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Pd(II)-Catalyzed Enantioselective Desymmetrization of Polycyclic Cyclohexenediones: Conjugate Addition versus Oxidative Heck

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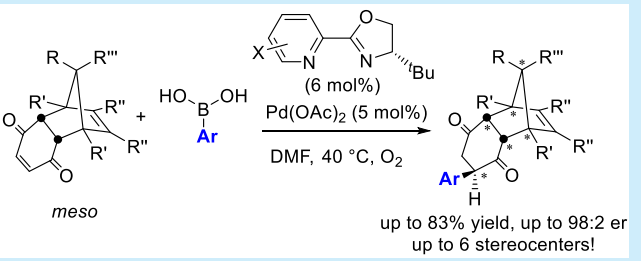
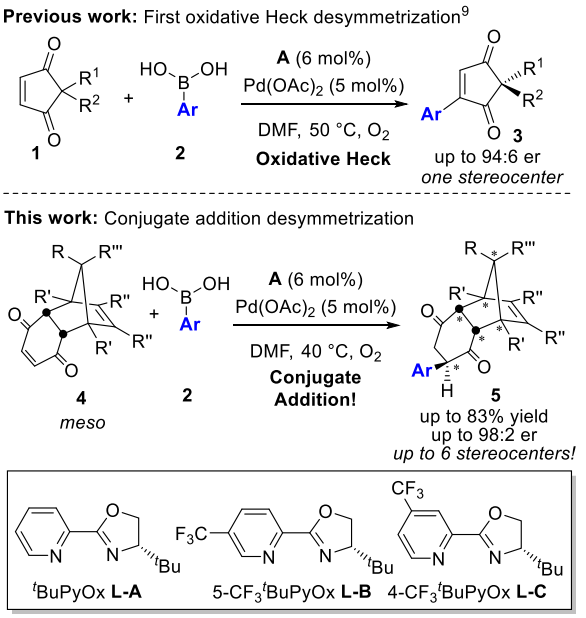
Supporting Information

ABSTRACT: Pd(II)-catalyzed desymmetrization of polycyclic cyclohexenediones has been achieved with high enantio- and diastereoselectivities. Up to five contiguous stereocenters are desymmetrized, while simultaneously, an additional stereocenter is created by the enantioselective conjugate addition. Surprisingly, the conjugate addition products dominate even under typical oxidative Heck conditions, and these observations may provide some insight into the competition between the two related reactions.



Pd(II)-catalyzed oxidative Heck[1] and conjugate addition[2] reactions are two mechanistically related[3] chemical transformations that have recently been exploited for various elegant catalytic enantioselective reactions.[4,5] The use of Pd(II) rather than Pd(0) generally allows for lower temperatures, as well as compatibility with air-stable *N,N*-bidentate ligands, such as pyridine-oxazoline (PyOx)[6] (Scheme 1).[1a] Exploiting Pd(II) catalysis for enantioselective desymmetrization[7] reactions, however, has been much less explored but is a potentially powerful method for installing multiple stereocenters or problematic all-carbon quaternary stereocenters[8] in an efficient one-step procedure. As a proof of concept, we recently developed the first Pd(II)-catalyzed oxidative Heck desymmetrization of cyclopentenediones **1** (Scheme 1), which provides a novel and expedient way of enantioselectively desymmetrizing all-carbon quaternary centers.[9,10]

Scheme 1. Pd(II)-Catalyzed Desymmetrizations



In an effort to challenge the Pd(II) desymmetrization methodology even further, we sought to investigate polycyclic cyclohexenediones **4** (Diels−Alder adducts of benzoquinones and cyclopentadienes) as potential substrates. If this process is successful, up to five contiguous stereocenters, including all-carbon quaternary centers, can be desymmetrized in one efficient step. Previous strategies for desymmetrizing **4** include selective reduction of one of the ketones[11] and organocatalyzed addition−elimination of nitroalkanes.[12] The desymmetrized scaffolds are important as they have been exploited as chiral building blocks in natural product syntheses,[13] so new ways of desymmetrizing such scaffolds would be of interest. Herein, we present the first Pd(II)-catalyzed intermolecular[14] conjugate addition desymmetrization reaction, whereby *meso* substrates **4** are desymmetrized to form up to six stereocenters in one step (Scheme 1). Surprisingly, conjugate addition products **5** dominate, even under conditions that would typically yield oxidative Heck products, and these observations may provide some insight into the competition between the two related reactions.

Selected optimization studies using substrate **4a** are presented in Table 1 (see the Supporting Information for further optimization studies). Using previously established oxidative Heck conditions[15] (entry 1) surprisingly yielded only conjugate addition product **5a** in 74% yield and >20:1 dr. Because this constitutes the first intermolecular Pd(II)-catalyzed conjugate addition desymmetrization reaction and successfully achieves our initial aim of desymmetrizing multiple contiguous stereocenters (four in this case, with the added

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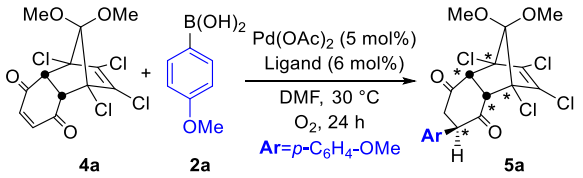
Table 1. Selected Optimization Studies



entry	ligand	time (h)	temp (°C)	yield (%)[a,b]	er[d]
1	1,10-phenanthroline	24	rt	74	–
2	**L-A**	24	30	16	93:7
3	**L-A**	24	40	25[e]	92:8
4[c]	**L-A**	24	40	16	nd[h]
5	**L-A**	24	50	63	85:15
6[f]	**L-A**	72	30	80	92:8
7[f]	**L-C**	72	30	14[d]	nd[h]
8[f]	**L-B**	72	30	trace	nd[h]
9[f,g]	**L-A**	72	30	35[d]	nd[h]

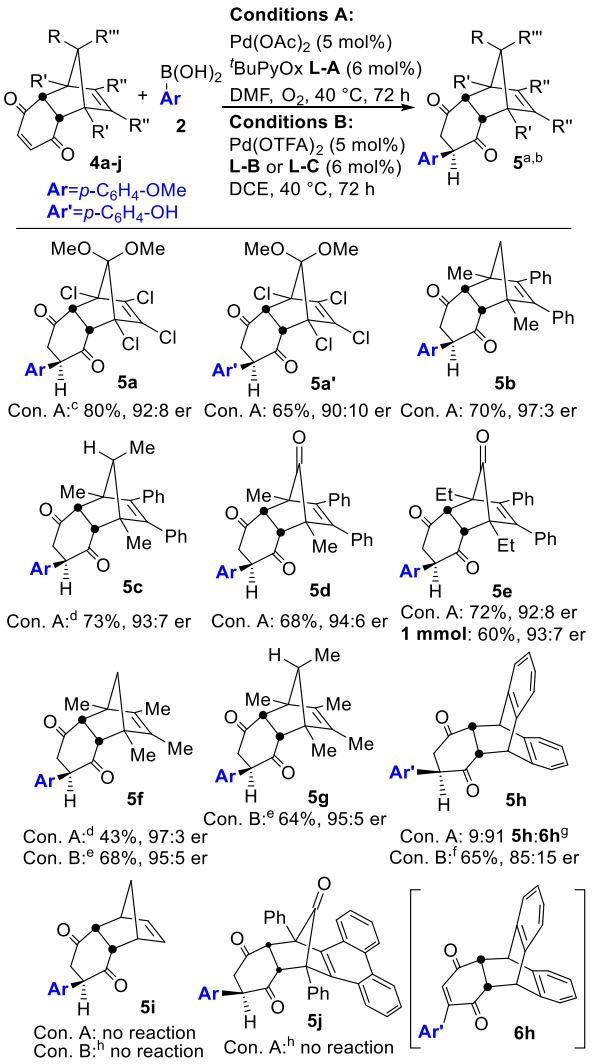
[a]Isolated yields. [b]dr of >20:1. [c]Carried out in air. [d]er determined by CSP-HPLC. [e]Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [f]For 72 h. [g]DMA as the solvent. [h]Not determined.

bonus of creating a fifth stereocenter), we were pleased with the result and progressed to investigate the enantioselective reaction using chiral PyOx ligands (entries 2–9). Initial attempts using ^{t}BuPyOx ligand **L-A** at 30 and 40 °C led to very promising enantiomeric ratios (93:7 and 92:8, respectively) but poor yields (16% and 25%, entries 2 and 3, respectively). Replacing the O_2 atmosphere with air is also detrimental to the yield (entry 4).[16] Although higher temperatures improve the yield (50 °C, 63%), it is at the expense of the er (85:15, entry 5). Pleasingly, increasing the reaction time to 72 h at the lower temperature of 30 °C successfully improves the yield to 80% without affecting the er (entry 6). Switching from ligand **L-A** to **L-C** or **L-B** resulted in very poor conversions (entry 7 or 8, respectively), while substituting DMF for the less ligating dimethylacetamide (DMA) also decreased the reactivity (entry 9).

With optimized conditions in hand, a substrate scope screen of various polycyclic cyclohexenediones **4** was performed (Scheme 2). First, however, a slightly higher temperature of 40 °C was found to be more appropriate for the general substrate scope screen as it improved conversions without adversely affecting the enantiomeric ratios. Substrate **4b**, with dimethyl substitution at the bridgehead positions and diphenyl substitution at the alkene, proceeds smoothly with a good yield and an excellent er (**5b**, 70%, 97:3 er). Methyl substitution at the methylene bridge in **4c** is also well-tolerated (**5c**, 73%, 93:7 er), which means that five contiguous stereocenters have been successfully desymmetrized, and further creating a sixth (see also **5g**). Acid sensitive acetal functionality and chlorides are well-tolerated (**5a**, 80%, 92:8 er; **5a′**, 65%, 90:10 er), but more importantly, unprotected ketone functionality does not interfere with the reaction, with **4d** and **4e** furnishing the desired conjugate addition products **5d** (68%, 94:6 er) and **5e** (72%, 92:8 er), respectively, in good yields and enantiomeric ratios.

So far, dichloro and diphenyl substitutions at the alkene have been shown to be tolerated well under our original conditions A, regardless of substitution at the bridgehead or methylene bridge positions. Tetramethyl-substituted Diels–Alder adduct

Scheme 2. Substrate Scope of Polycyclic Cyclohexenediones



[a]Isolated yield; dr of >20:1; er determined by CSP-HPLC. [b]On a 0.1 mmol scale. [c]At 30 °C. [d]$Pd(OAc)_2$ (10 mol %) and ^{t}BuPyOx **L-A** (11 mol %). [e]5-CF_3-^{t}BuPyOx **L-B** (6 mol %), on a 0.05 mmol scale. [f]4-CF_3-^{t}BuPyOx **L-C** (6 mol %). [g]**6h** is the oxidative Heck product. [h]1,10-Phenanthroline as the ligand.

4f, however, performs sluggishly under these optimized conditions, albeit with a very good er (**5f**, 43%, 97:3 er; see the Supporting Information for optimization). At this point, we decided to investigate more typical conjugate addition conditions[4b] (conditions B). It was found that conditions B worked well to furnish **5f** and **5g** in 68% and 64% yields, respectively, with a good 95:5 er.

The behavior of the Diels–Alder adduct of benzoquinone and anthracene **4h** was very different from that of substrates **4a–g** under optimized conditions A, yielding an inseparable mixture of oxidative Heck (**6h**) and conjugate addition (**5h**) products (91:9 **6h**:**5h**). Thus far, substrate **4h** is the only one to produce any oxidative Heck product **6** (*vide infra*). However, under more typical conjugate addition conditions B, conjugate addition product **5h** is furnished exclusively (65%, 85:15 er). Unexpectedly, neither conditions A nor conditions B could afford desired product **5i** from the less substituted substrate **4i** (see the Supporting Information). We postulate that the presence of the less substituted alkene (cf. **4a–h**) at

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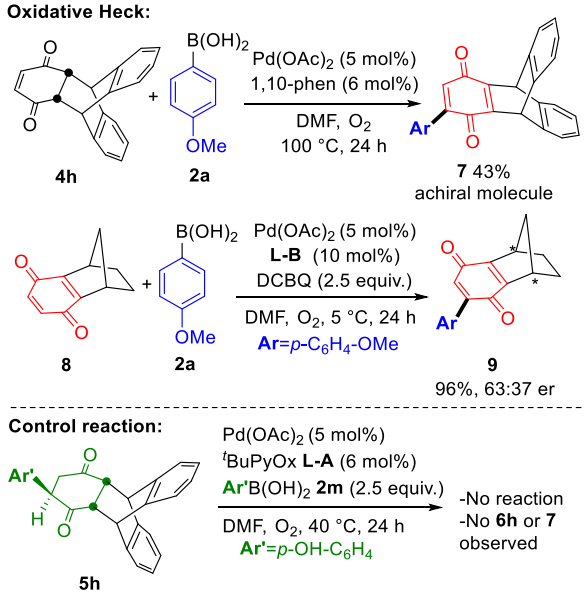
the far end of the molecule is interfering with the catalytic cycle, potentially causing the substrate to act as a bidentate diene ligand for Pd(II) (see the Supporting Information). The Diels–Alder adduct of benzoquinone and phencyclone **4j** also fails to form any desired product **5j**, although this could be attributed to the very poor solubility of **4j**.

A 1 mmol scale reaction to produce **5e** under the exact same conditions demonstrates that the reaction is scalable, albeit with a slight decrease in yield compared to that of the small scale reaction (60% and 93:7 er vs 73% and 92:8 er).

Because **4h** is the only substrate of those screened to show any sign of oxidative Heck product **6h** under what would typically be considered oxidative Heck conditions (conditions A, inseparable 9:91 **5h**:**6h** mixture), we were keen to investigate whether the reaction could be pushed to yield solely oxidative Heck product **6h**. While higher temperatures were found to favor oxidative Heck over conjugate addition, *in situ* dehydrogenation[17] of **6h** to form benzoquinone **7** was also favored at higher temperatures. Thus, benzoquinone **7** (which is, unfortunately, achiral)[18] is the sole observable product at 100 °C (Scheme 3). It should be noted that resubjecting

Scheme 3. Oxidative Heck to Benzoquinones 7 and 9 and Control Reaction

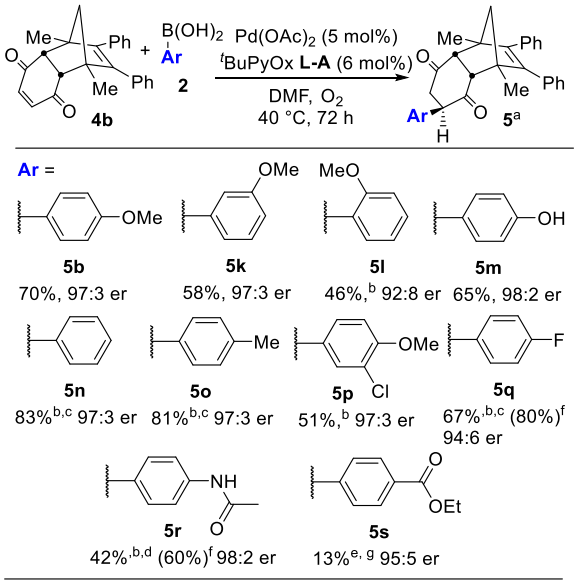


conjugate addition product **5h** to reaction conditions A results in recovered **5h** and no oxidative Heck product **6h** or benzoquinone **7** (Scheme 3). This control reaction indicates that oxidative Heck product **6h** observed in Scheme 2 is not the result of dehydrogenation of **5h** but a true oxidative Heck reaction from **4h**.

For comparison, a benzoquinone[19,20] substrate **8** was also found to form chiral benzoquinone product **9**.[21] In this case, oxidative Heck coupling successfully occurs to form **9** in an excellent 96% yield but with a poor 63:37 er.[22] It is interesting to note that the ease of reacting **8** compared to **4i** indicates that the alkene in **4i** is indeed most likely responsible for its nonreactivity (*vide ante*).[23] Benzoquinone substrate **8** is more planar and less puckered compared to related enediones **4a–g**, and the relative accessibility of the *endo* face in **8** may potentially account for the disparity in enantiomeric ratios.

Next, the arylboronic acid scope was investigated (Scheme 4). The results for **5b** (*para*, 70%, 97:3 er), **5k** (*meta*, 58%, 97:3 er), and **5l** (*ortho*, 46%, 92:8 er) show a clear trend based on sterics, with the *ortho*-substituted arylboronic acid reacting most sluggishly (**5l**), although only a slight drop in er is observed (92:8 vs 97:3). The unprotected hydroxyl group is also compatible under these conditions (**5m**, 65%, 98:2 er). Phenyl- and *p*-tolylboronic acids both furnished desired products **5n** and **5o** in good yields and excellent enantiomeric ratios (83% and 81%, respectively, 97:3 er). Electron-withdrawing halogens are tolerated in the reaction, with *m*-chloro-*p*-methoxy-phenylboronic acid and *p*-fluorophenylboronic acid furnishing **5p** (51%, 97:3 er) and **5q** (67%, 96:4 er), respectively. *p*-Amidophenylboronic acid reacted more sluggishly (**5r**, 42%), although the er of 98:2 is excellent. Increasing the electron-withdrawing substituent from *p*-F to *p*-ethoxyester caused a decrease in reactivity (**5s**, 13%) but still gave a good er of 95:5. Although the reactivity shows some sensitivity to the sterics and electronics of the arylboronic acids, enantiomeric ratios remain very good throughout.

Scheme 4. Arylboronic Acid Substrate Scope



[a]Isolated yields; dr of >20:1; er determined by CSP-HPLC. [b]$Pd(OAc)_2$ (10 mol %) and **L-A** (11 mol %). [c]Increased catalyst and ligand loading to promote full conversion to product due to co-elution with the starting material during column chromatography. [d]Reacted for 92 h. [e]Portionwise addition of catalyst and ligand at 5/6 mol % at the start and then a further 5/6 mol % after 24 h. [f]Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [g]Reacted at 50 °C.

The absolute stereochemistry of the conjugate addition products was determined through single-crystal X-ray crystallography of compound **5a** (see the Supporting Information).[24] The dr is excellent throughout (>20:1) for **4a–h**, presumably because the aryl prefers to be delivered from the less hindered *exo* face. According to literature reports, the migratory insertion step is enantio-determining and the aryl group transmetallates *trans* to the *tert*-butyl group of the chiral oxazoline ligand to avoid steric hindrance.[25] On the basis of these assumptions, a model for asymmetric induction **TS-A** is shown in Figure 1. Of the two possible *trans* approaches

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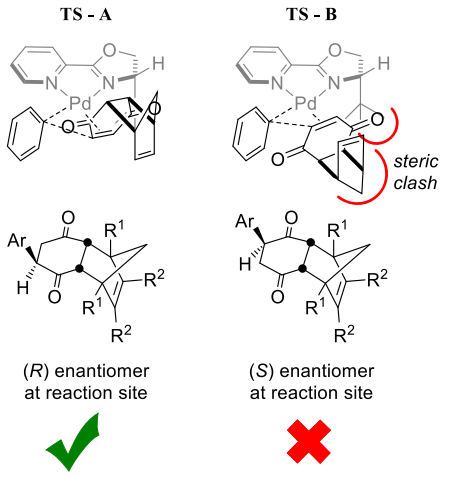
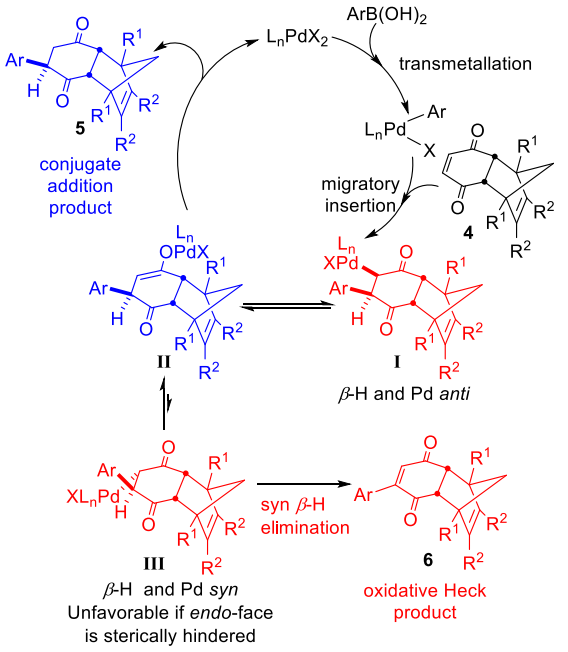


Figure 1. Postulated model for asymmetric induction (substituents omitted for the sake of clarity).

shown, only **TS-A** gives the correct enantiomer. **TS-B** is presumably unfavorable due to steric hindrance between the top of the bicyclic bridge and the *tert*-butyl group of the chiral ligand. **TS-A** avoids this steric clash and results in the observed *R* geometry.

The postulated mechanism for oxidative Heck versus conjugate addition reaction is shown in Scheme 5,[3] which

Scheme 5. Plausible Mechanism for Pd(II)-Catalyzed Conjugate Addition versus Oxidative Heck



may provide insight into why only conjugate addition products are observed for **4a−g**, even under typical oxidative Heck conditions, while **4h** and **8** are the only substrates to show any oxidative Heck products. Following transmetalation and migratory insertion, Pd-enolate intermediate **I** has the *β*-H *anti* to Pd (for cyclic substrates), so *syn*-*β*-H elimination cannot immediately occur. To access oxidative Heck product **6**, conditions that promote isomerization of the Pd-enolate **I** → **II** → **III** are presumably necessary, to place the *β*-H *syn* to Pd, for the desired *syn*-*β*-H elimination to take place. Should isomerization of **I** to **III** be unfavorable, then the competing protonolysis to form conjugate addition product **5** will dominate. However, placing the Pd in the sterically hindered *endo* face in **III** is presumably very unfavorable for tricyclic systems **4a−g** (compared to monocyclic systems such as **1**), which may explain why these substrates form only conjugate addition product **5**. Benzoquinone **8**, however, has a much more accessible *endo* face, so placement of Pd in its *endo* face (**III**) is much more favorable, thereby allowing for oxidative Heck couplings. By the same argument, substrate **4h**, with its unique tricyclic core structure (cf. **4a−g**), is thought to exhibit oxidative Heck reactivity due to the more favorable isomerization to **III**.

In conclusion, we have developed the first Pd(II)-catalyzed intermolecular conjugate addition desymmetrization reaction. Desymmetrization of *meso* polycyclic cyclohexenediones **4** via a conjugate addition reaction furnishes up to five contiguous stereocenters while also creating an additional stereocenter in one efficient step, in up to 98:2 er and >20:1 dr. Surprisingly, only conjugate addition product **5** is observed for substrates **4a−g** even under typical oxidative Heck reaction conditions, while oxidative Heck is observed with substrates **4h** and **8**. The observed trend is thought to be due to steric hindrance in the *endo* face of **4a−g** disfavoring the necessary Pd-enolate isomerization step (**I** to **III**) required for the oxidative Heck process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03293.

Optimization studies, all experimental details, characterization, and copies of NMR data (PDF)

Accession Codes

CCDC 1946937 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) We have previously found that polar aprotic solvents tend to promote the Pd(II)-catalyzed oxidative Heck reaction while chlorinated solvents such as DCE are typically used to promote the conjugate addition reaction. See refs 3 and 4 versus ref 5.

(16) While the conjugate addition reaction does not technically require any oxidant, Pd(II)-catalyzed oxidative side reactions such as homocoupling of **2** and phenol formation from **2** form Pd(0). While these side reactions typically only occur in <10% combined yields, running the reaction in O_2 is thought to help by reoxidizing any Pd(0) formed via these side reactions back to the active Pd(II) catalyst.

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(21) Benzoquinones can act as an oxidant to Pd(0) and thus be reduced to the corresponding hydroquinones; DCBQ is therefore added as an oxidant in this case.

(22) With ligand **A**, **9** is formed in 52% yield and 66:34 er. See the Supporting Information for studies of the optimization of **8**.

(23) Attempts were made to selectively reduce the more electron rich alkene in **4i**, but these were not successful.

(24) All other absolute stereochemistry assignments are by analogy.

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