.20. $[\alpha]_D^{20}$ −44°.

4.7.4. (S)-1-Methyl-2-((R)-5-phenyl-cyclopent-1-enyloxymethyl)-pyrrolidine (**5d**)

Using method A, compound **5d** was obtained in 98% de and 54% yield after purification by column chromatography on silica-gel (*iso*-hexane/triethylamine, 96:4). Using method C, compound **5d** was obtained in 92% de and 65% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 80:16:4). ^{1}H NMR δ 7.29 (ddd, *J*=0.9, 1.9, 7.2 Hz, 2H), 7.22–7.15 (m, 3H), 4.68 (dt, *J*=1.5, 2.2 Hz, 1H), 3.82 (dd, *J*=5.7, 9.5 Hz, 1H), 3.79–3.74 (m, 1H), 3.57 (dd, *J*=6.7, 9.5 Hz, 1H), 2.99 (ddd, *J*=2.2, 7.1, 9.3 Hz, 1H), 2.50–2.34 (m, 3H), 2.32 (s, 3H), 2.22–2.15 (m, 1H), 1.88–1.59 (m, 5H), 1.48–1.35 (m, 1H); ^{13}C NMR δ 160.9, 144.6, 128.3, 127.6, 126.1, 95.8, 73.4, 63.9, 57.8, 50.3, 41.9, 32.6, 29.2, 27.7, 23.1; MS (70 eV) *m*/*z* (relative intensity) 257 (M^+, 2), 98 (24), 84 (100). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 79.1; H, 8.9. $[\alpha]_D^{20}$ −73°.

4.7.5. (S)-1-Methyl-2-((R)-5-naphthalen-1-yl-cyclopent-1-enyloxymethyl)-pyrrolidine (**5e**)

Using method A, compound **5e** was obtained in 96% de and 58% yield after purification by column chromatography on silica-gel (*iso*-hexane/triethylamine, 96:4). Using method C, compound **5e** was obtained in 92% de and 46% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 70:25:5). ^{1}H NMR δ 8.10 (ddd, *J*=1.1, 2.0, 8.3 Hz, 1H), 7.87–7.83 (m, 1H), 7.71 (dt, *J*=1.1, 8.2 Hz, 1H), 7.52–7.44 (m, 2H), 7.41 (dd, *J*=7.1, 8.2 Hz, 1H), 7.28 (dd, *J*=1.6, 7.1 Hz, 1H), 4.85 (dt, *J*=1.3, 2.4 Hz, 1H), 3.92 (dd, *J*=5.4, 9.5 Hz, 1H), 3.68 (dd, *J*=6.9, 9.5 Hz, 1H), 3.00 (ddd, *J*=2.0, 7.2, 11.5 Hz, 1H), 2.66–2.55 (m, 1H), 2.52–2.36 (m, 3H), 2.34 (s, 3H), 2.19 (dt, *J*=7.23, 9.68 Hz, 1H), 1.89–1.60 (m, 5H), 1.53–1.44 (m, 1H); ^{13}C NMR δ 160.2. 139.9, 134.2, 132.2, 128.8, 126.7, 125.7, 125.7, 125.3, 124.0, 123.8, 97.1, 73.3, 64.1, 57.7, 46.3, 41.8, 32.1, 29.4, 27.6, 23.1; MS (70 eV) *m*/*z* (relative intensity) 307 (M^+, 7), 98 (24), 84 (100). Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.28; H, 8.29; N, 4.45. $[\alpha]_D^{20}$ +10°.

4.7.6. 1-{4-[(R)-2-((S)-1-Methyl-pyrrolidin-2-ylmethoxy)-cyclopent-2-enyl]-phenyl}-ethanone (**5f**)

Using method A, compound **5f** was obtained in >98% de and 51% yield after purification by column chromatography on silica-gel (*iso*-hexane/diethyl ether/triethylamine, 70:25:5). Using method C, compound **5f** was obtained in 98% de and 44% yield after purification by column chromatography on silica-gel (*iso*-hexane/diethyl ether/triethylamine, 70:25:5). ^{1}H NMR δ 7.88 (dd, *J*=1.9, 6.5 Hz, 2H), 7.28 (dd, *J*=1.9, 6.5 Hz, 2H), 4.71 (dt, *J*=1.4, 2.3 Hz, 1H), 3.87–3.80 (m, 1H), 3.81 (dd, *J*=5.7, 9.5 Hz, 1H), 3.56 (dd, *J*=6.7, 9.5 Hz, 1H), 2.99 (ddd, *J*=2.3, 6.8, 9.2 Hz, 1H), 2.58 (s, 3H), 2.49–2.31 (m, 4H), 2.32 (s, 3H), 2.18 (ddd, *J*=7.3, 9.1, 9.7 Hz, 1H), 1.85–1.60 (m, 4H), 1.44–1.35 (m, 1H); ^{13}C NMR δ 198.1, 160.2, 150.5, 135.4, 128.6, 127.9, 96.3, 73.5, 63.9, 57.8, 50.4, 41.9, 32.4, 29.2, 27.7, 26.7, 23.1; MS (70 eV) *m*/*z* (relative intensity) 299 (M^+, 1), 98 (8), 84 (100). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.08; H, 8.61; N, 4.64. $[\alpha]_D^{20}$ −78°.

4.7.7. {4-[(R)-2-((S)-1-Methyl-pyrrolidin-2-ylmethoxy)-cyclopent-2-enyl]-phenyl}-phenyl-methanone (**5g**)

Using method A, compound **5g** was obtained in >98% de and 45% yield after purification by column chromatography on silica-gel (*iso*-hexane/diethyl ether/triethylamine, 70:25:5). Using method C, compound **5g** was obtained in >98% de and 56% yield after purification by column chromatography on silica-gel (*iso*-hexane/diethyl ether/triethylamine, 70:25:5). ^{1}H NMR δ 7.79 (dd, *J*=1.3, 8.3 Hz, 2H), 7.75 (d, *J*=8.5 Hz, 2H), 7.57 (ddt, *J*=1.3, 6.6, 7.3 Hz, 1H), 7.48–7.43 (m, 2H), 7.29 (d, *J*=8.3 Hz, 2H), 4.71 (dt, *J*=1.4, 2.3 Hz, 1H), 3.88–3.84 (m, 1H), 3.81 (dd, *J*=5.8, 9.6 Hz, 1H), 3.57 (dd, *J*=6.7, 9.5 Hz, 1H), 2.99 (ddd, *J*=2.2, 6.9, 9.2 Hz, 1H), 2.49–2.33 (m, 4H), 2.32 (s, 3H), 2.18 (ddd, *J*=7.4, 9.1, 9.5 Hz, 1H), 1.87–1.76 (m, 2H), 1.75–1.60 (m, 2H), 1.45–1.36 (m, 1H); ^{13}C NMR δ 169.7, 160.3, 149.9, 138.1, 135.6, 132.3, 130.4, 130.1, 128.3, 127.6, 96.4, 73.5, 63.9, 57.8, 50.4, 41.9, 32.4, 29.2, 27.8, 23.1; MS (70 eV) *m*/*z* (relative intensity) 362 (M^+, 5), 98 (18), 84 (100). Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.49; H, 7.28; N, 3.73. $[\alpha]_D^{20}$ −73°.

4.7.8. (S)-1-Methyl-2-[(R)-5-(4-trifluoromethyl-phenyl)-cyclopent-1-enyloxymethyl]-pyrrolidine (**5h**)

Using method A, compound **5h** was obtained in >98% de and 50% yield after purification by column chromatography on silica-gel (*iso*-hexane/diethyl ether/triethylamine, 90:6:4). Using method C, compound **5h** was obtained in >98% de and 57% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 70:25:5). ^{1}H NMR δ 7.53 (dd, *J*=0.8, 8.6 Hz, 2H), 7.29 (dd, *J*=0.7, 8.6 Hz, 2H), 4.71 (dt, *J*=1.4, 2.4 Hz, 1H), 3.86–3.81 (m, 1H), 3.81 (dd, *J*=5.8, 9.5 Hz, 1H), 3.57 (dd, *J*=6.6, 9.5 Hz, 1H), 2.99 (ddd, *J*=2.2, 6.8, 9.4 Hz, 1H), 2.49–2.31 (m, 4H), 2.32 (s, 3H), 2.19 (ddd, *J*=7.3, 9.2, 9.8 Hz, 1H), 1.87–1.61 (m, 4H), 1.45–1.36 (m, 1H); ^{13}C NMR δ 160.2, 148.8 (q, J^4_{C-F}=1.3 Hz), 128.47 (q, J^2_{C-F}=32.3 Hz), 128.0, 125.30 (q, J^3_{C-F}=3.8 Hz), 124.6 (q, J^1_{C-F}= 271.3 Hz), 96.4, 73.6, 63.9, 57.8, 50.2, 41.9, 32.4, 29.2, 27.7, 23.1; MS (70 eV) *m*/*z* (relative intensity) 326 (M^+, 8), 98 (31), 84 (100). Anal.

Calcd for $C_{18}H_{22}F_3NO$: C, 66.45; H, 6.82; N, 4.30. Found: C, 66.58; H, 6.86; N, 4.41. $[\alpha]_D^{20}$ −76°.

4.7.9. 4-[(R)-2-((S)-1-Methyl-pyrrolidin-2-ylmethoxy)-cyclopent-2-enyl]-benzonitrile (**5i**)

Using method A, compound **5i** was obtained in >98% de and 57% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 80:15:5). Using method C, compound **5i** was obtained in 98% de and 57% yield after purification by column chromatography on silica-gel (*iso*-hexane/ethylacetate/triethylamine, 80:15:5). ^{1}H NMR δ 7.56 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.4 Hz, 2H), 4.70 (dt, J=1.5, 2.5 Hz, 1H), 3.84–3.79 (m, 1H), 3.80 (dd, J=5.8, 9.5 Hz, 1H), 3.55 (dd, J=6.6, 9.5 Hz, 1H), 2.99 (ddd, J=2.4, 6.9, 9.3 Hz, 1H), 2.47–2.31 (m, 4H), 2.30 (s, 3H), 2.19 (dt, J=7.5, 9.5 Hz, 1H), 1.86–1.60 (m, 4H), 1.42–1.33 (m, 1H); ^{13}C NMR δ 159.7, 150.3, 132.2, 128.5, 119.4, 110.0, 96.7, 73.6, 63.9, 57.8, 50.5, 41.9, 32.2, 29.2, 27.7, 23.1; MS (70 eV) m/z (relative intensity) 283 (M^+, 10), 98 (33), 84 (100). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.35; H, 7.94; N, 9.98. $[\alpha]_D^{20}$ −94°.

4.8. Preparation of (*S*)-1,1-dimethyl-2-((*R*)-5-*o*-tolyl-cyclopent-1-enyloxymethyl)-pyrrolidine (7b)

Compound (*S*,*R*)-**5b** (27.1 mg, 0.10 mmol) was stirred with methyl iodide (2 mL) for 2 h at 40 °C. The solvent was removed in vacuo furnishing a yellow oil in quantitative yield. The product was then crystallized in *i*-PrOH providing white crystals of **7b**, which were used for X-ray crystallography. CCDC 683362. LC–MS, m/z= 286 [M^+]; HRMS [M^+] 286.2166, $C_{19}H_{18}NO^+$ requires 286.2171.

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Supplementary data

GC–MS and NMR data of products **4** and **5a**–**i**, and crystallographic and LC–MS data of the salt **7b** can be found in the online version. CCDC 683362 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.099.

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