Article

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Intermolecular Non-Covalent Hydroxy-Directed Enantioselective Heck Desymmetrization of Cyclopentenol: Computationally-driven Synthesis of Highly Functionalized *cis*-4-Aryl-Cyclopentenol Scaffolds

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KEYWORDS: Heck reactions, enantioselective reactions, homogeneous catalysis, DFT studies, cyclopentene scaffolds.

Abstract: New computationally-driven protocols for the Heck desymmetrization of 3-cyclopenten-1-ol with aryldiazonium tetrafluoroborates were developed. These new conditions furnished remarkable product selectivity originating from a resident hydroxyl group and the critical choice of the reaction solvent. Mechanistic insights gleaned from theoretical calculations of the putative transition states predicted toluene as an adequate solvent choice to attain high enantioselectivity by strengthening the non-covalent interaction of the substrate hydroxyl group and the chiral cationic palladium catalyst. Laboratory experiments validated the theoretical predictions, and by employing 2% MeOH/toluene as solvent, the Heck-Matsuda reaction provided exclusively the *cis*-4-aryl-cyclopentenols **3a-l** in good to excellent yields in enantiomeric excesses up to 99%. The performance of the new PyOx ligand (*S*)-4-*tert*-butyl-2-(3,5-dichloropyridin-2-yl)-4,5-dihydrooxazole was also successfully evaluated in the Heck-Matsuda desymmetrization of 3-cyclopenten-1-ol. The synthetic potential of these highly functionalized cis-4-aryl-cyclopentenols is illustrated by a gold-catalyzed synthesis of cyclopenta[*b*]benzofuran skeletons.

INTRODUCTION

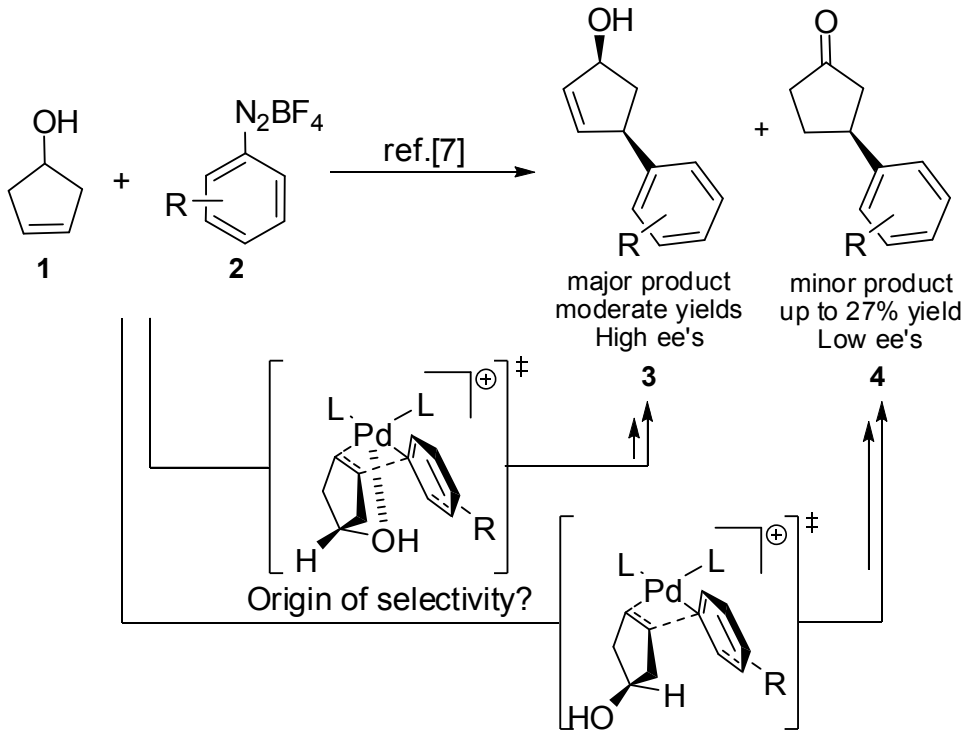
The Heck-reaction is a pivotal method for the formation of carbon-carbon bonds in organic synthesis.[1] An effective and very practical version of this reaction, the so-called Heck-Matsuda[2] reaction, relies on arenediazonium salts, mainly the tetrafluoroborates, as arylating reagents instead of the conventional aryl halides and triflates.2 Arenediazonium salts undergo rapid oxidative addition towards zerovalent palladium, thus providing a direct access to more reactive

cationic Heck intermediates. This usually fast, practical and effective arylating method has been attracting increased interest from the synthetic community in the last few years.[3] Furthermore, the Heck-Matsuda reaction has gained increased momentum recently with the discovery of its enantioselective version.[4]

In 2012, Correia and coworkers reported the first examples of the enantioselective Heck–Matsuda reaction, carrying out the desymmetrization of an unactivated olefin employing chiral bisoxazoline ligands.4 Shortly thereafter, Sigman and coworkers described the enantioselective Heck-Matsuda arylation of acyclic alkenyl alcohols using the redox-relay strategy.[5] Correia *et al.* also reported a similar strategy in 2013 in the enantioselective arylation of *cis* and *trans*-butenediols in route to the concise synthesis of γ–aryl-lactones in good chemical yields and enantiomeric excesses.[6]

More recently, we have also demonstrated the synthetic potential of the Heck-Matsuda desymmetrization strategy for the construction of arylated five-membered carbocyclic scaffolds starting from 3-cyclopenten-1-ol.[7] In spite of its synthetic potential, this particular desymmetrization method provided two quite distinct products as consequence of the reaction diastereoselectivity: the more highly functionalized *cis*-4-aryl-cyclopentenols **3**, as major products with the enantiomeric excesses (ee's) ranging from 85% to 99% (Scheme 1), and the minor 3-aryl-cyclopentanones **4**, in much lower ee's.

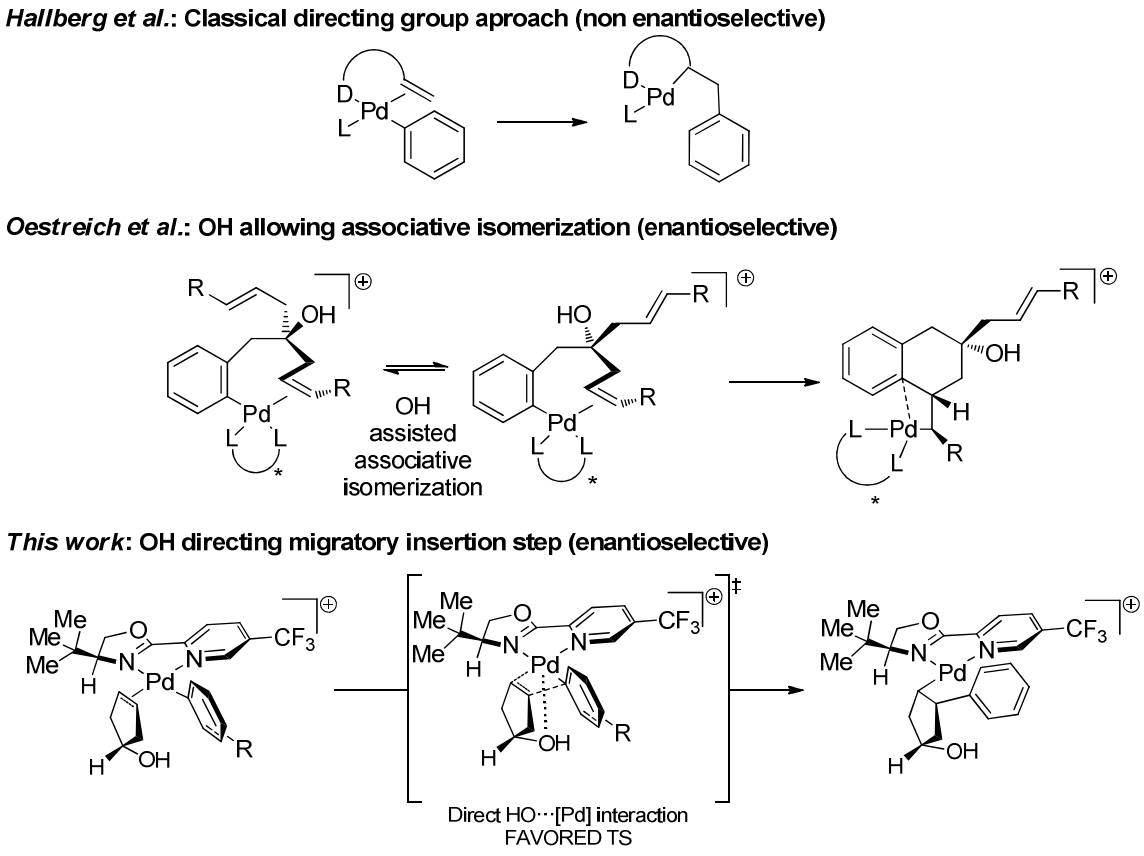
Scheme 1. Enantioselective Heck arylation of 3-cyclopenten-1-ol.



The origin of the product selectivity was attributed to a putative stabilizing interaction of the substrate hydroxyl group with the cationic palladium in an apparent substrate-directable Heck arylation. The concept of substrate directable chemical reactions to control regio and stereoselectivity was elegantly reviewed by Evans, Hoveyda and Fu in 1993.[8] Concerning Pd-catalyzed reactions, Hallberg and coworkers introduced the concept of "chelation control" by installing an appropriate donor group on the substrate to obtain high regioselectivity in intermolecular Heck reactions.[9] Alper and coworkers also suggested the critical role of a hydroxyl group in an enantioselective Pd-catalyzed cyclocarbonylation of allylic alcohols leading to γ-butyrolactones.[10] More recently, Morken and Blaisdell showed that a hydroxyl group can also act as a directing group in palladium-catalyzed cross-coupling reactions (Suzuki-Miyaura reaction).[11] In 2005, Oestreich and coworkers described an intriguing intramolecular

desymmetrizing Heck reaction of an open-chain bis-homoallylic alcohol moiety. According to the authors, the unprotected hydroxyl group would play a pivotal role in the enantio-determining step with the free hydroxyl group acting as a directing group.[12] However, in a subsequent paper, the same authors dismissed the hydroxyl group directing effect during the key migratory insertion step.[13] According to their new conclusions, the mechanism involved a rapid equilibration of diastereomeric alkene-palladium (II) complexes prior to the selectivity-determining event in a typical Curtin-Hammett scenario (Scheme 2). In the same vein, the authors emphasized that the stereochemical outcome was controlled by the chiral phosphine ligand while the hydroxyl group enabled an associative equilibration between intermediates.

Scheme 2. Directing groups in Heck reaction.



In spite of these scattered examples in the literature, to the best of our knowledge, strong evidence for an enantioselective heteroatom-directed Heck reaction is still elusive. Therefore, with the goal of evaluating the actual participation of the hydroxyl group in the Heck desymmetrization of 3-cyclopenten-1-ol, and possibly develop it into a more general synthetic method, we reinvestigated the arylation process by combining density functional theory (DFT) studies and laboratory experiments to validate, or not, our previous mechanistic rationale.7 Computational methods have been instrumental in understanding and predicting the mechanism of many stereo- and enantioselective catalytic systems.[14] DFT studies can be regarded as a first line of investigation to calculate the transition state energy required to form intermediates along the reaction coordinate under a variety of conditions, such as different solvents. Most ionic Heck reactions are carried out in polar solvents such as methanol, acetonitrile, dimethyl sulfoxide, dimethylacetamide, and *N*-methylpyrrolidone (NMP).1[b] Studies have shown that these solvents stabilize the catalytically active intermediates, thus leading to improved yields and selectivities.

Theoretical calculations for the enantioselective Heck-Matsuda reaction were previously performed by Wang *et al*. and Wiest *et al*. using the *N,N*-ligand PyOx.[15] However, our studies using this very same ligand focused on the role of the free hydroxyl group in the reaction's stereochemical outcome, and how it could be controlled to provide the desired *cis*-cyclopentenol Heck adduct **3** as its exclusive product.

In this report, we disclosed our findings concerning the new optimized conditions for the Heck-Matsuda desymmetrization of 3-cyclopenten-1-ol **1** with several aryldiazonium salts to provide exclusively the desired *cis*-4-aryl-cyclopentenol Heck products. These results were supported by DFT studies based on transition state energy using toluene or MeOH as solvent, favoring the exclusive formation of Heck product **3** in excellent yields and enantiomeric

excesses. The hydroxyl group in the substrate plays a crucial role through a non-covalent interaction with the cationic palladium in the diastereo- and enantio-determining step, thus controlling the product selectivity of the enantioselective Heck-Matsuda reaction.

RESULTS AND DISCUSSION

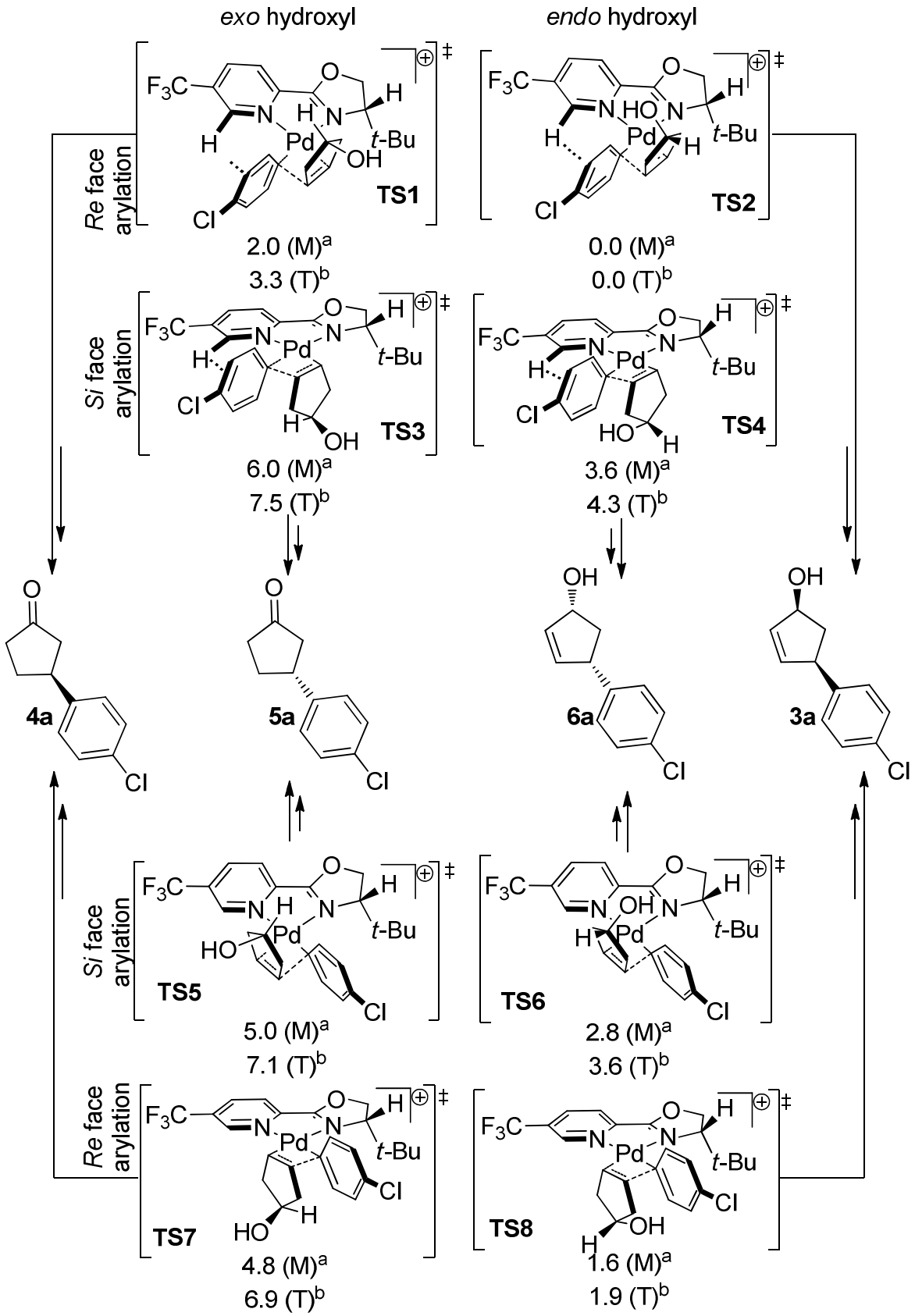
Computational Studies. One of our first objectives was to look for evidences regarding our initial hypothesis that a key interaction between the hydroxyl group in the achiral 3-cyclopenten-1-ol and the metal center was indeed providing additional stabilization in the migratory insertion transition state (TS), thus directing the stereochemical outcome of the Heck-Matsuda reaction (Scheme 1).

Our studies started with a complete search for all eight migratory insertion stereoisomeric transition states leading to both Heck products. These eight transition structures arise from three main factors: i) the relative position of the aryl group and olefin in the starting complex, ii) the endo/exo orientation of the substrate's hydroxyl group towards the metal center and, iii) the migratory insertion step in the *Re/Si* face of the olefin. It was assumed that this last stage refers to the enantio-determining step, since the aryl-palladium complexes are supposed to be in rapid equilibrium.[15] Consequently, the reaction enantioselectivity should depend solely on the energy difference between the transition states under typical Curtin-Hammett conditions.[16]

Additionally, we performed an investigation on the influence of the solvents (methanol and toluene) in the stereoselectivity of the reaction. The solvent effects were introduced by the SMD continuum solvation model.[17] Scheme 2 presents the calculated relative free energies for the transition states of the migratory insertion step in methanol (M) and toluene (T) solutions ($\Delta G^{\ddagger}_{sol}$), using 4-chlorophenyl diazonium tetrafluoroborate as a model arylating agent in view of

its clean Heck reactions in the laboratory, straightforward determination of the product ee's, and absolute stereochemistry confirmed by X-ray.7

Scheme 3. Computed energies (in kcal•mol^{-1}) for the migratory β-insertion transition states.


exo hydroxyl
endo hydroxyl
Re face arylation
Si face arylation
Si face arylation
Re face arylation
TS1
TS2
TS3
TS4
TS5
TS6
TS7
TS8
2.0 (M)a
3.3 (T)b
0.0 (M)a
0.0 (T)b
6.0 (M)a
7.5 (T)b
3.6 (M)a
4.3 (T)b
5.0 (M)a
7.1 (T)b
2.8 (M)a
3.6 (T)b
4.8 (M)a
6.9 (T)b
1.6 (M)a
1.9 (T)b
4a
5a
6a
3a

Reported energies are relative to the **TS2**, which was identified as the lowest energy structure. [a]Calculated $\Delta G^{\ddagger}$ values for transition state in methanol solvent (kcal•mol^{-1}). [b]Calculated $\Delta G^{\ddagger}$ values for transition state in toluene solvent (kcal•mol^{-1}).

According to our calculations, the transition state **TS2**, which has the hydroxyl in an *endo* orientation towards palladium, is the lowest energy transition state in both solvents. This result is in perfect agreement with our previous experimental results using methanol as solvent.[7] The next lowest energy transition state, **TS8**, also has the hydroxyl group in an *endo* orientation, but with the pyridine group of the PyOx ligand in position *trans* to the aryl moiety. The calculated energy for **TS8** is 1.6 and 1.9 kcal•mol^{-1} higher than the ones obtained for **TS2** in methanol and toluene, respectively. Most probably, such a difference is due to the steric hindrance of the *tert*-butyl moiety of PyOx ligand and the aryl-Cl group in **TS8** (see Support Information for more details about the optimized geometry of all transition states). Furthermore, **TS2** contains a stabilizing C-H π interaction which is absent in **TS8**.[15] Both transition states, **TS2** and **TS8**, are associated with adduct **3a** in methanol and toluene**.**

Product **4a** is expected to arise from a series of *syn*-*β*-hydrogen eliminations and *syn*-*β*-hydrogen reinsertions prior to H-PdL diffusion. These iterative relay step reactions were thoroughly investigated by Wang *et al*. and Wiest *et al*. using DFT methods.[15] Based on these studies, it is our reasonable assumption that the relay process is only possible when the hydroxyl group assumes an *exo* orientation in the migratory insertion step (see Scheme 1). Thus, the migratory insertion steps of **TS1** and **TS7** are the feasible pathways to the formation of **4a**. **TS1** has energy lower than that for **TS7** in both solvents (2.8 and 3.6 kcal•mol^{-1} in methanol and toluene, respectively). Based on these energy differences, it is reasonable to assume that product **4a** originates from **TS1**. We attributed the higher energy of **TS7** compared to **TS1** to the steric hindrance experienced between the *t*-Bu group of the ligand and the aryl moiety of the substrate.

High activation free energies were observed in methanol and toluene to produce adduct **5a (***ent*-**4a)** by the competitive paths involving **TS3** ($\Delta G^{\ddagger}_{sol}$ = 6.0 and 7.5 kcal•mol^{-1}) and **TS5** ($\Delta G^{\ddagger}_{sol}$ = 5.0 and 7.1 kcal•mol^{-1}). Adduct **6a** (*ent*-**3a**) can be obtained through **TS4** ($\Delta G^{\ddagger}_{sol}$ = 3.6 and 4.3 kcal•mol^{-1}) or **TS6** ($\Delta G^{\ddagger}_{sol}$ = 2.8 and 3.6 kcal•mol^{-1}) in minor amounts (see details in Scheme 3). Aryl cyclopentenol **6a** and the cyclopentenone **5a** were indeed minor stereoisomers in our experiments with methanol. These computational studies nicely support our previously reported experimental results.[7]

The influence of the solvent on the selectivity of these reactions was also addressed by computational studies. As depicted in Scheme 3, the difference between the barriers increased when methanol was replaced by toluene. It was especially important to understand the solvent effect on the barrier heights regarding the formation of compounds **3a** (**TS2**) and **4a** (**TS1**). As mentioned above, the transition state **TS1** in methanol is 2.0 kcal•mol^{-1} higher in energy than **TS2**. In toluene, this energetic difference increased to 3.3 kcal•mol$^{-1,}$ thus suggesting an increase in the selectivity for the formation of Heck product **3a** depending on the solvent.

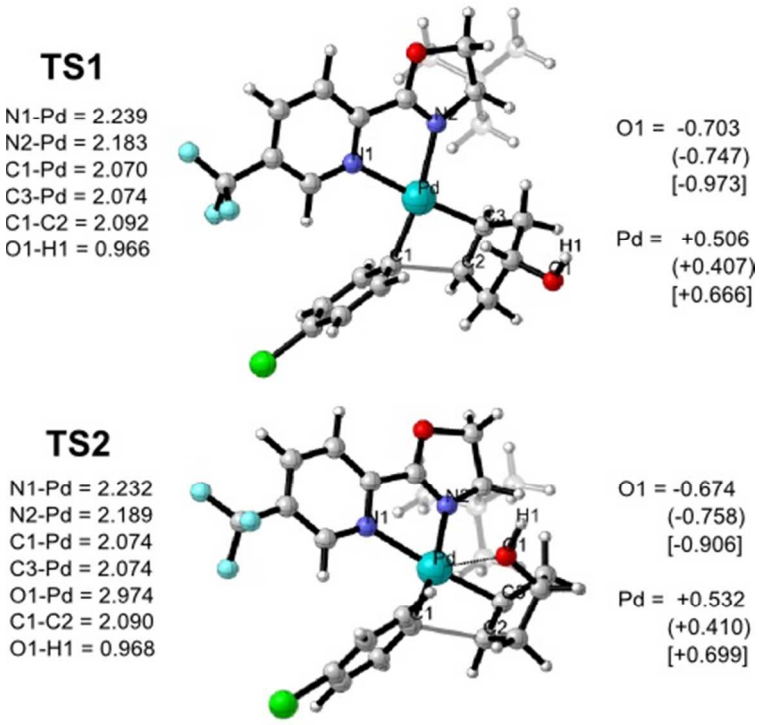


Figure 1. Calculated transition states **TS1** (*exo*-hydroxyl group) and **TS2** (*endo*-hydroxyl group). Distances for selected bonds are given in angstroms (Å). Mulliken charges, NBO charges (in parentheses), and APT charges (in square brackets) for the oxygen of hydroxyl group and the palladium(II) center atom.

Figure 1 shows the optimized geometries with selected bond lengths of **TS1** and **TS2**. Calculations suggest that an interaction between the hydroxyl group in an *endo* orientation to the metal center is the major factor responsible for the stabilization of **TS2** in comparison to **TS1**. This transition state is characterized by a non-covalent interaction between the hydroxyl group and palladium, with O1-Pd bond length of 2.974 Å. Mulliken, Natural Bond Orbital (NBO),[18] and the Atomic Polar Tensor (APT)[19] methods of population analysis were used to estimate the partial charges on the oxygen of the hydroxyl group and palladium (II). All population analyses (see Supporting Information) indicate the presence of strong electrostatic interaction between the negatively polarized hydroxyl group and the cationic palladium center. Similarly, Uyeda and

Jacobsen reported a detailed computational study on the enantioselectivity of ion-catalyzed asymmetric Claisen rearrangement where the enantioselectivity relied on attractive electrostatic interactions to preferentially stabilize a single transition state.[20]

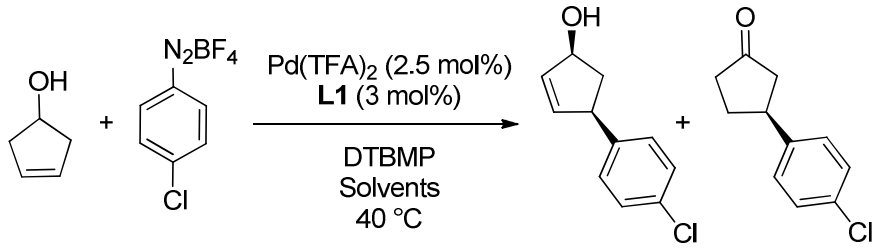
The magnitude of this attractive electrostatic interaction should correlate with the conformational bias of the substrate, and on the reaction medium. In methanol, the cationic palladium complexes are well solvated due to its polar nature. However, in methanol the substrate hydroxyl group might also engage in hydrogen bonds with the solvent. Consequently, this stabilizing electrostatic interaction should be rather weaker in methanol. On the other hand, in toluene the cationic palladium complexes are less solvated, making the attractive interaction between the substrate hydroxyl group and palladium center more effective, thus leading to a more pronounced differentiation between the two transition-states. As described in the next section, this energy difference is reflected in a much improved stereo and product selectivity towards the desired allylic 4-arylcyclopentenol adduct (**3**).

Experimental Studies. Our DFT calculations have shown that the hydroxyl group of the starting cyclopentenol has a strong stabilizing effect when at the *endo* position with respect to the cationic palladium, thus supporting our previous hypothesis. Equally important, those calculations also indicated that this stabilizing effect is even more pronounced in toluene. This fact suggests that toluene, or other less polar solvents, could provide the desired aryl cyclopentenol **3** as the exclusive Heck product in high enantioselectivity.

With the computational studies in hand, we evaluated their significance experimentally. The Heck arylations were then performed in different solvents to probe the reaction selectivity under these new conditions. Gratifyingly, the tested solvents showed significant effect on the reaction selectivity. Solvents like 1,4-dioxane, ethyl ether, acetone, dimethyl carbonate, PEG-300 and

hexane lead to the *cis*-aryl cyclopentenol as the overwhelming major product, albeit in low yields (14-31%; see SI for details). THF provided the desired aryl cyclopentenol **3a** in excellent yield and ee, with a good product selectivity of ~9:1 (Table 1, entry 1). In agreement with the computational studies, the reactions carried out in trifluorotoluene and toluene were much more selective, affording the aryl cyclopentenol **3a** as the exclusive Heck product in high ee's (Table 1, entry 2 and 3). Toluene gave the highest ee's (98%) in a good chemical yield of 71%. Given the high enantioselectivity observed in toluene, we investigated the effect of binary mixtures of solvents, especially toluene and methanol, as this latter solvent is a common one in most enantioselective Heck-Matsuda reactions. A 1:1 mixture toluene/methanol afforded the allylic alcohol **3a** in an improved yield of 82% along with aryl cyclopentanone **4a** (10% yield). By systematically decreasing the amount of methanol in toluene, we were able to find the optimum conditions to obtain only cyclopentenol **3a** in 88% yield and 99% ee, thus combining high ee's and chemical yields (Table 1, entry 6).

Table 1. Screening of solvents.



1 **2a** **3a** **4a**

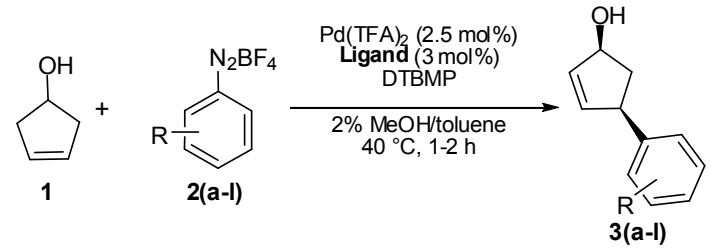
Entry	Solvent	Yield **3a** (%)	ee **3a** (%)	Yield **4a** (%)	ee **4a** (%)
1	THF	88	95	11	0
2	trifluorotoluene	27	97	Traces	-
3[a]	toluene	71	98	-	-

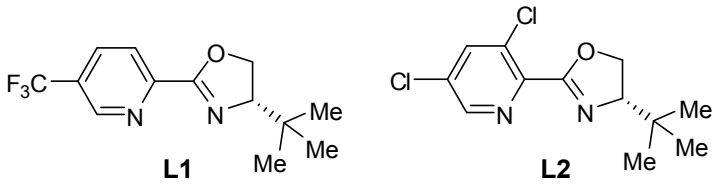
4	toluene:methanol (50:50)	82	95	10	8
5	toluene:methanol (95:5)	63	99	Traces	-
6[a]	toluene:methanol (98:2)	88	99	-	-
7[a]	toluene:methanol (99:1)	73	99	-	-

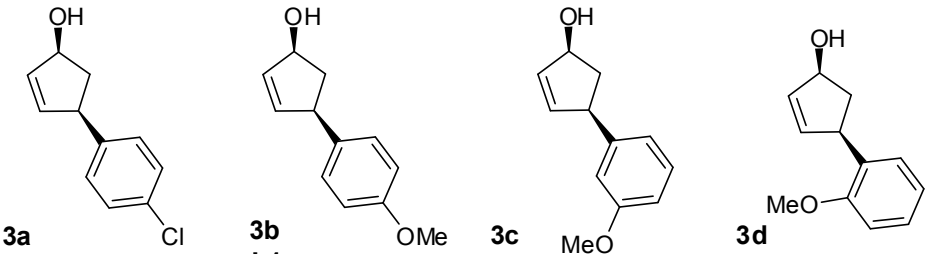
[a]Product **4a** was not observed.

To expand the synthetic potential of the Heck arylation under the new conditions, its scope was evaluated with several aryldiazonium salts containing electron donating (EDG) or electron withdrawing (EWG) groups in different substitution patterns. The design of new *N*,*N*-ligands for the Heck reactions or cross-coupling reaction is a subject of great general interest. Small changes in the electronics of these ligands can have a profound effect on the enantioselectivity, diastereoselective and chemical yields of the reactions.[21] Therefore, the new conditions also provided us with the opportunity to test the performance of the new PyOx ligand (*S*)-4-*tert*-butyl-2-(3,5-dichloropyridin-2-yl)-4,5-dihydrooxazole (**L2**) in the Heck arylation of cyclopentenol **1**, compared to the commercially available PyOx **L1** (Scheme 4).

Scheme 4. Scope of the new enantioselective Heck desymmetrization of 3-cyclopenten-1-ol using PyOx ligands **L1** and **L2**.





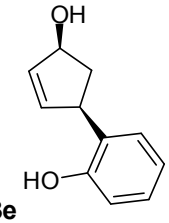


3a
L1: 92%; 99% ee
L2: 76%; 96% ee

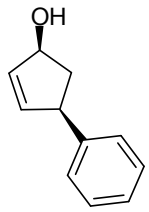
3b
L1: 81%; 94% ee
L2: 96%; 96% ee

3c
L1: 84%; 97% ee
L2: 86%; 97% ee

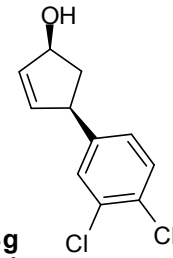
3d
L1: 90%; 94% ee
L2: 58%; 80% ee



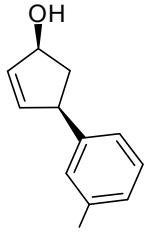
3e
L1[a]: 51%; 86% ee
L2[a]: 61%; 84% ee



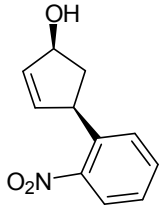
3f
L1: 85%; 97% ee
L2: 76%; 97% ee



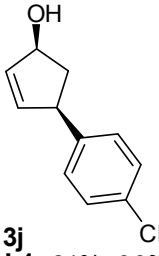
3g
L1: 76%; 97% ee
L2: 78%; 95% ee



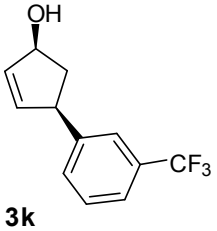
3h
L1: 86%; 96% ee
L2: 76%; 92% ee



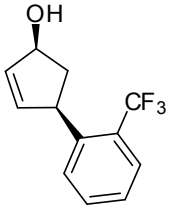
3i
L1[b]: 72%; 97% ee
L2[c]: 69%; 97% ee



3j
L1: 61%; 99% ee
L2: 76%; 99% ee



3k
L1: 76%; 98% ee
L2: 86%; 96% ee



3l
L1: 66%; 96% ee
L2: 72%; 98% ee

[a]Using 10 mol% of $Pd(TFA)_2$ and 11 mol% of the ligand [b]The corresponding ketone **4i** was obtained in 18% yield in 90% ee. [c]The corresponding ketone **4i** was obtained in 23% yield in 88% ee.

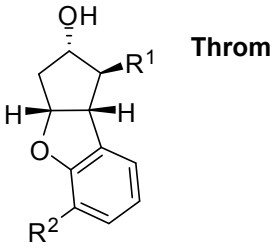
As indicated in Scheme 4, PyOx ligands **L1** and **L2** showed similar results in the enantioselective Heck–Matsuda reaction, with ligand **L2** performing slightly better for aryldiazonium salts bearing the electron donating *para*-methoxy substituent and the highly electron withdrawing CF_3 substituent. On the other hand, **L1** had performed better with *ortho*-substituted aryldiazonium salts. Enantiomeric excesses were very high in all instances, except for **3d** and **3e** using **L2**, for reasons not yet clear to us since **L2** performed well with other *ortho* substituted aryldiazonium salts, as exemplified by the Heck products **3i** and **3l**.

The intrinsic structural complexity incorporated in the *cis*-aryl-cyclopentenols **3a-l** gives them a considerable synthetic potential. To demonstrate this point, aryl cyclopentenol **3e** was used in the construction of the more complex chiral scaffold **7e** possessing the basic framework of many important drugs and/or bioactive natural products, such as the thromboxane inhibitor beraprost and the aplysins.[22] The thromboxane inhibitors have attracted intense medical interest in the last few years and have been the subject of many recent patents.[23] Therefore, the phenolic aryl cyclopentenol **3e** was submitted to gold-catalyzed allylic substitution, employing a recently developed procedure by Aponick *et al*.[24] The gold-catalyzed cyclization afforded the corresponding fused tricyclic system in good to excellent yield and diastereoselectivity. As expected, no enantiodepletion was observed in the tricyclic product (see SI, section 5), demonstrating the synthetic potential of the Heck-Matsuda method for the synthesis of complex chiral scaffolds (Scheme 5).

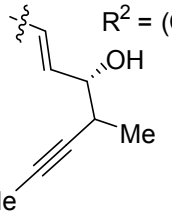
Scheme 5. Gold-catalyzed allylic substitution and bioactive compounds bearing the cyclopenta[*b*]benzofuran skeleton.

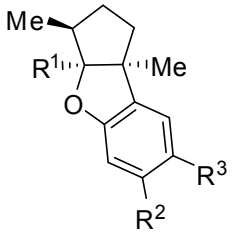
3e **7e** 92%

Examples of molecules containing the cyclopenta[*b*]benzofuran skeleton



Thromboxane inhibitors: R^1 =alkyl R^2 = alkyl (US5496849)

Beraprost: R^1=  $R^2 = (CH_2)_3CO_2H$



(**-)-Aplysin**: $R^1 = R^2 = Me$; $R^3 = Br$
(-)-Debromoaplysin: $R^1 = R^2 = Me$; $R^3 = H$
Aplysinol: $R^1 = CH_2OH$; $R^2 = Me$; $R^3 = Br$
Isoaplysin: $R^1 = CH_2Br$; $R^2 = Me$; $R^3 = H$

CONCLUSION

We have demonstrated that computational calculations provided key mechanistic insights regarding the role of the hydroxyl group in the Heck-Matsuda desymmetrization of 3-cyclopenten-1-ol. DFT calculations strongly agreed with our initial hypothesis of non-covalent stabilizing interaction between the substrate hydroxyl group and the cationic metal center. This critical interaction directs the olefin face undergoing arylation to provide a highly functionalized

five-membered ring product in high yield and enantiomeric excess. New and much improved reaction conditions were then developed employing a mixture of 2% methanol/-toluene, which, with very few exceptions, gave the desired *cis*-4-aryl-cyclopentenols **3a-l** as the exclusive Heck products in excellent ee and good to excellent chemical yields. These new chiral scaffolds bear considerable synthetic potential, which was illustrated by the construct of the more complex cyclopenta[*b*]benzofuran skeleton **7a**. Overall, the newly developed method brings new insights about the complexity of the Heck reactions and it demonstrates excellent scope. It is also very practical, mild providing fast reactions (1-2 h). Another feature is that it can be carried out under "open-vessel" conditions. Moreover, a new PyOx ligand **L2** was introduced with excellent potential for new enantioselective Heck and palladium-catalyzed reactions. These results open new opportunities for enantioselective synthesis of key intermediates based on cyclopentenes scaffolds. Studies to fully explore those potentials are ongoing and shall be reported in due course.

EXPERIMENTAL SECTION

General methods. All the reactions were carried out in a 4 mL or 20 mL vessel under air atmosphere, unless otherwise stated. Reaction temperatures different from room temperature are reported as the temperature of the bath surrounding the vessel. All Heck-Matsuda reactions solvents were used without any previous treatment and were obtained from commercial sources.

Hexane and ethyl acetate used for purification/chromatography were of technical grade and were distilled prior to use.

Commercially available reagents were used as received.

Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{245} plates, 0.25 mm thickness. Visualization was accomplished mainly with vanillin (although $KMnO_4$ and phosphomolybidic acid were also used) as staining solution, followed by heating.

Flash chromatography was performed on silica gel (230-400 mesh) using standard techniques and eluted with appropriated ethyl acetate/hexane mixtures.

NMR analyses were performed on 400 and 500 MHz spectrometers. Spectra were recorded in $CDCl_3$, or DMSO-d_6 (depending on the case, see compound description for more details). 1,3-Bis(trifluoromethyl)-5-bromobenzene was used as internal standard for the determination of chemical yields by ^{1}H NMR (at the methodology optimization stage). Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) or any residual solvent peak. The following residual signals of the deuterated solvents were used as references ($CDCl_3$; ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm. $(CD_3)_2SO$; ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.52 ppm). Data are reported as follows: chemical shift (δ), multiplicity, coupling constant *(J)* in Hertz, and integrated intensity. Abbreviations to denote the multiplicity of a particular signal are s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet) and m (multiplet).

HPLC analysis were performed with an UV detector at controlled column temperature with injection volume of 20 µL using Hexane/2-Propanol as solvent mixture in an isocratic system.

Optical rotations (α) were measured on polarimeter at 20 ^{o}C using a quartz glass cell (10 mm path length).

Infrared (IR) spectra were recorded in an FTIR using attenuated total reflectance (ATR) technique, with scans between 4000 and 650 cm^{-1}, with 8 cm^{-1} resolution. The compounds were analyzed in its pure form, on a germanium sample holder. The maximum absorbing frequencies are reported in cm^{-1}.

High-resolution MS measurements were obtained with a HDMS. Data was obtained in the V mode TOF (analizer) and ESI(+) mode (source). The major signals are quoted in *m*/*z*.

Melting points were measured in melting apparatus.

Ligands used in this study are commercially available, except for **L2**, which was synthesized by a modified literature procedure.[25]

All aryldiazonium tetrafluoroborates (**1**) were synthesized by a previously reported procedure.[26]

Computational methods. All electronic structure calculations were based on density theory functional (DFT).[27] The transition states were fully optimized in gas phase with local functional M06-L, suitable for description on thermochemical kinetics and noncovalent interactions of transition metals, inorganic and organometallic compounds.[28] The standard 6-31G(d) basis set was adopted for lighter atoms and relativistic pseudopotential method SDD[29] for Pd, approaches are denoted 6-31G(d), SDD(Pd). This basis set approach was performed for DFT investigation in other Pd catalyzed C-C cross coupling reaction based on PyOx ligand, with a successfully rationalization on reactivity and enantioselectivity.[30] Frequency calculations were carried out in order to verify that transition states have only one imaginary frequency. Intrinsic Reaction Coordinate (IRC) method also used to further authentic the transition states.[31] Solvent effects for methanol (M) and toluene (T) were introduced through SMD[17] method by single-point calculations in geometries optimized on gas phase at the SMD-M06-L/6-31G(d), SDD(Pd) level of theory. The transition states are discussed in free energy terms with solvent, thermal, enthalpy and entropic corrections at 298.15 K and 1 atm, reported in kcal•mol^{-1}. All calculations were performed with Gaussian 09 suite quantum chemical programs.[32]

(*S*)-4-(tert-butyl)-2-(3,5-dichloropyridin-2-yl)-4,5-dihydrooxazole (L2). L-*tert*-Leucinol (1.5 equiv, 8.67 mmol, 1.01 g), 3,5-dichloropicolinonitrile (1 equiv, 5.78 mmol, 1.00 g), $Zn(OAc)_2.2H_2O$ (2 mol%, 0.12 mmol, 25.3 mg) and 6 mL of hexane were added to a 15 mL pressure tube containing a stirring bar. The tube was tightly closed and immersed in an oil bath at 110 °C (Careful, pressure is developed), and the resultant mixture was kept stirring overnight at 110 °C in the pressurized tube. The flask was then slowly cooled to room temperature, and opened carefully (ammonia gas is released). The resulting mixture was concentrated in vacuum and then purified by column chromatography with hexanes:ethyl acetate as eluent. The product was obtained in 95% yield as a pale yellow oil (1.49 g, 5.46 mmol). This is a modified literature procedure.[25] $[\alpha]^{20}_{589}$(c 0.73, $CHCl_3$) = -60, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.54 (d, *J* = 2.0 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 4.44 (dd, *J* = 10.2, 8.6 Hz, 1H), 4.29 (ta, *J* = 8.4 Hz, 1H), 4.20 (dd, *J* = 10.2, 8.3 Hz, 1H), 1.00 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.8, 146.5, 143.7, 138.0, 133.5, 132.4, 77.4, 69.2, 34.1, 26.1. **HRMS (-ESI)** calculated for $C_{12}H_{14}Cl_2N_2O$ [M+H$^+$]: 273.0556; found 273.0574. **IR (neat, cm^{-1})** 2956, 2906, 2871, 1666, 1565, 1442, 1367, 1337, 1266, 1208, 1111, 1041, 961, 912, 830, 661, 577.

General procedures for the enantioselective Heck-Matsuda arylations. A 4 mL vessel containing a magnetic stir bar was charged with 2.5 mol% of $Pd(TFA)_2$, 3.0 mol% ligand (**L1** or **L2**) and a solution of 2% methanol in toluene (1.3 mL) (Note: except for compound **3e**, which demanded 10 mol% of $Pd(TFA)_2$ and 11 mol% of Ligand). The resulting light orange solution was then stirred for 10 min at 40 ^oC. At this point it was added 1.1 equiv of DTBMP (2,6-di-*tert*-butyl-4-methylpyridine; 0.11 mmol) and 2 equiv of olefin (**1**; 0.2 mmol), followed by addition of 1 equiv of the appropriate arenediazonium salt (**2**; 0.1 mmol). The reaction was monitored by TLC until complete consumption of the diazonium salt (*β*-napthol test) (2-6 h).[*] Next, the crude reaction mixture was concentrated in vacuum, and the products purified by flash chromatography using EtOAc/ Hexanes 30% as eluent to afford the Heck products (**3a-l** and **4i**).

Analytical data for compounds **3a**, **3b**, **3d**, **3e**, **3f**, **3h**, **3i**, **3j**, **3k** and **3l** has been previously reported.7

(1*S*,4*R*)-cis-4-(4-chlorophenyl)cyclopent-2-enol (3a). Compound **3a** was obtained as a light brown oil (using procedure A and **L1** it was obtained 17.9 mg, 0.092 mmol, 92% yield, >99% ee. Using procedure A and **L2** it was obtained 14.8 mg, 0.076 mmol, 76% yield, 96% ee). ee determined by HPLC analysis (Daicel IC 4.6 mm X 25 cm, column temperature 25 ^oC, Hexanes/*i*-PrOH 98:2, 1 mL/min, 225 nm, t_R = 14.8 min (minor) and t_R = 17.6 min (major). The compound has been fully characterized previously.7

(1*S*,4*R*)-*cis*-4-(4-methoxyphenyl)cyclopent-2-enol (3b). Compound **3b** was obtained as a light brown oil (using procedure A and **L1** it was obtained 15.4 mg, 0.081 mmol, 81% yield, 94% ee. Using procedure A and **L2** it was obtained 18.3 mg, 0.096 mmol, 96% yield, 96% ee). ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm X 25 cm, column temperature 25 ^oC, Hexanes/*i*-PrOH 98:2, 1 mL/min, 272 nm, t_R = 40.1 min (major) and t_R = 43.1 min (minor). The compound has been fully characterized previously.7

[*] *The test consists of mixing a β-naphthol solution with a small aliquot of the reaction mixture on a spot test plate (alternatively, a TLC plate can also be employed). Appearance of a deep red color indicates the presence of aryldiazonium salt.*

(1*S*,4*R*)-*cis*-4-(3-methoxyphenyl)cyclopent-2-enol (3c). Compound **3c** was obtained as a light yellow oil (using procedure A and **L1** it was obtained 16.0 mg, 0.084 mmol, 84% yield, 97% ee. Using procedure A and **L2** it was obtained 16.4 mg, 0.086 mmol, 86% yield, 97% ee). ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 95:5, 1 mL/min, 270 nm, t_R = 17.3 min (major) and t_R = 21.9 min (minor), $[\alpha]^{20}_{589}$(c 2.00, $CHCl_3$) = +69 (97% ee sample). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.23 (dd, *J* = 15.8, 8.0 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.79 – 6.72 (m, 2H), 5.98 (dt, *J* = 5.6, 2.0 Hz, 1H), 5.95 (dt, *J* = 5.5, 1.6 Hz, 1H), 4.98 – 4.88 (m, 1H), 3.80 (s, 3H), 3.79 – 3.74 (m, 1H), 2.85 (ddd, *J* = 13.7, 8.4, 7.4 Hz, 1H), 1.63 (s, 1H), 1.58 (ddd, *J* = 13.7, 6.2, 5.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 160.0, 146.9, 137.4, 134.7, 129.7, 119.8, 113.2, 111.8, 77.6, 55.3, 50.0, 44.0. **HRMS (-ESI)** calculated for $C_{12}H_{14}O_2$ [M+H$^+$]: 191.1067; found 191.1063. **IR (neat, cm^{-1})** 3359, 2938, 2839, 1603, 1586, 1489, 1438, 1267, 1159, 1045, 999, 878, 783, 749, 703.

(1*S*,4*R*)-*cis*-4-(2-methoxyphenyl)cyclopent-2-enol (3d). Compound **3d** was obtained as a light brown oil (using procedure A and **L1** it was obtained 17.1 mg, 0.090 mmol, 90% yield, 94% ee. Using procedure A and **L2** it was obtained 11.0 mg, 0.058 mmol, 58% yield, 80% ee). ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 99:1, 1 mL/min, 272 nm, t_R =55.8 min (minor) and t_R = 64.6 min (major). The compound has been fully characterized previously.7

(1'*S*,4'*R*)-*cis*-2-(4'-hydroxycyclopent-2'-enyl)phenol (3e). Compound **3e** was obtained as a light brown oil: (using procedure A and **L1** it was obtained 10.0 mg, 0.051 mmol, 51% yield, 86% ee. Using procedure A and **L2** it was obtained 10,7 mg, 0.061 mmol, 61% yield, 84% ee.). ee determined by HPLC analysis (Daicel IC 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 95:5, 1 mL/min, 225 nm, t_R = 15.5 min (minor) and t_R = 18.0 min (major). The compound has been fully characterized previously.7

(1*S*,4*R*)-*cis*-4-phenylcyclopent-2-enol (3f). Compound **3f** was obtained as a light brown oil (using procedure A and **L1** it was obtained 13.6 mg, 0.085 mmol, 85% yield, 97% ee. Using procedure A and **L2** it was obtained 12.2 mg, 0.076 mmol, 76% yield, 97% ee). ee determined by HPLC analysis (Daicel AD 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 95:5, 0.8 mL/min, 210 nm, t_R = 11.7 min (minor) and t_R = 12.7 min (major). The compound has been fully characterized previously.7

(1*S*,4*R*)-*cis*-4-(3,4-dichlorophenyl)cyclopent-2-enol (3g). Compound **3g** was obtained as light brown oil (using procedure A and **L1** it was obtained 17.4 mg, 0.076 mmol, 76% yield, 97% ee. Using procedure A and **L2,** it was obtained 17.9 mg, 0.078 mmol, 78% yield, 95% ee). ee determined by HPLC analysis (Daicel IC 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 98:2, 1 mL/min, 225 nm, t_R = 14.8 min (minor) and t_R = 17.6 min (major), $[\alpha]^{20}_{589}$(c 1.76, $CHCl_3$) = +91 (97% ee sample). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.29 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.94 (dt, *J* = 5.6, 2.2 Hz, 1H), 5.82 (dt, *J* = 5.7, 1.6 Hz, 1H), 4.90 – 4.84 (m, 1H), 3.73 – 3.62 (m, 1H), 2.77 (ddd, *J* = 13.8, 8.4, 7.4 Hz, 1H), 1.51 (s, 1H), 1.46 (ddd, *J* = 13.8, 6.0, 4.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 145.5, 136.5, 135.4, 132.6, 130.6, 130.4, 129.5, 127.0, 77.3, 49.2, 43.7. **HRMS (-ESI)** calculated for $C_{11}H_{10}Cl_2O$ [M+H$^+$]: 229.0181; found 229.0184. **IR (neat, cm^{-1})** 3348, 2966, 2932, 1595, 1563, 1469, 1398, 1315, 1134, 1073, 1034, 826.

(1*S*,4*R*)-*cis*-4-(3-nitrophenyl)cyclopent-2-enol (3h). Compound **3h** was obtained as light brown oil (using procedure A and **L1** it was obtained 17.6 mg, 0.086 mmol, 86% yield, 96% ee. Using procedure A and **L2,** it was obtained 15.6 mg, 0.076 mmol, 76% yield, 92% ee). ee determined by HPLC analysis (Daicel AD 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 97:3, 1 mL/min, 210 nm, t_R = 41.7 min (minor) and t_R = 49.8 min (major). The compound has been fully characterized previously.7

(1*S*,4*R*)-*cis*-4-(2-nitrophenyl)cyclopent-2-enol (3i). Compound **3i** was obtained as light brown oil (using procedure A and **L1** it was obtained 14.8 mg, 0.072 mmol, 72% yield, 97% ee. Using procedure A and **L2,** it was obtained 14.2 mg, 0.069 mmol, 69% yield, 97% ee). ee determined by HPLC analysis (Daicel OJ-H 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 96:4, 1 mL/min, 225 nm, t_R = 24.9 min (minor) and t_R = 27.6 min (major). The compound has been fully characterized previously.7

(*S*)-3-(2-nitrophenyl)cyclopentanone (4i). Compound **4i** was obtained as light brown oil (using procedure A and **L1,** it was obtained 1.7 mg, 0.018 mmol, 18% yield, 90% ee. Using procedure A and **L2** it was obtained 4.7 mg, 0.023 mmol, 23% yield, 88% ee). ee determined by HPLC analysis (Daicel AD 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 97:3, 1 mL/min, 225 nm, t_R = 21.7 min (major) and t_R = 28.3 min (minor). The compound has been fully characterized previously.7

(1*S*,4*R*)-*cis*-4-(4-(trifluoromethyl)phenyl)cyclopent-2-enol (3j). Compound **3j** was obtained as light brown oil (using procedure A and **L1,** it was obtained 13.9 mg, 0.061 mmol, 61% yield, 98% ee. Using procedure A and **L2,** it was obtained 17.3 mg, 0.076 mmol, 76% yield, 94% ee). ee determined by HPLC analysis (Daicel IB-3 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 99:1, 1 mL/min, 225 nm, t_R = 26.5 min (major) and t_R = 28.9 min (minor). The compound has been fully characterized previously.7

(1*S*,4*R*)-*cis*-4-(3-(trifluoromethyl)phenyl)cyclopent-2-enol (3k). Compound **3k** was obtained as light brown oil (using procedure A and **L1** it was obtained 17.3 mg, 0.076 mmol, 76% yield, 98% ee. Using procedure A and **L2** it was obtained 19.6 mg, 0.086 mmol, 86% yield, 96% ee). ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 99:1, 1 mL/min, 272 nm, t_R = 25.0 min (major) and t_R = 26.5 min (minor). The compound has been fully characterized previously.7

(1*S*,4*R*)-*cis*-4-(2-(trifluoromethyl)phenyl)cyclopent-2-enol (3l). Compound **3l** was obtained as light brown oil (using procedure A and **L1** it was obtained 15.1 mg, 0.066 mmol, 66% yield, 96% ee. Using procedure A and **L2** it was obtained 16.4 mg, 0.072 mmol, 72% yield, 98% ee). ee determined by HPLC analysis (Daicel IB 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 99:1, 1 mL/min, 272 nm, t_R = 29.0 min (major) and t_R = 30.1 min (minor). The compound has been fully characterized previously.7

(3a*S*,8b*S*)-3a,8b-dihydro-1H-cyclopenta[b]benzofuran (7e). JohnPhosAuCl (3 mol%), AgOTf (3 mol%) and 30 mg of 4 Å activated molecular sieves where stirred in 0.5 mL of dry CH_2Cl_2 in the dark for 10 min. To this mixture, it was added a solution of corresponding phenol in 0.3 mL of dry CH_2Cl_2 and 0.5 mL of dry THF. The reaction was left stirring at ambient temperature, in dark, and monitored by TLC until complete consumption of the phenol. The solvent was then evaporated and the crude mixture was purified by column chromatography using EtOAc/hexanes as eluent to afford product **7e** as colorless oil (when starting from 38.7 mg or 0.22 mmol of **3e**, it was obtained 32 mg, 0.20 mmol, 92% yield). ee can be determined by HPLC analysis (Daicel OJ-H 4.6 mm X 25 cm, column temperature 25 ^{o}C, Hexanes/*i*-PrOH 98:2, 1 mL/min, 225 nm, t_R = 8.4 min (major) and t_R = 9.2 min (minor). $[\alpha]^{20}_{589}$(c 0.67, $CHCl_3$) = -42 (81 % ee sample). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.15 (d, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.03-6.00 (m, 1H), 5.87-5.84 (m, 1H), 5.82 (d, *J* = 8.1 Hz, 1H),

4.07 (t, *J* = 8.1 Hz, 1H), 2.93 (dd, *J* = 17.0, 8.1 Hz, 1H), 2.58 (d, *J* = 17 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 158.5, 135.5, 131.6, 129.6, 128.5, 124.9, 120.6, 110.1, 92.6, 43.4, 40.6. **HRMS (+ESI-TOF)** calculated for $C_{11}H_{10}O$ [M]: 158.0726; found 158.0720. **IR (neat, cm^{-1})** 2928, 1497, 1392, 1224, 968, 756.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, computational methods, characterization data and chiral HPLC analyses for compounds **3a-l**, **4i** and **7e**, and ^{1}H and ^{13}C NMR spectra for the new compounds **L2**, **3c**, **3g** and **7e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written with the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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