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Palladium Catalyzed Stereoselective Arylation of Biocatalytically Derived Cyclic 1,3-Dienes: Chirality Transfer via a Heck-Type Mechanism

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ABSTRACT: Microbial arene oxidation of benzoic acid with Ralstonia eutropha B9 provides a chiral highly functionalized cyclohexadiene, suitable for further structural diversification. Subjecting this scaffold to a Pd-catalyzed Heck reaction effects a regio- and stereoselective arylation of the cyclohexadiene ring, with 1,3-chirality transfer of stereogenic information installed in the microbial arene oxidation. Quantum chemical calculations explain the selectivity both by a kinetic preference for the observed arylation position and by reversible carbopalladation in competing positions. Further product transformation allowed the formation of a tricyclic ketone possessing four stereogenic centers. This demonstrates the capability of the method to introduce stereochemical complexity from planar nonchiral benzoic acid in just a few steps.

The biocatalytic transformation of arenes into dearomatized cis-dihydroxylated species can be achieved using arene dioxygenase enzymes via microbial arene oxidation (MAO).1 While complete oxidation affords a catechol, the use of mutant strains2 or recombinant organisms3 allows isolation of the intermediate chiral diol, enabling conversion of a flat arene into a chiral functionalized scaffold, suitable for further transformations. Many dioxygenase enzymes are known and generally lead to ortho/meta dihydroxylation with respect to pre-existing functionality.4 However, benzoate dioxygenase (BZDO), expressed by R. eutropha B9,5 transforms benzoic acid with complementary selectivity, affording ipso/ortho dihydroxylated product 1 as a single enantiomer (Scheme 1a). Compound 1 has been subjected to various transformations such as oxidations and acetalization6 and been used for preparing natural products7 and pharmaceuticals.8 One diversification approach could involve metal-catalyzed cross-coupling of the diene sp2-carbons.9 The Mizoroki−Heck reaction10 allows arylation of an alkene under Pd-catalysis and can potentially lead to chirality transfer from one ring carbon to another. Such chirality transfer has been demonstrated in the synthesis of C-glycosides,11 where the coupling effects a double bond migration and 1,3-chirality transfer (Scheme 1b). However, achieving selectivity with a diene such as 1 could be challenging. Studies of Pd-catalyzed reactions involving substrates obtained via MAO are limited,6c,12 and to the best of our knowledge, Heck arylation of 1 and its derivatives has not been described. Furthermore, this type of chirality transfer in intermolecular Heck reactions has not been investigated to any great extent outside of glycal arylations. We herein report...
our findings concerning the conversion of esters and amides, obtained from 1, into chiral arylated 1,4-dienes such as 3 (Scheme 1c). A quantum chemical study was also conducted to elucidate the origin of the high selectivity.

**Results and Discussion.** Ester 2a (Table 1), with an acetal protected cis-diol, was chosen as a suitable substrate and was subjected to Pd-catalyzed arylation with iodobenzene. With a diene such as 2a, several products can potentially be formed under these conditions. However, we were gratified to see that using iodobenzene, Pd(OAc)$_2$, and AgOAc in acetonitrile resulted in the completely regio- and diasteroselective arylation of 2a to form diene 3aa in 60% yield (Table 1, entry 1). Through this reaction, stereochemical information initially present in the diol moiety is transferred to a more distal position.

Other bases and silver sources are less effective (entries 2−4), but the amount of silver salt could be reduced to 1.4 equiv, maintaining the same reactivity (entry 5). However, a palladium loading of 10% and 4 equiv of the aryl iodide were necessary for full conversion and a high degree of product formation. A range of phosphine ligands were subsequently screened (entries 6−9), and P((4-CF$_3$)C$_6$H$_4$)$_3$ (entry 9) was identified as most effective. After reassessing the reaction conditions, the use of P((4-CF$_3$)C$_6$H$_4$)$_3$ allows the palladium and ligand loading to be reduced to 5% and 10%, respectively, while maintaining comparable reactivity (entry 10; see Supporting Information (SI) for full optimization).

With the optimized conditions in hand, we investigated the scope of arylation reagents using ester 2a (Scheme 2). Aryl iodides with electron-rich or -neutral substituents at the para position perform comparably well, providing the arylated products in good yields (compounds 3aa−3ad). Electron-deficient arenes afford products in somewhat lower yields (3ae−3af). Notably, 1-bromo-4-iodobenzene reacts selectively at the Ar−I bond, producing 66% of 3ae. Different substitution patterns on the aryl ring are also tolerated with 2- or 3-substituted aryl iodides (3af−3am). In terms of limitations, certain functional groups are not tolerated on the aryl iodide, including aldehyde, phenol, and amine. Whereas indole can be coupled to the 7-position (3am), other heterocyclic aryl iodides are unsuccessful. Likewise, other aryl halides or pseudohalides do not react under these conditions. A crystal structure of compound 3ah (Figure 1) verifies this structure unequivocally.

We next investigated the scope of the starting diene. In addition to ester 2a, amides and secondary esters perform well, affording 3ba−3db in good yields (Scheme 3). Furthermore, a Weinreb amide, as in 3eb, could be applied and is potentially useful for postfunctionalization. Substrates 1 and 4−6 were also tested but did not afford arylated products.

### Table 1. Optimization of the Pd-Catalyzed Arylation of 2a with Iodobenzene

| entry | base base (equiv) | additive | 3aa (%)$^b$ |
|-------|-------------------|----------|-------------|
| 1     | AgOAc 2           | −        | 60          |
| 2     | NaOAc 2           | −        | 24          |
| 3     | DIPEA 2           | −        | 34          |
| 4     | Ag$_2$CO$_3$ 2    | −        | 18          |
| 5     | AgOAc 1.4         | −        | 61          |
| 6     | AgOAc 1.4 PPh$_3$| 70       |
| 7$^c$| AgOAc 1.4 dppe    | 70       |
| 8     | AgOAc 1.4 P(OEt)$_3$| 64     |
| 9     | AgOAc 1.4 P((4-CF$_3$)C$_6$H$_4$)$_3$| 78       |
| 10$^d$, $^e$| AgOAc 1.4 P((4-CF$_3$)C$_6$H$_4$)$_3$| 80       |

$^a$Performed under reflux conditions in a Carousel 12 Plus Reaction Station from Radleys, using a metal heating block. $^b$NMR yield. $^c$10 mol % dppe. $^d$5 mol % Pd(OAc)$_2$. $^e$10 mol % P((4-CF$_3$)C$_6$H$_4$)$_3$. $^f$Performed in a Carousel 12 Plus Reaction Station from Radleys, using a metal heating block. NMR yields (isolated yields in parentheses). Products formed with complete diastereoselectivity.
We subsequently explored further synthetic transformations of products 3. Cleavage of the acetal in 3ba and 3bf, using CF₃COOH, afforded ketones 7ba and 7bf in high yields (Scheme 4, route A). Compound 7bf, containing a ketone and a proximal ester group, could potentially undergo an intramolecular Claisen condensation, and this feature was investigated. Treating 7bf with NaOMe in methanol led to the formation of aromatized fluorenone 8 in 71% yield, following elimination of H₂O. While this demonstrates the applicability of these products as enolates, valuable stereochemical information is lost here. To explore other possibilities, we subjected 3bi, with two acetal functionalities, to acidic conditions, envisaging that both groups could be deprotected in one step (Scheme 4, route B). A subsequent acid-catalyzed aldol reaction could then result in a cyclized product. We were delighted to see that the use of p-TsOH in wet acetonitrile led to the formation of tricyclic compound 9. Remarkably, this product, which contains four stereogenic centers, forms with complete diastereoselectivity. This reaction demonstrates that our method can be utilized to build up significant molecular complexity from a flat achiral starting material, benzoic acid.

In order to explain the high regioselectivity and facial selectivity of the transformation, we have performed a quantum chemical study, relying on Density Functional Theory (DFT) calculations. Our calculations, which were done with Gaussian16,13 were mostly performed at the B3LYP-D3/def2-TZVP//def2-SVPD level of theory. The Solvent Model Density (SMD) method was used to include implicit consideration of acetonitrile solvation effects.14 More details of the calculations are given in the Supporting Information. The B3LYP-D3 functional has a reported mean average deviation from CCSD(T)/CBS results of 1.6 and 2.3 kcal/mol for barrier heights and reaction energies, respectively, in a selection of Pd-catalyzed reactions.15 The method has also previously been used to model Heck reactions.16

The formation of 3aa, without phosphine ligands, was chosen as a model system for our calculations (Table 1, entry 5). Because the experimental reaction was performed with a silver additive in a polar solvent, a fast halide abstraction from palladium was assumed. In other words, all structures were modeled using acetate and acetonitrile ligands. An extensive screening of migratory insertion transition states and their conformational space was conducted (see SI). Transition state structures (TS1–TS8) for the eight possible arylation pathways are shown in Figure 2. For each possibility, the complexes are depicted in their lowest energy ligand conformations. The lowest energy pathway, TS1 (see SI, Figure S86), leads to C–C bond formation in the C-4 position,
on the face anti to the acetone moiety. It corresponds well to previously reported Heck-type migratory insertion transition states, with an almost fully formed Pd–C bond along with a developing C–C bond. Our calculations predict that TS1 is favored by 1.8 kcal/mol over the second lowest, TS2 (Figure 2). The predominance of TS1 in determining the reaction outcome agrees well with our experimental results, in which 3aa is the only observed Heck product. In addition to TS2, other transition states near in energy to TS1 might contribute under our experimental conditions. These are TS3, predicted to lie 2.1 kcal/mol higher than TS1, as well as TS4 and TS5, higher by 2.3 and 2.4 kcal/mol, respectively.

The insertion products following TS1, TS2, and TS3 all correspond to structures with palladium bound to an sp³-carbon. These structures, IN1, IN2, and IN3, are all relatively close in energy, with IN2 somewhat less stable, possibly due to steric effects from installing the palladium syn to the acetone. Insertion product IN5 is different and is significantly more stable compared to IN1-3. The difference can be explained as a result of the formation of a palladium π-allyl system. The insertion products IN2 and IN3 do not have any available β-hydrogens, and therefore both lack obvious forward reaction paths toward a Heck-type product (the same holds true for the insertion product following TS4).

One possibility in the absence of β-hydrogens is a reverse carbopalladation. In a Heck-type reaction, the migratory insertion is generally viewed as irreversible; however, there are known examples of β-carbon elimination when no β-hydrogens are available. We have estimated the backward reaction barriers for migratory insertion products IN2 and IN3 to ∼21 kcal/mol and ∼26 kcal/mol, respectively. These barriers imply that such processes are accessible under the experimental conditions. Therefore, if formed, the formation of IN2 and IN3 should be reversible, and these should be able to proceed to Heck-product 3aa. With a backward reaction barrier of ∼33 kcal/mol, the formation of IN5 is irreversible.

In contrast to IN2 and IN3, intermediate IN1 possesses a hydrogen in a syn orientation with respect to the palladium. As expected, a β-hydride elimination is predicted to follow. The β-hydride elimination forming product 3aa was computed to have a barrier of 16 kcal/mol (TS9). In accordance with the increased stability of the π-allyl system, the barrier for β-hydride elimination in IN5 (TS10) was calculated to be 26 kcal/mol, which should be attainable under the experimental conditions. If formed, IN5 should proceed to form Heck-product 10 (Figure 2).

Conclusions. We here present a methodology for Pd-catalyzed diastereoselective arylation of dienes derived from...
enzymatic cis-dihydroxylation of benzoic acid. This approach allows for a chirality transfer from the diol moieties of these microbial arene oxidation products to a more distal position, increasing the chiral pool of molecules available by enzymatic dearmatization. The reaction effects coupling of a range of aryl iodides in moderate to excellent yields and selectivity and provides the opportunity to form tricyclic scaffolds via further transformations. A quantum chemical investigation indicates that there is a kinetic preference for arylation in the observed position. Interestingly, it was also found that reversibility in the other accessible carbopalladations might be kinetically relevant for the high selectivity toward the formed Heck product.

**ASSOCIATED CONTENT**

■ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00708.

Experimental procedures and spectroscopic data, and X-ray data for compound 3ah (PDF)

Computational chemistry details (Geometries of all calculated structures are available on ioChem-BD; see http://dx.doi.org/10.19061/iochem-bd-6-23) (PDF)

**Accession Codes**

CCDC 1961899 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 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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