JOC The Journal of Organic Chemistry

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Intermolecular Noncovalent Hydroxy-Directed Enantioselective Heck Desymmetrization of Cyclopentenol: Computationally Driven Synthesis of Highly Functionalized *cis*-4-Arylcyclopentenol Scaffolds

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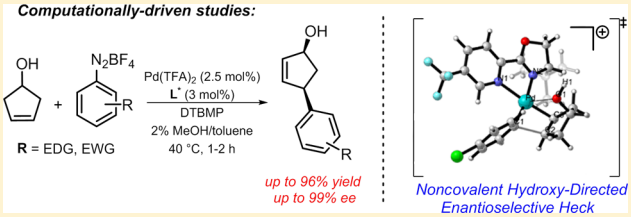
Supporting Information

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 noncovalent 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-arylcyclopentenols **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-arylcyclopentenols 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 toward 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 past 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 co-workers 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 co-workers 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 en 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 a consequence of the reaction diastereoselectivity: the more highly functionalized *cis*-4-arylcyclopentenols **3**, as major products with the enantiomeric excesses (ee's) ranging from 85% to 99% (Scheme 1), and the minor 3-arylcyclopentanones **4**, in much lower ee's.

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 co-workers introduced the

Received: December 16, 2015
Published: February 2, 2016

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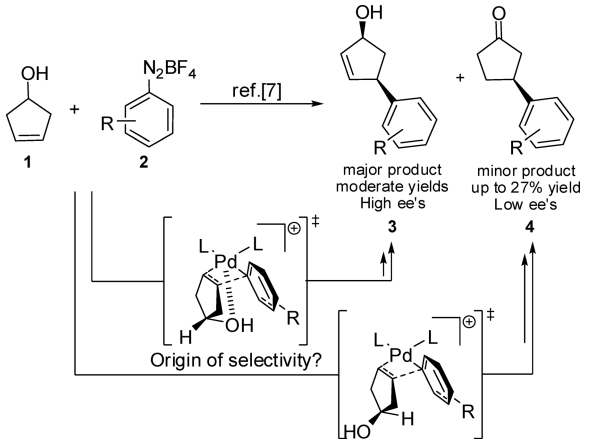
DOI: 10.1021/acs.joc.5b02846
J. Org. Chem. 2016, 81, 2010−2018

Scheme 1. Enantioselective Heck Arylation of 3-Cyclopenten-1-ol



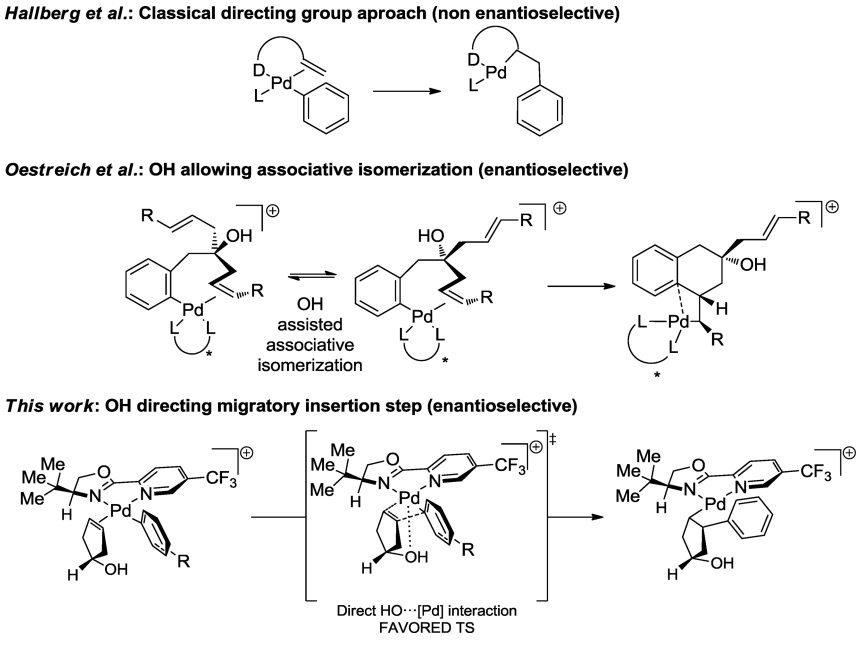
concept of "chelation control" by installing an appropriate donor group on the substrate to obtain high regioselectivity in intermolecular Heck reactions.[9] Alper and co-workers also suggested the critical role of a hydroxyl group in an enantioselective Pd-catalyzed cyclocarbonylation of allylic alcohols 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 co-workers 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 enantiodetermining 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.

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).[1b] 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.

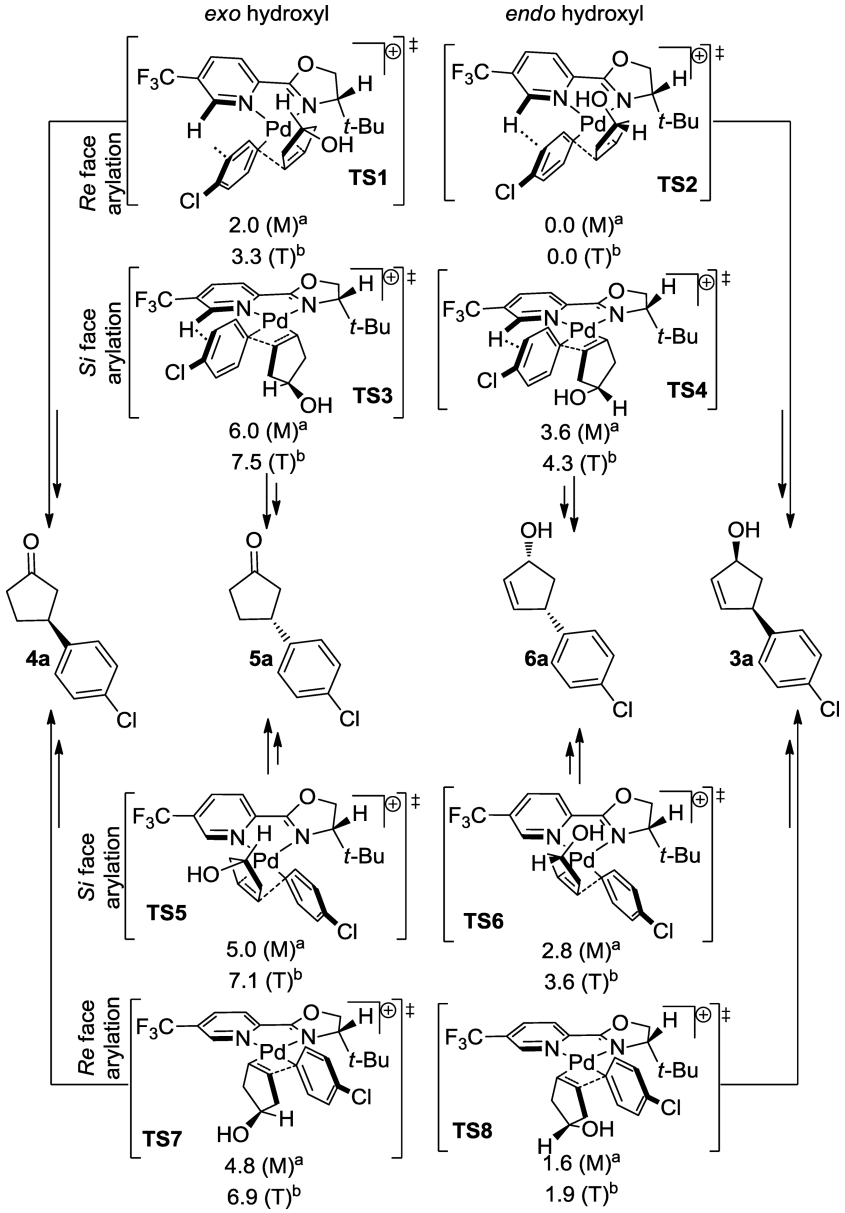
In this report, we disclosed our findings concerning the new optimized conditions for the Heck–Matsuda desymmetrization of 3-cyclopenten-1-ol **1** with several aryldiazonium salts to provide exclusively the desired *cis*-4-aryl-cyclopentenol Heck products. These results were supported by DFT studies based

Scheme 2. Directing Groups in Heck Reaction



DOI: 10.1021/acs.joc.5b02846
J. Org. Chem. 2016, 81, 2010–2018

Scheme 3. Computed Energies (in kcal·mol^{-1}) for the Migratory β-Insertion Transition States*



*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}).

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 noncovalent interaction with the cationic palladium in the diastereo- and enantiodetermining 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 evidence 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 toward 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 enantiodetermining step, since the arylpalladium complexes are supposed to be in rapid equilibrium.[17] 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

DOI: 10.1021/acs.joc.5b02846
J. Org. Chem. 2016, 81, 2010–2018

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-chlorophenyldiazonium 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 analysis.[7]

According to our calculations, the transition state **TS2**, which has the hydroxyl in an *endo* orientation toward 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 the Supporting Information for more details about the optimized geometry of all transition states). Furthermore, **TS2** contains a stabilizing C−H π interaction that 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). Arylcyclopentenol **6a** and the cyclopentenone **5a** were indeed minor stereoisomers in our experiments with methanol. These computational studies nicely support our previously reported experimental results.[9]

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 shows the optimized geometries with selected bond lengths of **TS1** and **TS2**. Calculations suggest that an

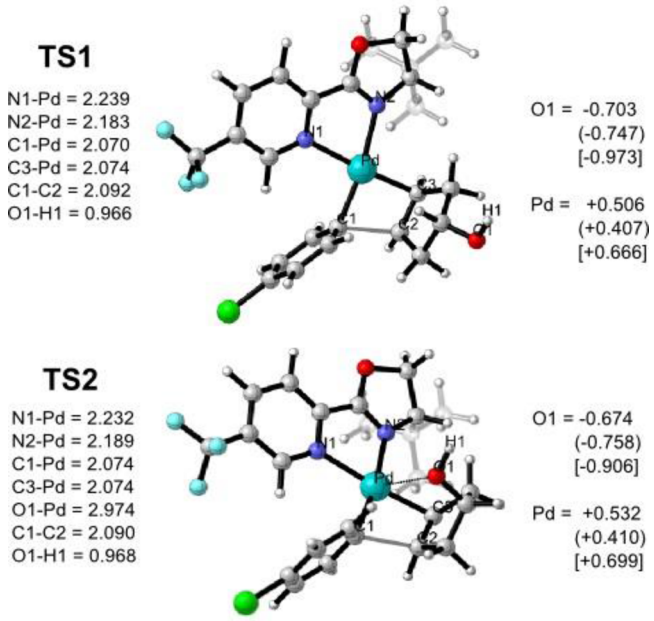


Figure 1. Calculated transition states **TS1** (*exo*-hydroxyl group) and **TS2** (*endo*-hydroxyl group). Distances for selected bonds are given in angstroms. Mulliken charges, NBO charges (in parentheses), and APT charges (in square brackets) for the oxygen of the hydroxyl group and the palladium(II)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

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 noncovalent interaction between the hydroxyl group and palladium, with an 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 the 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 toward the desired allylic 4-arylcyclopentenol adduct (**3**).

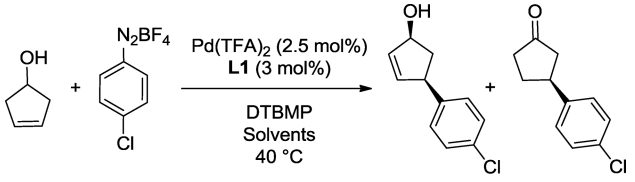
Experimental Studies. Our DFT calculations have shown that the hydroxyl group of the starting cyclopentenol has a strong stabilizing effect when at the *endo* position with respect

DOI: 10.1021/acs.joc.5b02846
J. Org. Chem. 2016, 81, 2010−2018

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 led to the *cis*-aryl cyclopentenol as the overwhelming major product, albeit in low yields (14−31%; see the Supporting Information 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

Table 1. Screening of Solvents



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

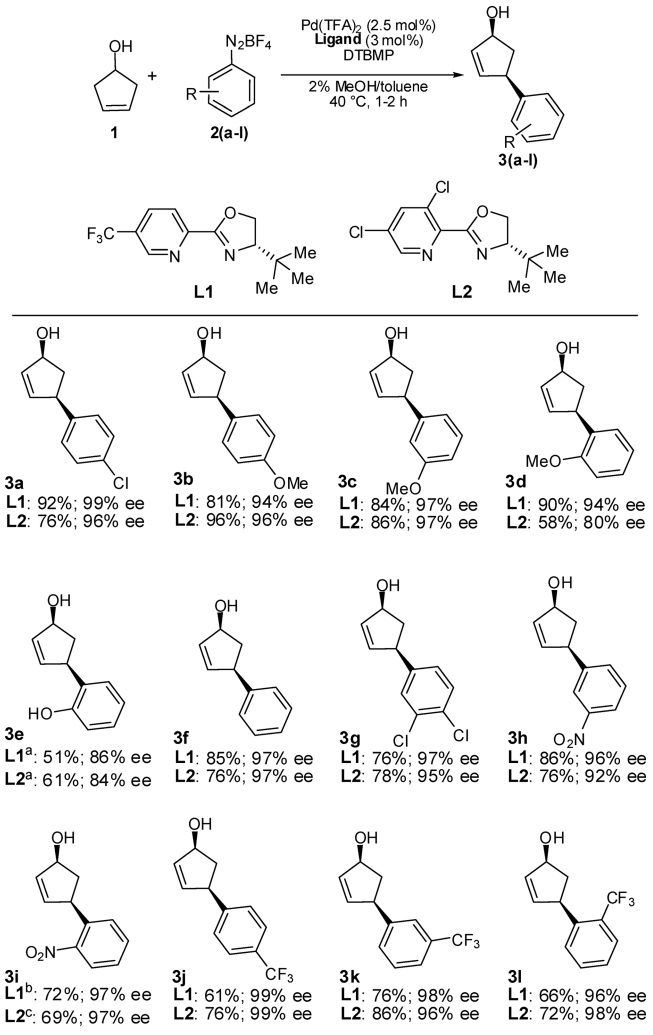
entry	solvent	yield **3a** (%)	ee **3a** (%)	yield **4a** (%)	ee **4a** (%)
1	THF	88	95	11	0
2	trifluorotoluene	27	97	traces	
3[a]	toluene	71	98		
4	toluene/methanol (50:50)	82	95	10	8
5	toluene/methanol (95:5)	63	99	traces	
6[a]	toluene/methanol (98:2)	88	99		
7[a]	toluene/methanol (99:1)	73	99		

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

agreement with the computational studies, the reactions carried out in trifluorotoluene and toluene were much more selective, affording the arylcyclopentenol **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).

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 and 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



[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 *p*-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**.

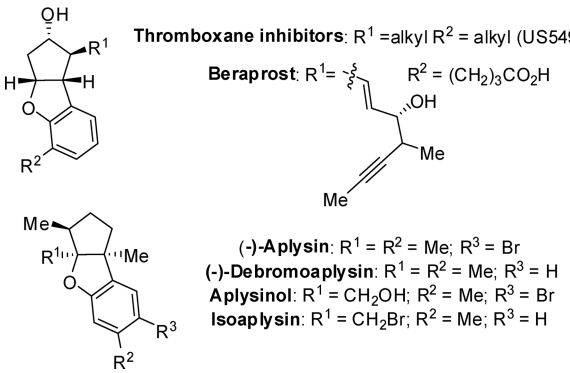
DOI: 10.1021/acs.joc.5b02846
J. Org. Chem. 2016, 81, 2010−2018

The intrinsic structural complexity incorporated in the *cis*-arylcyclopentenols **3a–l** gives them a considerable synthetic potential. To demonstrate this point, arylcyclopentenol **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 past 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 the Supporting Information, 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



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 noncovalent 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-arylcyclopentenols **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 construction 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 demonstrates excellent scope. It is also very practical and 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 of the reactions were carried out in a 4 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 the appropriate 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 analyses were performed with an UV detector at controlled column temperature with an injection volume of 20 μL using hexane/2-propanol as solvent mixture in an isocratic system. Optical rotations (α) were measured on a polarimeter at 20 °C using a quartz glass cell (10 mm path length). Infrared (IR) spectra were recorded in an FTIR using the 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 HDMS. Data was obtained in the V mode TOF (analyzer) 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 the gas phase with local functional M06-L, suitable for description on thermochemical kinetics and noncovalent interactions of transition metals and inorganic and organometallic compounds.[28] The standard 6-31G(d) basis set was adopted for lighter atoms and a relativistic pseudopotential method SDD[29] for Pd; approaches are denoted 6-31G(d) and SDD(Pd). This basis set approach was performed for DFT investigation in other Pd-catalyzed C–C cross-coupling reactions based on the PyOx ligand with a

DOI: 10.1021/acs.joc.5b02846
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successfully rationalization on reactivity and enantioselectivity.[30] Frequency calculations were carried out in order to verify that transition states have only one imaginary frequency. The intrinsic reaction coordinate (IRC) method was also used to further authenticate the transition states.[31] Solvent effects for methanol (M) and toluene (T) were introduced through the SMD[17] method by single-point calculations in geometries optimized on the gas phase at the SMD-M06-L/6-31G(d) and SDD(Pd) levels 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 (caution: 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 vacuo 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:[30] $[\alpha]^{20}_{589}$ = −60 (*c* 0.73, $CHCl_3$); ^{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) calcd 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 % of ligand (**L1** or **L2**), and a solution of 2% methanol in toluene (1.3 mL) (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 °C. At this point, 1.1 equiv of DTBMP (2,6-di-*tert*-butyl-4-methylpyridine; 0.11 mmol) and 2 equiv of olefin (**1**; 0.2 mmol) were added, 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). [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.] Next, the crude reaction mixture was concentrated in vacuum, and the products were purified by flash chromatography using EtOAc/hexanes 30% as eluent to afford the Heck products (**3a−l** and **4i**).

Analytical data for compounds **3a,b,d−f,h−l** have been previously reported.[7]

*(1S,4R)-cis-4-(4-Chlorophenyl)cyclopent-2-enol (**3a**).* Compound **3a** was obtained as a light brown oil (using procedure A and **L1**, 17.9 mg, 0.092 mmol, 92% yield, >99% ee was obtained; using procedure A and **L2**, 14.8 mg, 0.076 mmol, 76% yield, 96% ee was obtained); ee determined by HPLC analysis (Daicel IC 4.6 mm × 25 cm, column temperature 25 °C, 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]

*(1S,4R)-cis-4-(4-methoxyphenyl)cyclopent-2-enol (**3b**).* Compound **3b** was obtained as a light brown oil (using procedure A and **L1**, 15.4 mg, 0.081 mmol, 81% yield, 94% ee was obtained; using procedure A and **L2**, 18.3 mg, 0.096 mmol, 96% yield, 96% ee was obtained); ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm × 25 cm, column temperature 25 °C, 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]

*(1S,4R)-cis-4-(3-Methoxyphenyl)cyclopent-2-enol (**3c**).* Compound **3c** was obtained as a light yellow oil (using procedure A and **L1**, 16.0 mg, 0.084 mmol, 84% yield, 97% ee was obtained; using procedure A and **L2**, 16.4 mg, 0.086 mmol, 86% yield, 97% ee was obtained); ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm × 25 cm, column temperature 25 °C, hexanes/*i*-PrOH 95:5, 1 mL/min, 270 nm, t_R = 17.3 min (major) and t_R = 21.9 min (minor): $[\alpha]^{20}_{589}$ = +69 (*c* 2.00, $CHCl_3$) (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) calcd 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.

*(1S,4R)-cis-4-(2-Methoxyphenyl)cyclopent-2-enol (**3d**).* Compound **3d** was obtained as a light brown oil (using procedure A and **L1**, 17.1 mg, 0.090 mmol, 90% yield, 94% ee was obtained; using procedure A and **L2**, 11.0 mg, 0.058 mmol, 58% yield, 80% ee was obtained); ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm × 25 cm, column temperature 25 °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**, 10.0 mg, 0.051 mmol, 51% yield, 86% ee was obtained; using procedure A and **L2**, 10.7 mg, 0.061 mmol, 61% yield, 84% ee was obtained); ee determined by HPLC analysis (Daicel IC 4.6 mm × 25 cm, column temperature 25 °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]

*(1S,4R)-cis-4-Phenylcyclopent-2-enol (**3f**).* Compound **3f** was obtained as a light brown oil (using procedure A and **L1**, 13.6 mg, 0.085 mmol, 85% yield, 97% ee was obtianed; using procedure A and **L2**, 12.2 mg, 0.076 mmol, 76% yield, 97% ee was obtained); ee determined by HPLC analysis (Daicel AD 4.6 mm × 25 cm, column temperature 25 °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]

*(1S,4R)-cis-4-(3,4-Dichlorophenyl)cyclopent-2-enol (**3g**).* Compound **3g** was obtained as a light brown oil (using procedure A and **L1**, 17.4 mg, 0.076 mmol, 76% yield, 97% ee was obtained; using procedure A and **L2**, 17.9 mg, 0.078 mmol, 78% yield, 95% ee was obtained); ee determined by HPLC analysis (Daicel IC 4.6 mm × 25 cm, column temperature 25 °C, hexanes/*i*-PrOH 98:2, 1 mL/min, 225 nm, t_R = 14.8 min (minor) and t_R = 17.6 min (major): $[\alpha]^{20}_{589}$ = +91 (*c* 1.76, $CHCl_3$) (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) calcd 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.

*(1S,4R)-cis-4-(3-Nitrophenyl)cyclopent-2-enol (**3h**).* Compound **3h** was obtained as a light brown oil (using procedure A and **L1**, 17.6 mg, 0.086 mmol, 86% yield, 96% ee was obtained; using procedure A and **L2**, 15.6 mg, 0.076 mmol, 76% yield, 92% ee was obtained; ee determined by HPLC analysis (Daicel AD 4.6 mm × 25 cm, column temperature 25 °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]

*(1S,4R)-cis-4-(2-Nitrophenyl)cyclopent-2-enol (**3i**).* Compound **3i** was obtained as a light brown oil (using procedure A and **L1**, 14.8 mg, 0.072 mmol, 72% yield, 97% ee was obtained; using procedure A and **L2**, 14.2 mg, 0.069 mmol, 69% yield, 97% ee was obtained); ee determined by HPLC analysis (Daicel OJ-H 4.6 mm × 25 cm, column

DOI: 10.1021/acs.joc.5b02846
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temperature 25 °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 a light brown oil (using procedure A and **L1**, 1.7 mg, 0.018 mmol, 18% yield, 90% ee was obtianed; using procedure A and **L2**, 4.7 mg, 0.023 mmol, 23% yield, 88% ee was obtained); ee determined by HPLC analysis (Daicel AD 4.6 mm × 25 cm, column temperature 25 °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]

(1S,4R)-cis-4-(4-(Trifluoromethyl)phenyl)cyclopent-2-enol (3j). Compound **3j** was obtained as a light brown oil (using procedure A and **L1**,13.9 mg, 0.061 mmol, 61% yield, 98% ee was obtained; using procedure A and **L2**, 17.3 mg, 0.076 mmol, 76% yield, 94% ee was obtained); ee determined by HPLC analysis (Daicel IB-3 4.6 mm × 25 cm, column temperature 25 °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]

(1S,4R)-cis-4-(3-(Trifluoromethyl)phenyl)cyclopent-2-enol (3k). Compound **3k** was obtained as a light brown oil (using procedure A and **L1**, 17.3 mg, 0.076 mmol, 76% yield, 98% ee was obtained; using procedure A and **L2**, 19.6 mg, 0.086 mmol, 86% yield, 96% ee was obtained); ee determined by HPLC analysis (Kromasil 10 Cellucoat 4.6 mm × 25 cm, column temperature 25 °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]

(1S,4R)-cis-4-(2-(Trifluoromethyl)phenyl)cyclopent-2-enol (3l). Compound **3l** was obtained as a light brown oil (using procedure A and **L1**, 15.1 mg, 0.066 mmol, 66% yield, 96% ee was obtained; using procedure A and **L2**, 16.4 mg, 0.072 mmol, 72% yield, 98% ee was obtained; ee determined by HPLC analysis (Daicel IB 4.6 mm × 25 cm, column temperature 25 °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]

(3aS,8bS)-3a,8b-Dihydro-1H-cyclopenta[b]benzofuran (7e). JohnPhosAuCl (3 mol %), AgOTf (3 mol %), and 30 mg of 4 Å activated molecular sieves were stirred in 0.5 mL of dry CH_2Cl_2 in the dark for 10 min. To this mixture was added a solution of the corresponding phenol in 0.3 mL of dry CH_2Cl_2 and 0.5 mL of dry THF. The reaction was allowed to stir at ambient temperature in the 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 a colorless oil (when starting from 38.7 mg or 0.22 mmol of **3e**, 32 mg, 0.20 mmol, 92% yield was obtained); ee determined by HPLC analysis (Daicel OJ-H 4.6 mm × 25 cm, column temperature 25 °C, hexanes/*i*-PrOH 98:2, 1 mL/min, 225 nm, t_R = 8.4 min (major) and t_R = 9.2 min (minor): $[\alpha]^{20}_{589}$ = −42 (*c* 0.67, $CHCl_3$) (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) calcd 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02846.

Cartesian structure (XYZ)

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** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.O.S., R.A.A., V.H.M.S., A.A.C.B., and C.R.D.C. acknowledge the financial support of the São Paulo Research Foundation (FAPESP) (Grant Nos. 2013/00544-0, 2013/25639-4, 2013/04813-6, 2015/01491-3, 2011/23832-6, and 2013/07600-3). B.M.S. thanks the Brazilian Ministry for Education (CAPES) for a fellowship. M.A. thanks Third World Academy of Science (TWAS) and the Brazilian National Research Council (CNPq), for a postdoctoral fellowship. A.A. thanks the Florida−Brazil Linkage Institute for their support of our programs.

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DOI: 10.1021/acs.joc.5b02846
J. Org. Chem. 2016, 81, 2010−2018