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# Enantiopure 2-aryl-2-methyl cyclopentanones by an asymmetric chelation-controlled Heck reaction using aryl bromides: increased preparative scope and effect of ring size on reactivity and selectivity

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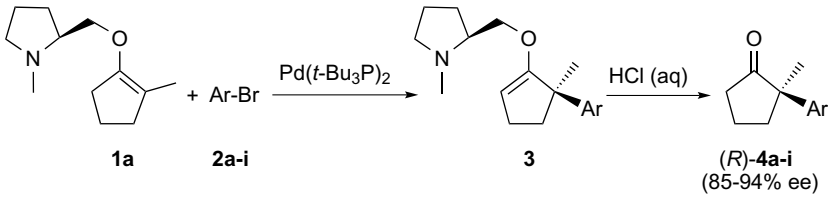
**Abstract**—Quaternary 2-aryl-2-methyl cyclopentanones were obtained in 85–94% ee via Pd(0)-catalyzed chelation-controlled asymmetric arylation of a cyclopentenyl ether with aryl bromides and subsequent hydrolysis. Two new cyclohexenyl ethers were synthesized and evaluated as Heck substrates with both aryl iodides and bromides under different reaction conditions. Arylations of the six-membered vinyl ether 1-methyl-2-(*S*)-(cyclohex-1-enyloxymethyl)-pyrrolidine with aryl bromides were achieved with *t*-$Bu_3P$-promoted palladium catalysis using either classical or microwave heating. Isolated Heck products were also obtained in high diastereoselectivities (94–98% de).


## 1. Introduction

The palladium-catalyzed Heck reaction[1–7] has become an invaluable and unique tool for carbon–carbon bond formation[8] in organic synthesis.[9–11] With cyclic olefins, the stereochemical outcome can be controlled by using either chiral bidentate ligands[12] or substrate-bound catalyst directing groups.[13,14] Although the enantioselective construction of tetra-substituted carbon centers can be achieved by the application of intramolecular Heck reactions,[15,16] the formation of quaternary carbons[17] in high stereopurity remains a challenge when using an intermolecular approach.[18]

The pioneering work by Hartwig et al. and Buchwald et al. at the turn of the century spurred substantial research around Pd(0)-catalyzed α-arylation of carbonyl compounds.[19,20] Today, this direct method ranks among one of the most powerful methods in organic synthesis despite the requirements for a strong base and inert reaction conditions.[20] In pivotal work, Buchwald et al. demonstrated an enantioselective and direct α-arylation procedure of cyclic ketones providing a chiral quaternary α-carbon center in 88–94% ee utilizing palladium(0) catalysis, an axially chiral ligand, and NaO*t*-Bu as the base.[20] An inconvenience with this method was the requirement to block the non-alkylated α-carbon to avoid arylation at this position.




**Scheme 1.**

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We have previously reported the smooth generation of quaternary aryl, methyl carbon centers at the 2-position of cyclopentanone employing a chelation-controlled Heck reaction[21,22] with a catalyst-presenting (*S*)-1-methyl-2-pyrrolidine auxiliary.[23,24] Herein, we report a highly diastereoselective[25] Heck methodology for the construction of quaternary carbons using a suitable palladium-catalyst, aryl bromides, and tetra-substituted olefin **1a** (Scheme 1). Formed Heck products **3** were hydrolyzed to the corresponding 2-aryl-2-methyl cyclopentanones **4** in high to excellent enantiomeric purities. Six-membered, non-C2-methyl substituted products **5** were also isolated in high diastereomeric excess after the monoarylation of tri-substituted olefin **1c** (Scheme 4).

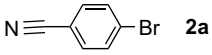
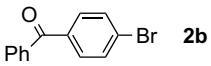
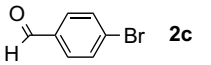
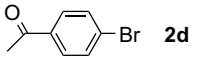
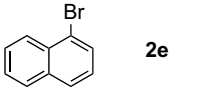
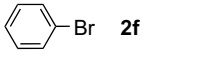
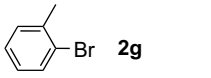
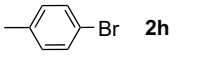
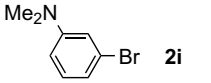
## 2. Results and discussion

### 2.1. Reactions with five-membered cyclic olefin 1a

In our previous studies, tetra-substituted vinyl ether **1a** was arylated with seven different aryl iodides and two reactive aryl bromides employing standard $Pd(OAc)_2$ as the precatalyst, furnishing 2-aryl-2-methyl cyclopentanones **4** in moderate to good yields and with excellent enantioselectivities (90–98% ee).[24] Unfortunately, the published procedure using $Pd(OAc)_2$ as a precatalyst was found to be limited to activated aryl bromides. Based on the positive results using sluggish aryl chlorides,[23] and with the overall aim of developing a general aryl bromide protocol, we decided to evaluate the model reaction between **1a** and **2c** employing the bulky 14-electron catalyst $Pd(t\text{-}Bu_3P)_2$.[26] The Heck coupling of olefin **1a** (1.0 equiv, 0.15 mmol) with aryl bromide **2c** (1.3 equiv) in the presence of LiCl (2.0 equiv), NaOAc (1.2 equiv), $K_2CO_3$ (1.2 equiv), and 5.0 mol % of $Pd(t\text{-}Bu_3P)_2$ in 2.2 mL of aqueous DMF (10% water) furnished full conversion after 9 h of oil-bath heating at 100 °C (Scheme 2). The LiCl, NaOAC, and $K_2CO_3$ combination was crucial for obtaining full conversion[22] keeping in mind that the base effect[27] in Pd-catalysis can play an important role.

The monoarylated Heck product **3c** was obtained in excellent diastereomeric purity according to $^1H$ NMR and was isolated in 69% yield after silica chromatography in the presence of $Et_3N$. Lower catalyst loading did not produce full conversion of the starting materials. Notably, compound **3c** has a free aldehyde functionality along with a masked keto group, providing the opportunity to utilize the reactive aldehyde group for further transformations without affecting the protected ketone (Scheme 2). The reaction was repeated, and product **3c** after cooling was directly hydrolyzed by the addition of 0.5 mL concd HCl to produce **4c** in 68% yield and 94% ee (Table 1, entry 3). This successful protocol was applied with nine different aryl bromides carrying both electron-withdrawing, electron-donating, and potentially palladium(II)-chelating substituents in *para*-, *meta*-, and *ortho* positions. In all the cases, the arylated products were hydrolyzed in situ, providing 2-aryl-2-methyl cyclopentanones **4** in decent two-step one-pot yields with good to excellent enantiomeric purities (85–94% ee) (see Table 1). Electronic influences did not seem to affect the enantioselectivity much. However, sterically congested

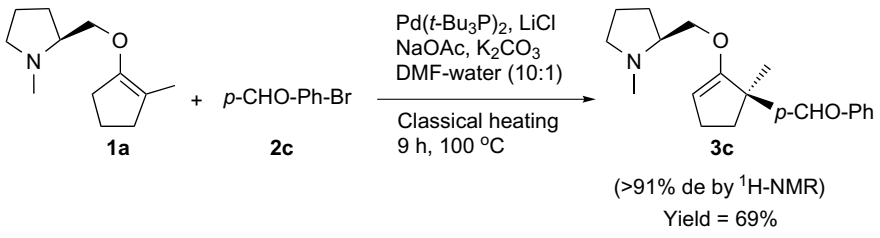
**Table 1.** Asymmetric arylation of **1a** with aryl bromides and subsequent hydrolysis

| Entry | Aryl bromide | Time (h) | Isolated yield[a] | ee[b] (%) |
|---|---|---|---|---|
| 1 |  **2a** | 10 | 62 (%) **4a** | 92 |
| 2 |  **2b** | 10 | 60 (%) **4b** | 91 |
| 3 |  **2c** | 10 | 68 (%) **4c** | 94 |
| 4 |  **2d** | 10 | 64 (%) **4d** | 93 |
| 5 |  **2e** | 14 | 58 (%) **4e** | 90 |
| 6 |  **2f** | 10 | 54 (%) **4f** | 89 |
| 7 |  **2g** | 36 | 45 (%) **4g** | 85[c] |
| 8 |  **2h** | 14 | 60 (%) **4h** | 91 |
| 9 |  **2i** | 10 | 62 (%) **4i** | 92 |

[a] The reactions were performed at 100 °C under air with **1a** (0.15 mmol, 1.0 equiv) using 5.0 mol % of $Pd(t\text{-}Bu_3P)_2$. Ketones (*R*)-**4** were obtained after hydrolysis with concd HCl (aq). Isolated yields are the average of three runs. Purity >95% by GC–MS.

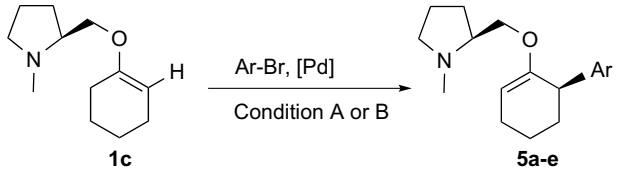
[b] Ee of (*R*)-**4** by chiral HPLC (average of three runs).

[c] Additional 5.0 mol % of $Pd(t\text{-}Bu_3P)_2$ was added after 20 h.




**Scheme 2.**

*ortho*-functionalized aryl bromide **2g** furnished the lowest enantiomeric excess. Due to the slow reaction with hindered **2g**, an extra portion of Pd($t$-$Bu_3P$)$_2$ was added after 20 h to give complete conversion of **1a** (Table 1, entry 7). Furthermore, concomitant hydrolysis of **1a** and dehalogenation of **2g** resulted in the somewhat low yield of **4g** (45%).[28]




**Scheme 4.**

## 2.2. Reactions with six-membered cyclic olefin 1c

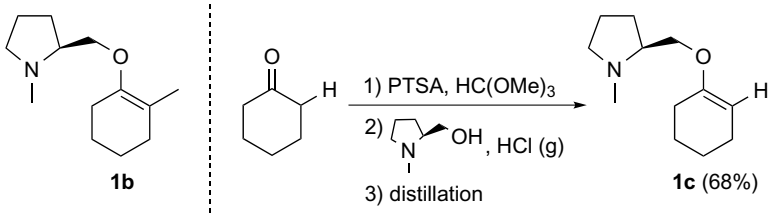
In order to evaluate the general usefulness of the 1-methyl-2-pyrrolidine moiety as a stereocontrolling arylpalladium presenting group, we decided to synthesize 1-methyl-2-(*S*)-(2-methyl-cyclohex-1-enyloxymethyl)-pyrrolidine **1b** and 1-methyl-2-(*S*)-(cyclohex-1-enyloxymethyl)-pyrrolidine **1c** and to investigate the appropriate Heck arylation reactions using both aryl iodides and bromides. Vinyl ether **1b** was synthesized as described in the literature[23] and **1c** was synthesized via a similar acid-catalyzed transacetalization–elimination process in 68% isolated yield (Scheme 3 ).[24]

Unfortunately, tetra-substituted olefin **1b** failed to participate in the arylations despite numerous attempts using different reaction conditions including both aryl bromides and iodides as arylpalladium precursors. Hydrolysis of **1b**, the release of palladium-catalyst poisoning (*S*)-1-methyl-2-pyrrolidine-methanol,[21,22,28] and homocoupling of the arylating agents were the dominating processes, quickly deteriorating the catalytic system and consuming the starting materials. Next, tri-substituted vinyl ether **1c** was studied under similar arylation reactions using aryl iodides as arylating agents and Pd(OAc)$_2$ as the precatalyst at 100 °C. Disappointingly, reactions were either slow or non-yielding and biaryl formations were predominant.[29] It has, however, been noted earlier that aryl iodides provide low yields in the arylation of tri-substituted vinyl ethers.[22] Due to the poor outcome of the reactions using aryl iodides, we shifted our attention toward the use of aryl bromides as substrates for the arylation of **1c**.

High-density microwave processing of sealed reaction mixtures has the potential to speed-up chemistry development by increasing reaction rates and providing high reaction control.[30,31] Hence, we decided to use this heating method under inert conditions to quickly identify productive reaction conditions by employing aryl bromides. In order to improve the thermostability of the catalytic system, microwave-stable Herrmann's catalyst was used in combination with the preligand [($t$-Bu)$_3$PH]BF$_4$.

A Heck reaction using **1c** (1.0 equiv, 0.075 mmol), aryl bromide **2j** (2.0 equiv) in the presence of LiCl (2.0 equiv), NaOAc (1.2 equiv), $K_2CO_3$ (1.2 equiv), 5.0 mol % of air-stable Herrmann's palladacycle, and 10.0 mol % [($t$-Bu)$_3$PH]BF$_4$ in 2.2 mL of aqueous DMF (10% water) under controlled irradiation at 150 °C for 90 min (conditions A) resulted in the full conversion of **1c**. The C2-arylated vinyl ether **5e** showed excellent diastereopurity by GC–MS (97%) and $^1$H NMR analysis, and was isolated in 42% yield after silica chromatography in the presence of $Et_3N$. In order to show the preparative scope of this microwave method, conditions A were utilized with four additional aryl bromides furnishing Heck products **5a–d** with moderate yields (34–38%) but with excellent diastereoselectivities (94–98% de, Table 2). However, under the same conditions, three other electron deficient aryl bromides were tried but gave unimpressive results (4-Ac-Ph-Br, 25%; 4-CN-Ph-Br, 20%; 4-CHO-Ph-Br, 30%). Aiming to improve the yield of the arylated product **5**, we decided to investigate similar coupling reactions with traditional heating and the more active, but less thermostable 14-electron catalyst Pd($t$-$Bu_3P$)$_2$. A test reaction between **1c** (1.0 equiv, 0.15 mmol) and **2j** (1.3 equiv) in the presence of LiCl (2.0 equiv), NaOAc (1.2 equiv), $K_2CO_3$ (1.2 equiv), and 5.0 mol % of Pd($t$-$Bu_3P$)$_2$ in 2.2 mL of aqueous DMF (10% water) at 100 °C for 40 h (conditions B) resulted in a better yield of **5e** (55%) and intact high diastereoselectivity. Based on this positive outcome, all arylation reactions were performed also under conditions B, furnishing improved yields in two additional cases (Table 2, entries 3 and 4) although no product formations were observed for electron deficient aryl bromides.

Despite the use of an excess amount of **2** under both conditions A and B, only trace amounts of diarylated product could be detected. To some extent, the lower yields in the arylations of tri-substituted cyclohexene vinyl ether **1c**,[32] compared to cyclopentene derivative **1a**, can be explained by the slow reaction kinetics, allowing concomitant hydrolysis of **1c** to rival. The low reaction rates might be due to the conformational flexibility of the six-membered ring and the lack of ring strain release upon insertion. The results




**Scheme 3.**

**Table 2.** Diastereoselective arylation of **1c** with aryl bromides

| Entry | Aryl bromide | Condition | Time | Isolated yield[a] (%) | | de[b] (%) | $[\alpha]_D^{23,c}$ |
|---|---|---|---|---|---|---|---|
| 1 |  **2e** | **A** | 90 min | 38 | **5a** | 95 | −31 |
| | | **B** | 40 h | 35 | | 98 | |
| 2 |  **2f** | **A** | 90 min | 38 | **5b** | 98 | −52 |
| | | **B** | 40 h | 36 | | 98 | |
| 3 |  **2g** | **A** | 90 min | 34 | **5c** | 94 | −54 |
| | | **B** | 52 h | 46 | | 98 | |
| 4 |  **2h** | **A** | 90 min | 37 | **5d** | 96 | −40 |
| | | **B** | 40 h | 40 | | 94 | |
| 5 |  **2j** | **A** | 90 min | 42 | **5e** | 97 | −50 |
| | | **B** | 40 h | 55 | | 98 | |

[a] Condition A: the reactions were performed at 150 °C under microwave heating with **1c** (0.075 mmol, 1.0 equiv) using 5.0 mol % of Herrmann's palladacycle and 10.0 mol % of $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$. Condition B: the reactions were performed at 100 °C using classical heating with **1c** (0.15 mmol, 1.0 equiv) using 5.0 mol % $\text{Pd}(t\text{-Bu}_3\text{P})_2$. Isolated yields are average of three runs. Purity >95% by GC–MS.

[b] De of (−) isomer of **5** by GC–MS (average of three runs) and $^1$H NMR.

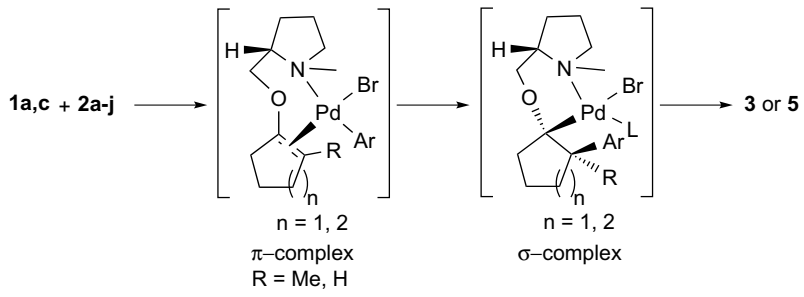
[c] Specific rotation values are an average of three measurements.

are in agreement with the reported sluggish arylation of 3,4-dihydro-2*H*-pyran using chiral P,N-ligands.[33]

The introduction of a metal-directing auxiliary[22,25,34–36] to afford both high stereocontrol[24,25,37] and effective reactivity enhancement in Heck couplings was justified by the reaction outcome. In short, the coordination between the amine and the palladium(II) center leads to the formation of the arylated six-membered σ-complex intermediate (Scheme 5).[35,38] With olefin **1a**, the insertion preferentially occurs from the *Si*-face due to the control of the chirally defined (*S*)-pyrrolidine ring, providing the (*R*)-**3** Heck products. The recently published DFT calculations[39] for the arylation of **1a** and measured specific rotation values[24] strongly support this conclusion. The absolute configuration of the aryl substituted carbon in six-membered vinyl ethers **5** was assigned as (*R*) based on X-ray crystallography analysis of the methyl ammonium salt of the five-membered analogue.[40] Microwave irradiation probably accelerates the arylation of **1c** due to the higher reaction temperature. Nevertheless, the high diastereopurities of products **5a**–**e**, which were obtained at 150 °C under microwave heating, are impressive.[41–43] Additional unfavorable steric requirements for arylpalladium insertion probably account for the failure to arylate methyl substituted cyclohexenyl ether **1b**.

## 3. Conclusion

In conclusion, we have identified efficient reaction conditions for diastereoselective Heck arylations of five- and six-membered cyclic vinyl ethers with aryl bromides using a chiral palladium(II)-presenting (*S*)-1-methyl-2-pyrrolidine auxiliary to control the stereochemistry. Arylated products from the tetra-substituted cyclopentene vinyl ether **1a** were hydrolyzed to the corresponding 2-aryl-2-methyl cyclopentanones, which were obtained in excellent enantiomeric excess (85–94% ee). Despite slow reaction rates and relatively low yields, arylation reactions with the tri-substituted cyclohexene vinyl ether **1c** were highly diastereoselective (de >98%). Microwave-heating at 150 °C accelerated the arylations[38,44] of the six-membered vinyl ether, and the reaction times were reduced from 52 to 40 h to 90 min. We believe that the synthesis of 2-aryl-2-methyl cyclopentanones from aryl bromides in 85–94% ee using $K_2CO_3$ as a weak base may provide an attractive alternative to direct α-arylation in the presence of strong




**Scheme 5.**

base.[19,20,45] Continued studies to extend the chelation-controlled methodology to include also open chain analogues are currently ongoing in the laboratory.

## 4. Experimental

### 4.1. General

All traditionally heated syntheses were performed at 100 °C using a preheated metal block equipped with magnetic stirring under an air atmosphere in vials fitted with Teflon-lined screw caps. Microwave-assisted syntheses were carried out at 150 °C in a Smith/Emrys™ Synthesizer single-mode microwave cavity producing controlled irradiation at 2450 MHz. The temperature of the reaction mixture was measured by an on-line built-in IR sensor. GC–MS analyses were performed with a CP-SIL 8 CB Low Bleed (30 m × 0.25 mm) or a CP-SIL 5 CB Low Bleed (30 m × 0.25 mm) capillary column using a 40–300 °C temperature gradient and EI ionization. RP-LC–MS analyses were performed using a Chromolith SpeedROD RP-18e column (50 × 4.6 mm) and a quadrupole mass spectrometer using a 4 mL/min $CH_3CN/H_2O$ gradient (0.05% HCOOH) and detection by UV (DAD) and MS (ESI+). $^1H$ and $^{13}C$ NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. Chemical shifts for $^1H$ and $^{13}C$ are referenced to TMS via the solvent signals ($^1H$, $CHCl_3$ at 7.26 ppm; $^{13}C$, $CDCl_3$ at 77.0 ppm). HRMS experiments were performed for new compounds on a 7-T hybrid linear ion trap (LTQ) FT mass spectrometer modified with a nanoelectrospray ion source. Silica Gel 60 (0.040–0.063 mm, E. Merck, No. 9385) was used for column chromatography and Silica Gel 60 $PF_{254}$ containing gypsum (0.045 mm) was used for radial thin-layer chromatography. Enantiomerical purities were analyzed by chiral HPLC (Chiracel OD-H; 0.46 × 25 cm, PS = 5 μm or Reprosil Chiral-NR/Reprosil Chiral NR-R; 4.6 × 250 mm, PS = 8 μm, with degassed isohexane/2-propanol, flow rate 0.5 or 1.0 mL/min and detection at 220 nm). The chiral HPLC column (Chiracel OD-H) was protected by a guard column (Chiralcel OD 0.46 × 5 cm, PS = 10 μm). Optical rotations were measured in $CHCl_3$ (*c* 1, *T* = 23 °C). All the isolated compounds were >95% pure as deduced by GC–MS and all isolated yields were calculated as an average of three separate reactions.

### 4.2. Materials

Bis(tri-*t*-butylphosphine)palladium(0), $Pd(OAc)_2$, and tri-*t*-butylphosphonium tetrafluoroborate were obtained from Strem Chemicals. 2-Methylcyclopentanone, 2-methylcyclohexanone, cyclohexanone, trimethyl orthoformate, (*S*)-(−)-1-methyl-2-pyrrolidine-methanol, aryl iodides and all aryl bromides were commercially available and used as obtained. All other reagents obtained from commercial sources were also used as received. Compounds **1c**, **3c**, and **5a**–**e** have not been reported and they were characterized according to the guideline. Vinyl ethers **3c** and **5a**–**e** gradually decomposed in air, prohibiting elemental analysis. Compounds **1a**,**b**, **4a**–**i** are known compounds.[24] Spectral data and optical rotations were in agreement with the literature values.[23,24]

### 4.3. Synthesis of 1-methyl-2-(*S*)-(cyclohex-1-enyloxymethyl)-pyrrolidine 1c

Cyclohexanone (152.8 mmol, 14.9 g) and trimethylorthoformate (168.1 mmol, 17.8 g) were stirred with 4-toluenesulfonic acid monohydrate (0.764 mmol, 0.145 g) at 0 °C for 40 min. The reaction mixture was allowed to warm to room temperature and after another 40 min a distillation was performed to remove methyl formate at 45 °C. (*S*)-(−)-1-Methyl-2-pyrrolidine-methanol (50.9 mmol, 5.87 g) was dissolved in 15 mL toluene and precipitated with HCl (g). The slurry was transferred to the distillation residue and heated at 100 °C for 26 h. The oil-bath temperature was raised to 130 °C to facilitate a slow distillation. Toluene (15 mL), forming an azeotrope with methanol, was added once a day during 4 days. The distillation was stopped when GC–MS analysis of the residue showed complete consumption of the amino alcohol. The addition of sodium hydroxide (10 M, aq, 50 mL) and subsequent extraction with diethyl ether provided a red brown crude product after drying over $K_2CO_3$ and concentration. Purification on a silica column using 95:5 hexane/triethylamine provided **1c** in 68% isolated yield as a pale yellow colored oil. $^1H$ NMR (400 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 4.60 (t, $J = 3.6$ Hz, 1H), 3.65 (dd, $J = 5.3$, 9.5 Hz, 1H), 3.53 (dd, $J = 5.9$, 9.2 Hz, 1H), 3.08–3.04 (m, 1H), 2.52–2.45 (m, 1H), 2.41 (s, 3H), 2.26–2.19 (m, 1H), 2.07–2.01 (m, 4H), 1.98–1.90 (m, 1H), 1.78–1.54 (m, 7H); $^{13}C$ NMR (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 154.8, 93.7, 69.4, 64.4, 57.8, 41.7, 28.9, 27.8, 23.6, 23.0, 22.9, 22.8; GC–MS (70 eV) *m*/*z* (relative intensity) 195 ($M^+$, 1), 98 (5), 84 (100). Elemental Anal. Calcd: C, 73.80; H, 10.84. Found: C, 74.10; H, 10.80.

### 4.4. Synthesis of {4-[1-(*R*)-methyl-2-(1-methyl-pyrrolidin-2-(*S*)-ylmethoxy)-cyclopent-2-enyl]-formyl}-benzene 3c

The reactants were added to a reaction vial in the following order: **2c** (0.19 mmol, 0.024 g), enol ether **1a** (0.15 mmol, 0.029 g), $Pd(t\text{-}Bu_3P)_2$ (5.0 mol %, 0.004 g), NaOAc (0.18 mmol, 0.015 g), LiCl (0.30 mmol, 0.013 g), $K_2CO_3$ (0.18 mmol, 0.025 g), DMF (2 mL), and water (0.2 mL). The tube was closed, and the contents were magnetically stirred and heated at 100 °C for 9 h in a preheated metal block under an air atmosphere. The reaction was interrupted when GC–MS analysis showed complete conversion. After cooling, the reaction mixture was diluted with diethyl ether and was washed five times with NaOH (0.1 M, aq). The combined aqueous phases were additionally extracted twice with diethyl ether. The ether phases were combined and dried with $K_2CO_3$ (s). Concentration and silica column chromatography (hexane/diethyl ether/triethylamine, 1:1:0.05) yielded pure product **3c** (69%) with de >91%. $^1H$ NMR (400 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 9.97 (s, 1H), 7.82–7.77 (m, 2H), 7.50–7.46 (m, 2H), 4.65 (t, $J = 2.5$ Hz, 1H), 3.82 (dd, $J = 6.1$, 9.5 Hz, 1H), 3.63 (dd, $J = 6.0$, 9.5 Hz, 1H), 3.05–2.98 (m, 1H), 2.54–2.44 (m, 1H), 2.4 (s, 3H), 2.31–2.17 (m, 3H), 2.15–1.99 (m, 2H), 1.93–1.80 (m, 1H), 1.80–1.60 (m, 2H), 1.56–1.41 (m, 4H);

$^{13}$C NMR (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 192.1, 162.8, 155.4, 134.2, 129.6, 126.8, 95.0, 73.3, 63.8, 57.7, 51.3, 41.7, 40.9, 29.0, 25.8, 25.0, 22.9; GC–MS (70 eV) *m*/*z* (relative intensity) 299 ($M^+$, 2), 98 (8), 84 (100). High resolution MS calculated for $C_{19}H_{25}NO_2$: $[M+H]^+$ 300.1964, found 300.1957.

### 4.5. General procedure for the Heck arylation of 1a with aryl bromides under classical conditions with subsequent hydrolysis producing 4

The reactants were added to a reaction vial in the following order: aryl bromide **2** (0.19 mmol), enol ether **1a** (0.15 mmol, 0.029 g), Pd(*t*-$Bu_3P)_2$ (5.0 mol %, 0.004 g), NaOAc (0.18 mmol, 0.015 g), LiCl (0.30 mmol, 0.013 g), $K_2CO_3$ (0.18 mmol, 0.025 g), DMF (2 mL), and water (0.2 mL). The tube was closed, and the contents were magnetically stirred and heated at 100 °C for 10–36 h in a preheated metal block under an air atmosphere. The reaction was interrupted when GC–MS analysis showed complete conversion of **1a**. After cooling, 0.5 mL HCl (aq, satd) was added, and the mixture was stirred for 30 min. After complete hydrolysis of **3** according to GC–MS analysis, the reaction mixture was diluted with 10 mL 0.5 M HCl and extracted five times with diethyl ether. The ether phases were washed twice with NaOH (0.1 M, aq) and dried with $K_2CO_3$(s). Concentration and silica column chromatography afforded pure products **4**.

### 4.6. General procedure for Heck arylation of 1c with aryl bromides under conditions A and B producing 5

**4.6.1. Conditions A.** A thick wall glass vial (0.5–2.0 mL) with a Teflon coated stirring bar was charged with aryl bromide **2** (0.15 mmol), vinyl ether **1c** (0.075 mmol, 0.015 g), Herrmann's palladacycle (5.0 mol %, 0.002 g), [(*t*-$Bu)_3PH]BF_4$ (10.0 mol %, 0.004 g), NaOAc (0.09 mmol, 0.0075 g), $K_2CO_3$ (0.09 mmol, 0.0125 g), and LiCl (0.15 mmol, 0.0065 g). DMF/$H_2O$ (2 mL/0.2 mL) was thereafter added followed by sealing the vial under nitrogen. The vial was heated to 150 °C under microwave irradiation for 90 min. After cooling, the reaction mixture was diluted with $CH_2Cl_2$ and was washed five times with NaOH (0.1 M, aq). The combined aqueous phases were additionally extracted twice with $CH_2Cl_2$. The organic phases were combined and dried with $K_2CO_3$(s). Concentration and purification of the crude product using radial thin-layer chromatography (hexane/diethyl ether/triethylamine, 86:10:4) yielded pure products **5**. All the isolated products were >95% pure according to GC–MS.

**4.6.2. Conditions B.** The reactants were added to a reaction vial in the following order: aryl bromide **2** (0.19 mmol), vinyl ether **1c** (0.15 mmol, 0.029 g), Pd(*t*-$Bu_3P)_2$ (5.0 mol %, 0.004 g), NaOAc (0.18 mmol, 0.015 g), LiCl (0.30 mmol, 0.013 g), $K_2CO_3$ (0.18 mmol, 0.025 g), DMF (2 mL), and water (0.2 mL). The tube was closed and the contents were magnetically stirred and heated at 100 °C for 40–52 h in a preheated metal block under an air atmosphere. The reaction was interrupted when GC–MS analysis showed complete conversion of **1c**. After cooling, the reaction mixture was diluted with $CH_2Cl_2$ and then washed five times with NaOH (0.1 M, aq). The combined aqueous phases were additionally extracted twice with $CH_2Cl_2$. The organic phases were combined and dried with $K_2CO_3$(s). Concentration and purification of the crude product using radial thin-layer chromatography (hexane/diethyl ether/triethylamine, 86:10:4) furnished pure products **5**. All the isolated products were >95% pure according GC–MS.

**4.6.3. [2-(*R*)-2-(1-Methyl-pyrrolidine-2-(*S*)-ylmethoxy)-cyclohex-2-enyl]-naphthalene 5a.** (Conditions A: 38% yield and 98% de, conditions B: 35% yield and 95% de).

$^1$H NMR (400 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 1.34–1.69 (m, 4H), 1.70–1.85 (m, 3H), 2.03–2.12 (m, 1H), 2.15–2.30 (m, 3H), 2.32 (s, 3H), 2.38–2.52 (m, 1H), 2.80–3.04 (m, 1H), 3.51–3.56 (m, 1H), 3.62–3.67 (m, 1H), 3.79–3.85 (m, 1H), 4.96 (t, $J = 4.0$ Hz, 1H), 7.33–7.36 (m, 1H), 7.39–7.46 (m, 2H), 7.75–7.81 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 19.6, 23.0, 24.1, 29.2, 32.9, 40.7, 44.5, 57.6, 64.4, 70.0, 97.1, 125.1, 125.7, 126.5, 126.9, 127.47, 127.55, 127.59, 132.1, 133.4, 142.0, 154.7; GC–MS (70 eV) *m*/*z* (relative intensity) 321 ($M^+$, 12), 141 (13), 115 (5), 98 (14), 84 (100); High resolution MS calculated for $C_{22}H_{27}NO$: $[M+H]^+$ 322.2171, found 322.2166. $[\alpha]_D^{23} = -31$ (*c* 1, $CHCl_3$).

**4.6.4. [(*R*)-2-(1-Methyl-pyrrolidine-2-(*S*)-ylmethoxy)-cyclohex-2-enyl]-benzene 5b.** (Conditions A: 38% yield and 98% de, conditions B: 36% yield and 98% de).

$^1$H NMR (400 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 1.35–1.39 (m, 3H), 1.60–1.84 (m, 4H), 1.96–2.07 (m, 1H), 2.10–2.30 (m, 3H), 2.33 (s, 3H), 2.42–2.53 (m, 1H), 2.85–3.11 (m, 1H), 3.44–3.53 (m, 1H), 3.53–3.70 (m, 1H), 3.75–3.83 (m, 1H), 4.90 (t, $J = 4.2$ Hz, 1H), 7.17–7.20 (m, 2H), 7.24–7.34 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 19.4, 22.9, 23.8, 29.0, 32.7, 41.5, 44.1, 57.4, 64.1, 69.8, 96.8, 125.8, 127.9, 128.1, 144.5, 154.8; GC–MS (70 eV) *m*/*z* (relative intensity) 271 ($M^+$, 8), 115 (9), 98 (12), 84 (100); High resolution MS calculated for $C_{18}H_{25}NO$: $[M+H]^+$ 272.2014, found 272.2008. $[\alpha]_D^{23} = -52$ (*c* 1, $CHCl_3$).

**4.6.5. {2-[1-(*R*)-2-(1-Methyl-pyrrolidine-2-(*S*)-ylmethoxy)-cyclohex-2-enyl]-methyl}-benzene 5c.** (Conditions A: 34% yield and 94% de, conditions B: 46% yield and 98% de).

$^1$H NMR (400 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 1.32–1.40 (m, 1H), 1.43–1.58 (m, 2H), 1.60–1.80 (m, 4H), 1.93–2.01 (m, 1H), 2.07–2.26 (m, 3H), 2.31 (s, 3H), 2.34 (s, 3H), 2.36–2.45 (m, 1H), 2.90–3.01 (m, 1H), 3.41–3.47 (m, 1H), 3.66–3.70 (m, 1H), 3.72–3.77 (m, 1H), 4.92 (t, $J = 4.1$ Hz, 1H), 7.05-7.15 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 19.2, 19.4, 22.9, 23.9, 29.0, 30.5, 40.4, 41.4, 57.5, 64.0, 70.0, 96.9, 125.3, 125.7, 127.9, 130.1, 135.7, 142.2, 155.1; GC–MS (70 eV) *m*/*z* (relative intensity) 285 ($M^+$, 7), 115 (9), 98 (20), 84 (100). High resolution MS calculated for $C_{19}H_{27}NO$: $[M+H]^+$ 286.2171, found 286.2177. $[\alpha]_D^{23} = -54$ (*c* 1, $CHCl_3$).

**4.6.6. {4-[1-(*R*)-2-(1-Methyl-pyrrolidine-2-(*S*)-ylmethoxy)-cyclohex-2-enyl]-methyl}-benzene 5d.** (Conditions A: 37% yield and 96% de, conditions B: 40% yield and 94% de).

$^1$H NMR (400 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 1.39–1.59 (m, 3H), 1.66–1.90 (m, 4H), 1.95–2.04 (m, 1H), 2.09–2.25 (m, 3H), 2.30 (s, 3H), 2.34 (s, 3H), 2.37–2.44 (m, 1H), 2.92–2.97 (m, 1H), 3.41–3.45 (m, 1H), 3.58–3.69 (m, 1H), 3.70–3.76 (m, 1H), 4.92 (t, $J = 3.9$ Hz, 1H), 7.04–7.15 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 19.1, 21.0, 22.9, 23.9, 29.2, 32.8, 41.7, 43.5, 57.6, 64.0, 70.3, 95.7, 127.9, 128.6, 135.1, 141.5, 155.0; GC–MS (70 eV) *m/z* (relative intensity) 285 ($M^+$, 8), 115 (5), 98 (12), 84 (100). High resolution MS calculated for $C_{19}H_{27}NO$: $[M+H]^+$ 286.2171, found 286.2176. $[\alpha]_D^{23} = -40$ (*c* 1, $CHCl_3$).

**4.6.7. {3-[1-(*R*)-2-(1-methyl-pyrrolidine-2-(*S*)-ylmethoxy)-cyclohex-2-enyl]-methyl}-benzene 5e.** (Conditions A: 42% yield and 97% de, conditions B: 55% yield and 98% de).

$^1$H NMR (400 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 1.37–1.45 (m, 1H), 1.46–1.59 (m, 2H), 1.61–1.84 (m, 4H), 1.95–2.05 (m, 1H), 2.11–2.29 (m, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 2.41–2.51 (m, 1H), 2.91–3.03 (m, 1H) 3.41–3.52 (m, 2H), 3.75–3.81 (m, 1H), 4.89 (t, $J = 4.0$ Hz, 1H), 6.96–7.00 (m, 3H), 7.13–7.17 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 19.4, 21.5, 22.9, 23.9, 29.0, 32.8, 41.5, 44.0, 57.5, 64.1, 69.8, 96.8, 125.2, 126.5, 127.8, 129.0, 137.3, 144.4, 154.9; GC–MS (70 eV) *m/z* (relative intensity) 285 ($M^+$, 9), 115 (7), 98 (17), 84 (100); High resolution MS calculated for $C_{19}H_{27}NO$: $[M+H]^+$ 286.2171, found 286.2172. $[\alpha]_D^{23} = -50$ (*c* 1, $CHCl_3$).

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