Development of Stereocontrolled Palladium(II)-Catalyzed Domino Heck/Suzuki β,α-Diarylation Reactions with Chelating Vinyl Ethers and Arylboronic Acids

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A stereoselective and 1,4-benzoquinone-mediated palladium(II)-catalyzed Heck/Suzuki domino reaction involving metal coordinating cyclic methylamino vinyl ethers and a number of electronically diverse arylboronic acids has been developed and studied. Diastereomeric ratios up to 39:1 and 78% isolated yields were obtained. The stereoselectivity of the reaction was found to be highly dependent on the nature of the arylboronic acid and the amount of water present in the reaction mixture. Thus, a domino β,α-diylation–reduction of chelating vinyl ethers can now be accomplished and stereochemically controlled, given that optimized conditions and an appropriate chiral auxiliary are used. To the best of our knowledge, this represents the first example of a stereoselective, oxidative Heck/Suzuki domino reaction in the literature.

Introduction

C–C bond formations are paramount in organic synthesis and have captured the focus of chemists since the very beginning of modern organic chemistry.[1] Palladium(0)- and palladium(II)-catalyzed coupling reactions have emerged as efficient and selective methods for the arylation and vinylation of a range of organopalladium precursors.[2] Among the palladium(0)-catalyzed couplings, the Heck–Mizoroki and Suzuki–Miyaura reactions are two of the most prominent examples.[3] This was recently recognized by the Royal Swedish Academy of Sciences who awarded Richard F. Heck, Ei-ichi Negishi and Akira Suzuki the 2010 Nobel prize in Chemistry.[4]

Recent advances[5] in palladium(II)-catalyzed oxidative Heck reactions[6] have allowed the use of an organometallic reactant as an alternative to aryl halides or pseudo halides. Regeneration of the catalytically active palladium(II) species is facilitated by employing a terminal reoxidant, usually metal salts, dioxygen or 1,4-benzoquinone (p-BQ). Two of the most common organometallic substrates used in the oxidative Heck reaction are aryl- or vinylboronic acids. Assuming that β-hydride elimination can be suppressed after the carbopalladation step, a subsequent transmetalation–reductive elimination sequence can occur, which would lead to an additional Suzuki-type arylation. The ability of palladium(II) to facilitate the addition of nucleophiles to alkenes is well described, and a variety of olefin difunctionalization reactions have been developed.[7] However, domino difunctionalization reactions via a migratory insertion–transmetalation pathway are still relatively unexplored.[8] The main challenge of the above-mentioned process is to identify structural features or conditions, where the carbopalladation occurs with high regioselectivity[9] and in which β-hydride elimination can be suppressed, allowing the palladium(II) α-species to transmetalate with, for example, an arylboronic acid or other substrates, and thereafter undergo reductive elimination.[10]

Previously, our research group reported a novel palladium(II)-catalyzed domino Heck/Suzuki β,α-diarylation of an achiral dimethylaminoethyl-substituted vinyl ether using an excess of arylboronic acid in combination with p-BQ.[10c] For the domino Heck/Suzuki reaction, we proposed a mechanism involving a chelation-controlled carbopalladation step,[11] which was supported by recent density functional theory (DFT) calculations, highlighting the crucial role of p-BQ in the catalytic process.[12] Since the diarylation reaction requires an olefin equipped with a metal coordinating group, control of the stereochemical outcome of the reaction should be possible by choosing an appropriate chiral catalyst-directing moiety, allowing the generation of diastereomically enriched α-intermediates II (Scheme 1). Given that we have previously performed stereoselective palladium(0)-catalyzed Heck–Mizoroki reactions using a (S)-N-methyl-pyrrolidine-based chiral directing group,[13] we were interested in exploring a similar approach in the Heck/Suzuki domino diarylation using chelating olefins 1–3 and arylboronic acids 4 (Scheme 1). Interestingly, the hydrochloride salts of this class of diarylated, amino-substituted ether products (5–7) have previously been reported to possess antihistamine activity, but the reported synthetic route requires long reaction times and stoichiometric amounts of sodium metal.[14]

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Results and Discussion

Based on our previous experience, the stereoselective domino reaction was first attempted with functionalized vinyl ether 1 (Scheme 2). In an initial test, one equivalent of olefin 1 was added to a vial containing three equivalents of boronic acid 4a, a slight excess of p-BQ (1.1 equiv) and catalytic amounts of Pd(O$_2$CCF$_3$)$_2$ (0.05 equiv) in 1,4-dioxane (1.5 mL) at 40 $^\circ$C (entry 1, Table 1). Analysis of the crude material by GC–MS and $^1$H NMR showed that the $\beta_{\alpha}$-diarylated product 5a was successfully formed in the reaction with a diastereomeric ratio (d.r.) of 3.7:1 and a 5:1 ratio of compound 5 to 8. In an attempt to improve the selectivity of the reaction, different solvents were screened. Disappointingly, polar solvents such as acetonitrile, N,N-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) increased the amount of monoarylated Heck product 8a (entries 2–4, Table 1). Toluene was also tested as the reaction medium, but the rate decreased dramatically and a significant amount of starting material 1 remained unreacted, even after 36 h at 40 $^\circ$C. Increasing the equivalents of arylboronic acid seemed to decrease the required reaction time (c.f. entries 1, 13, 14, and 25–30, Table 1). When Pd(OAc)$_2$ was used, the d.r. increased slightly. However, this was accompanied by a lower ratio of compound 5 to 8 and lower yields.

Entries 7–30 in Table 1 represent a determinant (D)-optimal design set $^{[15]}$ in which 4-methoxyphenylboronic acid (4a) and 4-acetylphenylboronic acid (4b) were used in order to assess differences in the reaction outcome due to electronic effects. Additionally, the following factors were evaluated in the screening process: solvent volume, arylboronic acid equivalents, palladium equivalents and temperature. Unfortunately, no statistically significant model was obtained for the ratio of compound 5 to 8, however, two significant models were obtained for the stereoselectivity shown by both 4a ($R^2 = 0.81$, $Q^2 = 0.46$) and 4b ($R^2 = 0.84$ and $Q^2 = 0.62$), as well as for the yield of 5b ($R^2 = 0.78$ and $Q^2 = 0.51$). According to these findings, lower amounts of Pd(O$_2$CCF$_3$)$_2$ and increased amounts of arylboronic acid 4 would benefit the stereochemical outcome of the reaction with respect to 5. Lower temperatures showed a tendency to increase stereoselectivity, but the results were not statistically significant. The amount of solvent studied in these experiments proved to be insignificant for both the stereoselectivity and yield of 5. Interestingly, the same factors controlling the stereoselectivity also appeared to influence the yield of 5b.$^{[16]}$

The results shown in Table 1 also indicate that the stereoselectivity is strongly governed by electronic effects (e.g., entries 17 and 18). Thus, phenylboronic acid 4c was tested using conditions that, according to the screening design, should furnish high yields and good stereoselectivity, meaning low catalyst loading and an excess of phenylboronic acid (entry 1, Table 2). Surprisingly, the stereoselectivity of this reaction was poor, and the yield was moderate. Hence, we opted to test other conditions in which only the temperature was increased (entry 2, Table 2) or the temperature was increased and the amount of catalyst was decreased (entry 3, Table 2) and finally one example in which the temperature and the amount of arylboronic acid were increased (entry 4, Table 2). Unfortunately, none of these experiments yielded satisfactory stereoselectivities and yields.

To ensure that the results obtained with 4c were not anomalous, the conditions depicted by entry 2 of Table 2 were tested with an array of different arylboronic acids. Nearly half of the tested arylboronic acids (Table S3, Supporting Information)$^{[17]}$ produced only trace amounts of product 5, and the remaining arylation substrates yielded diarylated products with low stereoselectivities. These results suggest that factors other
than catalyst loading and the amount of boronic acid have a profound effect on the stereochemical outcome of the reaction.

Water concentration studies

As shown in Table 1, diastereomeric ratios up to 39:1 could be achieved using 4a in low to moderate yields (entries 9, 11 and 17, Table 1). However, these results could not be reproduced using other arylboronic acids. The lack of reproducibility in reactions involving boronic acids has been linked to variations in water content,\(^{[18]}\) which is partially dependent on the solvent employed.\(^{[19]}\) As shown in Table 2, the reaction outcomes are significantly affected by water concentration in the solvent. Therefore, this solvent selection is essential to achieve reproducible results.

Table 2. Heck/Suzuki domino diarylation of 4c with 1 employing conditions based on the results obtained from Table 1.\(^{[14]}\)

| Entry | Temp [°C] | Pd(O₂CCF₃)₂ [equiv] | 4c | Time [h] | Ratio | d.r. | Yield [%] | Product |
|-------|-----------|-----------------------|----|----------|--------|------|----------|---------|
| 1     | 25        | 0.20                  | 4  | 36       | >100:1 | 1.4:1 | 52       | 5c      |
| 2     | 40        | 0.02                  | 4  | 24       | >100:1 | 1.9:1 | 42       | 5c      |
| 3     | 40        | 0.01                  | 4  | 72       | >100:1 | 1.6:1 | 24       | 5c      |
| 4     | 50        | 0.02                  | 2  | 6        | >100:1 | 1.4:1 | 43       | 5c      |

[\(a\)] Reagents and conditions: a) Olefin 1 (0.21 mmol, 1 equiv), 4c, 0.2 equivalents, Pd(O₂CCF₃)₂, solvent, Δ. [\(b\)] Entries 25–30 are triplicates in the D-optimal reaction design. [\(c\)] Determined by GC–MS analysis of the crude product. [\(d\)] Determined by 1H NMR analysis of the crude product. [\(e\)] Monoarylated product was not detected. [\(f\)] Pd(OAc)₂ was used. [\(g\)] No data. [\(h\)] Overnight (o.n.) reaction time (12–16 h).
under inert conditions using 1, water-free 1,4-dioxane, recrystallized p-BQ (from absolute ethanol) and phenylboronic acid 4c (recrystallized from acetone or diethyl ether). The water content was then varied from 0.5 to 200 equivalents, keeping the total reaction volume constant at 1.5 mL. As depicted in Figure 1, an increased amount of water improved the diastereoselectivity up to a d.r. of 6.7:1 but reduced the product yield down to below 30%. However, accompanied with improved diastereoselectivity, an increased water content also resulted in a decreased conversion of 1 and an increased formation of β-monophenylated Heck product 8c, which might account for the reduced yield of 5c.

As we were unable to identify reaction conditions that simultaneously afforded high yields and stereoselectivities, we decided to examine the effect of a different catalyst-presenting group on the stereoselectivity. Enantiomer-enriched vinyl ether 2 (enantiomeric ratio (e.r.) ≥ 49:1) was synthesized via a stereoselective ring enlargement of (S)-(1-methylpyrrolidin-2-yl)methanol\(^{\text{30}}\) followed by palladium(II)-catalyzed vinylation of (R)-1-methylpiperidin-3-ol (Scheme 3 A). Compound 2 was then submitted to a series of test reactions using aryloboronic acids 4a–k (Scheme 3 B). The results from these experiments showed that diastereomerically enriched products could be obtained, but, as was the case when 1 was used, the results varied significantly. Thus, the impact of the water concentration in the reaction between 2 and 4c was also explored. This system appeared to be even more sensitive to the amount of water, although the yields and stereoselectivities were comparable to the results obtained for compound 1 when approximately ten equivalents of water were used (Figure 2, d.r.: 5:1, 63% yield). With greater amounts of water (50 and 100 equiv), the reaction yield dropped dramatically preventing the determination of d.r.

Further attempts to find a more productive chiral auxiliary were undertaken, and racemic trans-N,N-dimethyl-2-(vinloxy)cyclohexanamine (rac-3) was synthesized\(^ {\text{21}}\) and tested with phenylboronic acid 4c employing the same conditions as in Table 3. Disappointingly, rac-7 was obtained in only 40% yield and with a d.r. of only 2:1 (Scheme 4). Further attempts to react rac-3 with other aryloboronic acids were discontinued at this point.

**Scope and limitations**

As can be seen from Figures 1 and 2, the amount of water required to obtain reasonable stereoselectivity and still retain useful yields is in the range of 10–20 equivalents for both olefins 1 and 2. Accordingly, we decided to explore the scope and limitations of this reaction, using chelating olefins 1 and 2 and ten equivalents of water. The preparative results for the domino diarylation-reduction of 1 and 2 with different aryloboronic acids 4 are presented in Table 3. Somewhat higher diastereoselectivity could be obtained using vinyl ether 2, but the yields were generally lower and longer reaction times were required. Further, in a number of cases, 2 failed to give any detectable amount of product (c.f., entries 3, 4 and 17, 18, respectively, Table 3). The reaction between 1 and boronic acid 4a or 4b produced 5a or 5b, respectively, in moderate yields and stereoselectivities, whereas the corresponding reactions with 2 afforded 6a and 6b in very low yields and stereoselectivities (entries 1, 19, 2 and 20, respectively, Table 3). In addition, \(^1\)H NMR analysis of the crude showed a low diarylated (6b) to monoaarylated (9b) product ratio of 1:1.4. Interestingly, sterically demanding ortho-substituted 4d produced 5d in low yield and stereoselectivity after reaction with 1, but no product was detected when 2 was used as the starting material (entries 3 and 4, Table 3). In contrast, 4g did not give productive results when reacted with 1, however, product 6g was ob-
**Table 3. Domino oxidative Heck/Suzuki reaction using vinyl ethers 1 and 2**

| Entry | Olefin | 4a-k | 5 or 6 | 8 or 9 | Yield [%] | Product |
|-------|--------|------|--------|--------|-----------|---------|
| 1     | 1      | 2    | 4a     | 24     | –22.6     | 52      | 5a      |
| 2     | 2      | 2    | 4d     | –      | –         | –       | 6d      |
| 3     | 1      | 2    | 4e     | 24     | –29.1     | 56      | 5e      |
| 4     | 1      | 2    | 4f     | 36     | –2.5      | 52      | 6f      |
| 5     | 1      | 2    | 4g     | 24     | –         | –       | 59      |
| 6     | 2      | 2    | 4h     | 36     | 8.7       | 49      | 6g      |
| 7     | 1      | 2    | 4i     | 24     | 8.4       | 47      | 5h      |
| 8     | 1      | 2    | 4j     | 36     | 15.6      | 30      | 6h      |
| 9     | 1      | 2    | 4k     | 24     | –11       | 62      | 5b      |
| 10    | 2      | 2    | 4l     | 24     | –         | –       | 10<sup>l</sup> |

- **[a]** Reagents and conditions: a) vinyl ether 1 or 2 (30 mg, 0.21 mmol), 4 (4 equiv), p-BQ (1.5 equiv), Pd(OOCF<sub>3</sub>)<sub>2</sub> (0.04 equiv), H<sub>2</sub>O (10 equiv), 1,4-dioxane (1.5 mL), 40 °C. [b] Optical rotation ([α]<sup>22</sup>D) was performed in chloroform for the diastereochemically enriched product. [c] Calculated by GC–MS and/or H NMR of the crude product. [d] Isolated yields unless stated otherwise. Product purity > 95% according to GC–MS and H NMR. [e] Product formation detected with GC–MS. [f] Calculated from NMR analysis with DMSO as an internal standard; not isolated.

- **Figure 2.** Influence of water content on the diastereoselectivity (d.r.) and yield (determined by NMR) of the chiral diphenylation of olefin 2 (see the Experimental Section for full details).
regardless of the choice of chelating olefin. This phenomenon might be a result of the polarity of the reaction media. Therefore, other solvents systems (acetonitrile/water; 1,4-dioxane/ionic liquids) were evaluated, but the 1,4-dioxane/water system consistently yielded the best results. Comparable diasteroselectivities were only obtained using acetonitrile/water mixtures, although the yields were substantially lower when this solvent combination was used, mainly due to an increased formation of the monoarylated oxidative Heck product.

**X-ray diffraction analysis**

To determine the absolute configuration of the Heck/Suzuki domino product, the reaction of 1 and 4a yielding 5a in high selectivity (d.r. > 19) was chosen for crystallization studies. After isolation of 5a, methyl iodide (0.5 mL) was used to methylate the amino group, providing the positively charged quaternary salt 11. The salt was recrystallized by the vapor diffusion crystallization method using diethyl ether/isobutanol:ethyl acetate (10:1). Analysis by X-ray crystallography showed that the auxiliary-directed attachment of the internal anisyl group provided the (S)-configuration of the tertiary benzylic carbon in 11 (Figure 3). Starting from chiral vinyl ether 1, this stereochemical outcome suggests a Re-face carbopalladation of complex I and subsequent formation of intermediate palladacycles II and III with high d.r. prior to reductive elimination to yield the dominant product (S) (Scheme 1).

**Conclusions**

An investigation of the scope and limitations of a novel palladium(II)-catalyzed Heck/Suzuki β,α-diarylation of chiral catalyst-presenting vinyl ethers 1–3 has been described, providing 1,2-diaryl ethers 5–7 in diastereomeric ratios of up to 39:1 and 78% isolated yield. Promising results show for the first time that a domino β,α-diarylation-reduction of chelating vinyl ethers can be stereochemically controlled, given the right conditions and an appropriate chiral auxiliary. In addition, the pivotal role of water in effecting the stereoselectivities has been investigated. We are currently exploring the use of computational calculations to design more efficient chiral auxiliaries.

**Experimental Section**

**General:** Column chromatography was performed on silica gel 60 (40–63 μm, Merck). Analytical thin layer chromatography (TLC) was performed using aluminum sheets precoated with silica gel 60 F254. Chromatographic spots were visualized using UV detection and/or ethanolic ninhydrin solution (2%), or ethanolic phosphomolybdic acid (5%) followed by heating. Dry column vacuum chromatography (DCVC) was performed using silica gel 60 (40–63 μm, Merck). Preparative thin layer chromatography (PTLC) was performed using silica gel 60 F254 (2 mm, Merck). Analytical GC–MS was performed on a Varian Saturn 3900/2100 system (Palo Alto, CA, USA) using a CP-Sil 5 or CP-Sil 8 CB low bleed capillary column (30 m × 0.25 mm) and electron impact (EI) ionization (70–300 °C, 20°C min⁻¹ or at 180–185°C, 0.1°C min⁻¹). Analytical reverse-phase (RP)-HPLC–MS was performed on a Gilson HPLC system (Middleton, WI, USA) with a Finnigan AQA electrospray ionization (ESI) quadrupole mass spectrometer and using an Onyx Monolithic C18 4.6 × 50 mm column (Phenomenex, Torrance, CA, USA) with CH₃CN/H₂O in 0.05% aq HCOOH as mobile phase at a flow rate of 4 mL min⁻¹. Optical rotation was measured using a Perkin-Elmer 241 polarimeter (NaD, 589 nm, Waltham, MA, USA). ¹H and ¹³C NMR spectra were recorded on a Varian Mercury Plus instruments (Palo Alto, CA, USA). Exact molecular masses were determined on a Micromass Q-Tof2 mass spectrometer equipped with an electrospray ion source. Collection of X-ray data for compound (S,5)-11 was performed at the Latvian Institute of Organic Synthesis (Riga, Latvia). CCDC-851225 contain(s) the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Screening design was planned with assistance of MODDE, version 9.0.0.0 (September 30, 2009), licensed by Umetrics AB.

**General procedure for the synthesis of diarylated products 5, 6 and rac-7:** Compound 4 (4 equiv), 1,4-benzoquinone (1.5 equiv),
the appropriate vinyl ether (0.21 mmol 1 or 2, or 0.18 mmol rac-3) and anhyd 1,4-dioxane (1.5 mL) were mixed in an 8 mL reaction vial. The mixture was recognized by vigorous stirring, after which Pd(OAc)$_2$ (0.04 eq) and H$_2$O (10 eqv) were added. The vial was capped and heated in a metal heating block at 40 °C for 24 or 36 h. The crude material was filtered through a short Al$_2$O$_3$ column (2 cm φ, 3 cm height) and eluted with 200 mL EtOAc/Et$_3$N (10:1) or until no more product was detected (typically, 100 mL eluent was sufficient). The solvent was evaporated in vacuo, and the crude was analyzed by GC–MS and/or NMR spectroscopy to elucidate the diastereoselectivity. The product was there-fore purified by gradient elution using DCVC$^{21}$ and isohexane/EtO/Et$_3$N as the eluent system (a maximum of 4 % Et$_3$N was used).

(5S)-1-methyl-2-(vinyl(oxymethyl))pyrroolidine (1): 1-Methylpiperidine-3-ol (5.00 g, 43.4 mmol) dissolved in ethyl vinyl ether (65 mL), 2,2'-bipyridine (406 mg, 2.6 mmol) and Pd(OAc)$_2$ (433 mg, 2.0 mmol) were added to a 250 mL three-necked flask and refluxed at 75 °C. Due to the volatile nature of the starting material, additional ethyl vinyl ether was added several times during the reaction to avoid complete evaporation as the reaction was kept open to drive the equilibrium towards product formation by evaporation of EtOH, which is formed as a by-product. Please note that when monitoring was not possible, the collection funnel was closed so that no starting material could evaporate. The mixture was moni-tored by GC–MS. When complete consumption of the starting ma-terial was detected (usually after reaction for 4–5 d), the tempera-ture was decreased to RT, the ethyl vinyl ether was evaporated, and the crude was diluted with EtOAc (100 mL) and washed with 2 mL aq NaOH (2 × 100 mL). The addition of brine was sometimes needed to assist phase separation. The organic phase was dried (K$_2$CO$_3$), filtered and concentrated in vacuo, and the crude was pu-rified by bulb-to-bulb distillation (65 °C, 50 mbar) or silica gel chro-matography (isohexane/EtO/Et$_3$N, 90:6:4) to give compound 1 as a colorless oil (2.80 g, 19.8 mmol, 46 %, $\text{Y}=0.2$). (isohexane/EtO/Et$_3$N, 90:6:4); $\text{HRMS (ESI)}$: m/z: 142 (100) [C$_8$H$_{15}$NO]$^+$ calculated for C$_8$H$_{15}$NO: 142.1237, found: 142.1232.

trans-N,N-Dimethyl-2-(vinylxoy)methyl)cyclohexanamine (rac-3): Vinyl-acetate (10 mL), trans-2(dimethylamino)cyclohexanol (600 mg, 4 mmol) and 6-methyl-2,2′-bipyrindine (57.4 mg, 0.34 mmol) were added to a 20 mL microwave vial, and the mixture was vigorously stirred. Pd(OAc)$_2$ (69.6 mg, 0.21 mmol) was added, and the microwave vial was irradiated for 30 min at 100 °C. The crude was concentrated and filtered through a column of aluminum oxide (2 cm φ, 4 cm height) with EtO/Et$_3$N (64:96, 200 mL). The acetylated by-product was separated from the vinylic product by DCVC using isohexane/EtO/Et$_3$N (100:0:0:80:24). After chromatog-raphy, the product was still contaminated with a small amount of 6-methyl-2,2′-bpyridine, and the product mixture was, therefore, pu-rified by bulb-to-bulb distillation (70 °C, 60 mbar) yielding pure product rac-3 as a colorless oil (206.0 mg, 1.2 mmol, 29 %); $\text{Rf}=0.2$ (isohexane/EtO/Et$_3$N, 80:16:4); $\text{H NMR (400 MHz, CDCl$_3$, 25 °C);} \delta=6.55$ (dd, $\text{J}_{\text{H},\text{H}}=2.0$ Hz, $\text{J}_{\text{H},\text{H}}=14.4$ Hz, 1 H, (E)-CH$_2$), 3.98 (dd, $\text{J}_{\text{H},\text{H}}=2.0$ Hz, $\text{J}_{\text{H},\text{H}}=6.8$ Hz, 1 H, (Z)-CH$_2$), 3.70 (dd, $\text{J}_{\text{H},\text{H}}=5.1$ Hz, $\text{J}_{\text{H},\text{H}}=9.8$ Hz, 1 H, OCH$_2$CH$_3$), 3.16 (dd, $\text{J}_{\text{H},\text{H}}=5.4$ Hz, $\text{J}_{\text{H},\text{H}}=9.8$ Hz, 1 H, OCH$_2$CH$_3$), 3.08 (m, 1 H, CH$_2$CH$_3$), 2.52–2.44 (m, 1 H, NCH$_3$), 2.40 (s, 3 H, NCH$_3$), 2.23 (m, 1 H, NCH$_3$), 1.99–1.89 (m, 1 H, CH$_2$CH$_3$), 1.83–1.61 ppm (m, 3 H, CH$_2$CH$_3$ and CH$_3$CH$_2$); $\text{HRMS (ESI)}$: m/z: 150 (100) [C$_8$H$_{14}$N$_2$O]$^+$ calculated for C$_8$H$_{14}$N$_2$O: 150.1601, found: 150.1597.

(2R,S)-1-methyl-3-(vinylxoy)piperidine (2): An oven-dried round bottom Schlenk flask containing ethyl vinyl ether (118 mL, 1.24 mol) was purged with O$_2$, and thereafter Pd(OAc)$_2$ (451.3 mg, 1.97 mmol) and 2,2′-bipyridine (310.0 mg, 1.97 mmol) were added under vigorous stirring. The mixture was stirred at 60 °C until all solids were dissolved and a clear bright yellow solu-tion was obtained. To prevent acetal formation,$^{20}$ Et$_3$N (0.69 mL, 4.97 mmol) was added before the addition of piperidine alcohol (2.90 g, 24.8 mmol) by cannula. The reaction was refluxed for 72 h or until GC–MS showed no further improvement. Excess ethyl vinyl ether was removed in vacuo, and the crude material (reddish oil was washed with 2 mL aq NaOH (3 × 150 mL) and EtOAc (150 mL). The organic phase was evaporated in vacuo, and bulb-to-bulb dis-tillation recovered unswashed/unreacted aminoalcohol (90 °C, 50 mbar) and gave purified compound 2 (65 °C, 58 mbar) as a color-less oil (1.31 g, 9.2 mmol, 37 % yield); $\text{Rf}=0.2$ (isohexane/EtOAc/ Et$_3$N, 90:6:4); $\text{HRMS (ESI)}$: m/z: 151.9 (98) [C$_8$H$_{14}$N]$^+$ calculated for C$_8$H$_{14}$N: 151.1232, found: 151.1227.

(5S)-1,2-Bis(4-methoxyphenylothio)methyl-1,1-dimethylpyrroloidin-1-ium iodide (11): Mel (0.5 mL) was added to a 4 mL
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Keywords: chirality • domino reactions • palladium • stereoselective catalysis • water effects

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