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Enantioselective Heck Arylation of Acyclic Alkenol Aryl Ethers: Synthetic Applications and DFT Investigation of the Stereoselectivity

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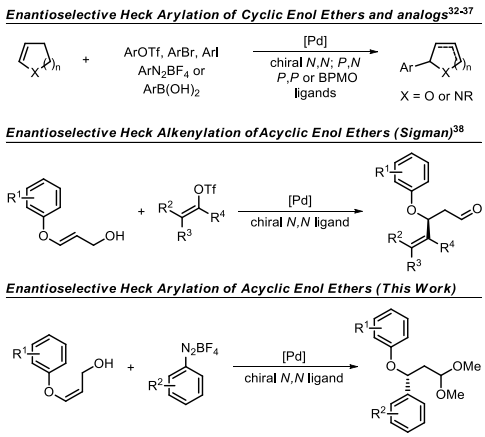
Abstract. Herein we report the enantioselective Heck-Matsuda arylation of acyclic *E* and *Z*-alkenyl aryl ethers. The reactions were carried out under mild conditions affording the enantioenriched benzyl ethers in a regioselective manner, moderate to good yields (up to 73%), and in good to excellent enantiomeric ratios (up to 97:3). The enantioselective Heck-Matsuda arylation has shown a broad scope (25 examples), and some key Heck-Matsuda adducts were further converted into more complex and valuable scaffolds including their synthetic application in the synthesis of (*R*)-Fluoxetine, (*R*)-Atomoxetine, and in the synthesis of an enantioenriched benzo[*c*]chromene. Finally, *in silico* mechanistic investigations into the reaction's enantioselectivity were performed using density functional theory.

Keywords: Asymmetric catalysis; Heck reaction; *N*,*N*-ligand; Homogeneous catalysis; Density functional calculations

Introduction

The palladium-catalyzed enantioselective Heck reactions are among the most versatile synthetic methods for the construction of stereogenic centers in organic compounds. In particular, Heck arylations have been instrumental in the synthesis of valuable novel materials, including new medicines and fine chemicals, constituting the activity of intense research interest worldwide.[1–5] Recent developments in the enantioselective Heck arylations have focused mostly on the use of chiral bisphosphine monoxides (BPMO),[6] *P*,*N*-ligands, *N*,*N*-ligands,[7] and phase-transfer chiral counterions,[8,9] although the popular bidentate phosphines are still commonplace.[10,11] Additionally, the introduction of selectivity-inducing strategies, such as the use of redox relay,[12–25] and directing groups have also greatly improved and extended the scope of this reaction.[26–31] However, in spite of its tremendous success involving nonactivated and cyclic electron-rich alkenes, the effective arylation of acyclic electron-rich alkenes has been lagging behind significantly. Among the cyclic activated alkenes that can be employed in enantioselective Heck reactions, it includes tetrahydropyrans, dihydrofurans, endocyclic enecarbamates, and enelactams.[32,33] Enantioselective arylations on these systems rely basically on the use of BPMO ligands both with aryl triflates and halides,[33,34] aryl boronic acids and N,N ligands,[35] or, to a lesser extent, diazonium salts and *N*,*N*-ligands.[36,37] Recently, an efficient palladium-catalyzed enantioselective Heck alkenylation of acyclic aryl enol ethers using alkenyl triflates was reported by Sigman and coworkers (Scheme 1a).[38] Despite holding considerable synthetic potential, to the best of our knowledge, the enantioselective Heck arylation of similar substrates has been attempted only recently, leading to modest results.[39] Herein, we report our investigations in this direction using arenediazonium salts (Heck-Matsuda reaction)[40–42] and chiral *N*,*N*-ligands. Critical to the success of this endeavor was the use of methanol both as a reaction solvent and protecting agent of the *β*-aryloxy aldehydes Heck products.



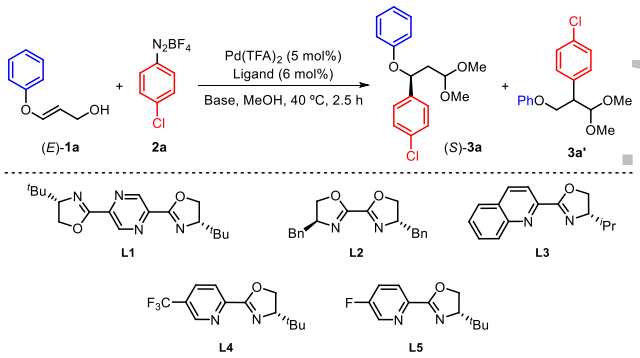
Scheme 1. Enantioselective Heck reactions of enol ethers and analogs.

Results and Discussion

We started our investigation with the Heck-Matsuda arylation of (*E*)-alkenyl phenyl ether **1a** using the 4-chlorophenyldiazonium salt **2a** (a readily available and very stable aryldiazonium salt) and our previously reported reaction conditions for similar Heck-Matsuda reactions (Table 1),[15] i.e., $Pd(TFA)_2$ as the palladium source in combination with the pyrazine-bisoxazoline ligand, (*S*)-PyraBox **L1**, basic zinc carbonate as base and methanol as a solvent at 40°C (entry 1, Table 1). From the outset of our studies, we envisioned the potential *β*-elimination of the expected *β*-aryloxy aldehyde as a critical issue, and we, therefore, reasoned that trapping the aldehyde in situ with methanol could be a convenient way to circumvent the aforementioned problem.[25] These initial conditions gave the desired regioisomeric Heck product (*S*)-**3a** in a modest 38% yield in a good enantiomeric ratio (e.r.) of 91:9. As expected, the aldehyde functionality formed after the redox relay process was smoothly converted into the corresponding dimethyl acetal under the reaction conditions. Due to the polar nature of the Heck-Matsuda arylation and the electronics of the alkenyl phenyl ether, the regioselectivity of the Heck reaction was expected to be high in favour of the *β* arylation. However, ^{1}H NMR of the crude reaction mixture indicated formation of a thermally unstable regioisomeric Heck product. We were unable to isolate and fully characterise the product obtained from arylation at the *α*-position, possibly due to its degradation during flash chromatography. Nevertheless, its structure was tentatively assigned by NMR analysis of the crude reaction mixtures (see SI). Screening of bases using $CaCO_3$, $ZnCO_3$ or DTBMP did not improve the yields (entries 2−4, Table 1), or the enantiomeric ratios. We then evaluated different chiral N,N ligands. The (*S*)-Box **L2** increased the yield of the product (*S*)-**3a** to 46% and improved the e.r. to 94:6 (entry 5, Table 1). (*S*)-QuinOx **L3** afforded the desired Heck product in 57% yield, but with the e.r. dropping drastically to a nearly racemic product (entry 6, Table 1). (*S*)-PyOx ligands **L4** and **L5** afforded (*S*)-**3a** in only modest yields and e.r. (entries 7 and 8, Table 1).

As shown in Table 1, the regioselectivity of the arylation was highly dependent on the reaction conditions. While changes on the base provided only minor differences in its regioselectivity, different ligands occasionally led to opposite regioselectivities.

Table 1. Evaluation of Heck arylation of (*E*)-**1a**[a]



Entry	Ligand	Base	(*S*)-3a[b]	e.r.[c]	r.r.[d]
1	L1	[f]	38	91:9	1:1.3
2	L1	$CaCO_3$	21	89:11	1:1.5
3	L1	$ZnCO_3$	24	92:8	1:2
4	L1	DTBMP	36	90:10	1:1.4
5	L2	[f]	46 (25[e])	94:6	2:1
6	L3	[f]	57	44:56	2:1
7	L4	[f]	34	86:14	1:1.5
8	L5	[f]	53	62:38	1.2:1

[a] Reaction conditions: (*E*)-**1a** (0.10 mmol), **2a** (0.20 mmol), $Pd(TFA)_2$ (5 mol%), ligand (6 mol% for **L1**; 12 mol% for **L2**−**L5**), base (0.01 mmol for $[ZnCO_3]_2[Zn(OH)_2]_3$, 0.11 mmol for $CaCO_3$ and DTBMP, and 0.05 mmol for $ZnCO_3$), MeOH (1.0 mL). [b] (%) Yield determined by ^{1}H NMR of the crude mixture using 3,5-bis(trifluoromethyl)bromobenzene as internal standard. [c] Enantiomeric ratio (e.r.) determined by chiral supercritical fluid chromatography (SFC) analysis of purified **3a**. [d] Regioisomeric ratio (r.r.) determined by ^{1}H NMR of the crude mixture. [e] 0.30 mmol scale; isolated yield. DTBMP = 2,6-Di-*tert*-butyl-4-methylpyridine. [f] $[ZnCO_3]_2[Zn(OH)_2]_3$.

To extend our studies and to get a better understanding of the arylation process, we prepared the (*Z*)-alkenol **1a** and submitted it to the same reaction conditions as above (Table 2). Gratifyingly, the *Z*-alkenol led not only to the Heck product with the opposite sense of chirality (*R*)-**3a** but also with an improved yield of 55% and an excellent e.r. of 95:5 using **L1** as ligand and $CaCO_3$ as base (entry 1, Table 2). Screening of bases showed that basic zinc carbonate, zinc carbonate, and DTBMP had a worse performance as compared to calcium carbonate regarding both yields and e.r.'s (entries 2−4, Table

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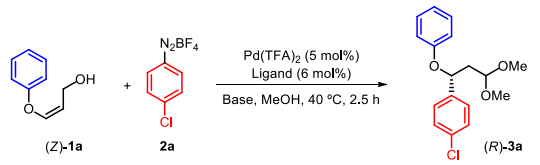
2). Bisoxazoline ligand **L2,** which had the best performance for (*E*)-**1a** proved unsuitable in this case, as both yield and er dropped significantly (entry 5, Table 2). Quinoline-oxazoline ligand **L3** furnished (*R*)-**3a** in a good yield of 60%, but in a racemic form (entry 6, Table 2). Ligands **L4** and **L5** provided lower yields and e.r. of the Heck product (entries 7-8, Table 2). $Pd(OAc)_2$ and $Pd_2(dba)_3$ gave similar results to $Pd(TFA)_2$ with slightly lower yields and e.r. (entries 9-10, Table 2). Finally, the olefin to aryldiazonium salt ratio was changed from 1:2 to 2:1, furnishing (*R*)-**3a** in good yield but with lower e.r. (entry 11, Table 2).

From the regioselectivity point of view, alkenol (*Z*)-**1a** favoured the desired regioisomer (*R*)-**3a**. The highest regioisomeric ratio was obtained only with an excess of the olefin (entry 7, Table 2), with a slight decrease in the enantiomeric ratio (compare with entry 1, Table 2). A few tests involving other solvents, such as dioxane, acetonitrile and dimethylcarbonate, together with a mixture of these solvents with 5% of MeOH, led to a reaction mixture containing up to 30% of the corresponding cinnamaldehyde derivative, the product of β-aryloxy elimination (see SI for details).

Table 2. Evaluation of Heck arylation of (*Z*)-**1a**[a]



Entry	Ligand	Base	3a[b]	e.r.[c]	r.r.[d]
1	**L1**	$CaCO_3$	55 (49[e])	95:5	3.8:1
2	**L1**	[i]	51	92:8	2.6:1
3	**L1**	$ZnCO_3$	30	93:7	1.4:1
4	**L1**	DTBMP	34	93:7	2.3:1
5	**L2**	$CaCO_3$	27	76:24	2.7:1
6	**L3**	$CaCO_3$	60	50:50	3.4:1
7	**L4**	$CaCO_3$	28	92:8	1.5:1
8	**L5**	$CaCO_3$	29	61:39	1.4:1
9[f]	**L1**	$CaCO_3$	49	92:8	3.7:1
10[g]	**L1**	$CaCO_3$	54	90:10	3.5:1
11[h]	**L1**	$CaCO_3$	55	90:10	5.7:1

[a)] Reaction conditions: (*Z*)-**1a** (0.10 mmol), **2a** (0.20 mmol), $Pd(TFA)_2$ (5 mol%), ligand (6 mol% for **L1**; 12 mol% for **L2**–**L5**), base (0.01 mmol for $[ZnCO_3]_2[Zn(OH)_2]_3$, 0.11 mmol for $CaCO_3$ and DTBMP, and 0.05 mmol for $ZnCO_3$), MeOH (1 mL). [b)] (%) Yield determined by ^{1}H NMR of the crude mixture using 3,5-bis(trifluoromethyl)bromobenzene as internal standard. [c)] Enantiomeric ratio (e.r.) determined by SFC analysis of purified **3a**. [d)] Regioisomeric ratio (r.r.) determined by ^{1}H NMR of the crude mixture. [e)] 0.30 mmol scale; isolated yield. [f)] $Pd(OAc)_2$ (5 mol%) was used as the palladium source. [g)] $Pd_2(dba)_3$ (2.5 mol%) was used as the palladium source. [h)] (Z)-**1a** (0.20 mmol) and **2a** (0.10 mmol) were used. [i)] $[ZnCO_3]_2[Zn(OH)_2]_3$.

With established conditions in hand, we moved on to investigate the reaction scope of the olefin (*Z*)-**1a** as substrate with different arenediazonium salts, in order to gain insight into the effect of the different electronics on the outcome of the reaction (Table 3). During this study, we noticed that the reaction time was critical in order to convert the aldehyde, the redox-relay Heck product, into the corresponding dimethylacetal derivatives. *Para*-chloro, -bromo and -fluoro arenediazonium salts afforded the desired arylated products **3a**, **3b,** and **3c** in moderate yields and excellent enantiomeric ratios (95:5; 95:5; and 94:6 respectively). *Meta*- and *ortho*-bromophenyldiazonium salts gave the corresponding **3d** and **3e** products in good yields and excellent e.r. (95:5 and 94:6 respectively). Arenediazonium salts containing a trifluoromethyl group in the *para* or *meta* positions, as well as a nitro group in the *ortho* position also proved efficient to produce the corresponding arylated compounds **3f**, **3g,** and **3h** in good yields and excellent e.r. (95:5; 94:6; and 95:5 respectively). Electron-donating groups on the arenediazonium salt were met with a decrease in the yield as shown for **3i** containing a 3,4,5-trimethoxy substitution pattern, nevertheless the e.r. was still a good 92:8. In contrast, a single methoxy group in the *ortho* position of the diazonium salt furnished the arylated product **3j** in low yield and low e.r. (70:30). Compared with the result obtained with **3h** containing an *ortho*-nitro group, we conclude that the low e.r. observed for **3j** is due to the different electronic properties of the arenediazonium salt. The electronically neutral benzenediazonium salt gave the arylated product **3k** in moderate yield and a good e.r. of 92:8.

The regioselectivity observed on the crude reaction mixture was always in favour of the *β*-arylated product. Just slight differences were observed depending on the electronics of the aryldiazonium salt. Ironically, the fact that the *α*-arylated dimethylacetal product seems to decompose on silica-gel chromatography, eased the purification of the desired products. Moreover, the scope shown in Table 3 demonstrates some bias of the Heck reaction towards electron-deficient aryldiazonium salts.

Table 3. Enantioselective Heck reaction of (*Z*)-**1a** with different arenediazonium salts[a]

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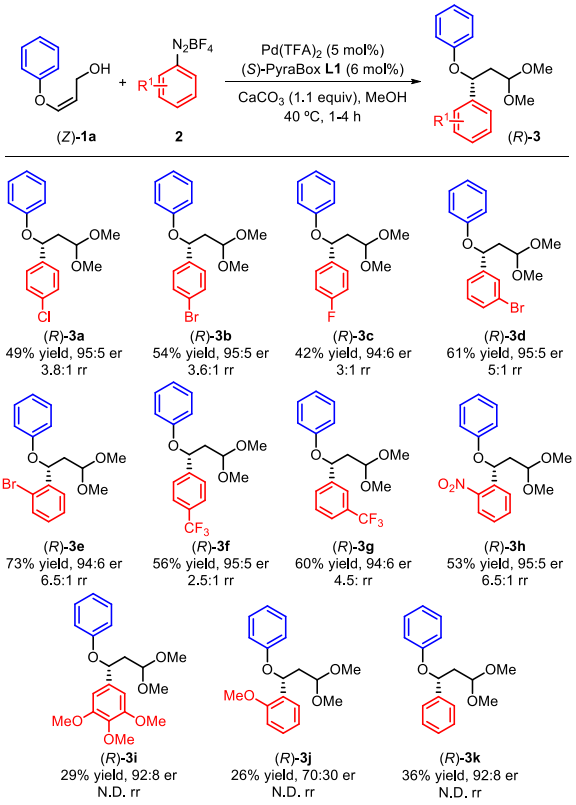
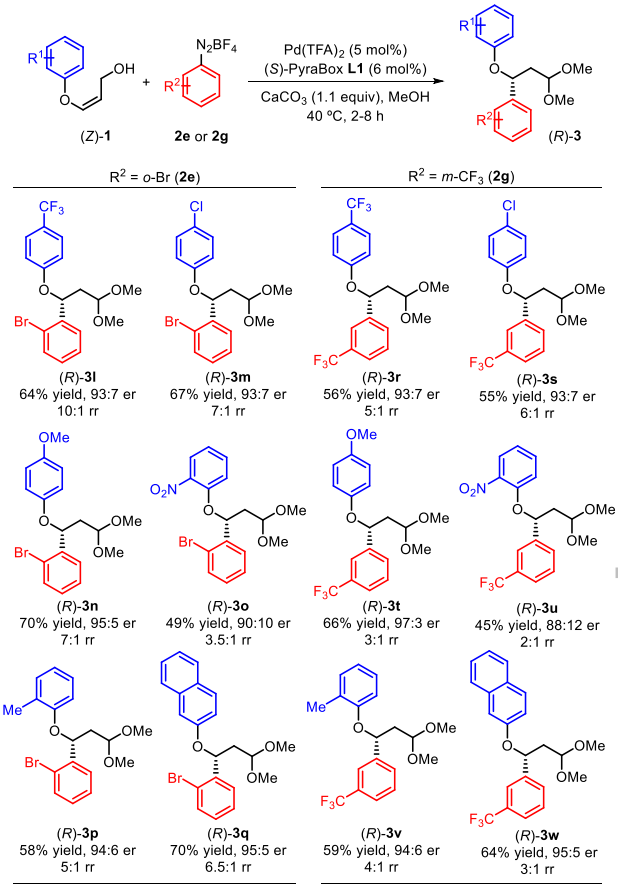


[a] Reaction conditions: (*Z*)-**1a** (0.30 mmol), **2** (0.60 mmol), $Pd(TFA)_2$ (5 mol%), **L1** (6 mol%), $CaCO_3$ (0.33 mmol). Isolated yields and enantiomeric ratios (e.r.) of the (*R*)-**3**, an average of two experiments. Regioisomeric ratio (r.r.) determined by ^1H NMR of the crude reaction mixture.

Next, to investigate the influence of the electronics of the enol ether in the arylation process we investigated the reaction of several phenoxy-substituted (*Z*)-olefins with *o*-bromo and *m*-trifluoromethyl-substituted arenediazonium salts, as these were the ones that performed best with olefin (*Z*)-**1a** (Table 4). Olefins with substituents in the *para* position of the phenoxy group afforded the arylated products in good yields and high e.r., even when different groups were used such as trifluoromethyl (**3l** and **3r**, Table 4), chlorine (**3m** and **3s**) and methoxy (**3n** and **3t**). Strong EWG on the *ortho* position, such as the nitro, led to a slight decrease in the yield and er (**3o** and **3u**). On the other hand, a weak electron-donating group, such a methyl group, on the same position gave the desired products in good yield and high e.r. (**3p** and **3v**). Finally, an olefin derived from *β*-naphthol was also tested furnishing the arylated compounds in good yield and excellent e.r. (**3q** and **3w**).

Table 4. Enantioselective Heck reaction of olefin (*Z*)-**1** derivatives and arenediazonium salts[a]



[a] Reaction conditions: (*Z*)-**1a** (0.30 mmol), **2** (0.60 mmol), $Pd(TFA)_2$ (5 mol%), **L1** (6 mol%), $CaCO_3$ (0.33 mmol). Isolated yields and enantiomeric ratios (e.r.) of the (*R*)-**3**, average of two experiments. Regioisomeric ratio (rr) determined by ^1H NMR of the crude reaction mixture.

Regarding the regioselectivity of the reaction, it can be observed that *o*-bromo-benzenediazonium salt **2e** led to better regioselectivities than *m*-CF_3 benzenediazonium salt **2g**. The worst r.r. was obtained for **3o** and **3u** containing an *o*-nitro group (3.5:1; and 2:1 respectively), whilst the best was **3l** (10:1) for the *o*-bromo-benzenediazonium salt (**2e**) and **3s** (6:1) for *m*-CF_3 benzenediazonium salt (**2g**). Olefins containing opposite electron-demanding groups did not affect the r.r. as much as it would be expected (compare **3l** and **3n**, and **3r** and **3t**). These results clearly show slight higher regioselectivity for olefins containing EWD groups in the aryloxy substituent.

To further extend the method, we evaluated olefins containing a secondary allylic alcohol moiety such as (*E*)-**4** and (*Z*)-**4** (Scheme 2). Surprisingly, the reaction of olefin **4** with arenediazonium salt **2e** under the conditions used in Table 4 failed. However, a simple change of base from $CaCO_3$ to $ZnCO_3$ has allowed the synthesis of arylated methyl ketones **5a** and **5b**, albeit in low yield and in moderate to excellent e.r. (Scheme 2). The enantiomer obtained was highly dependent on the geometry of the double bond of the olefins **4**.

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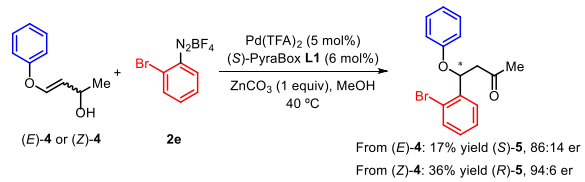
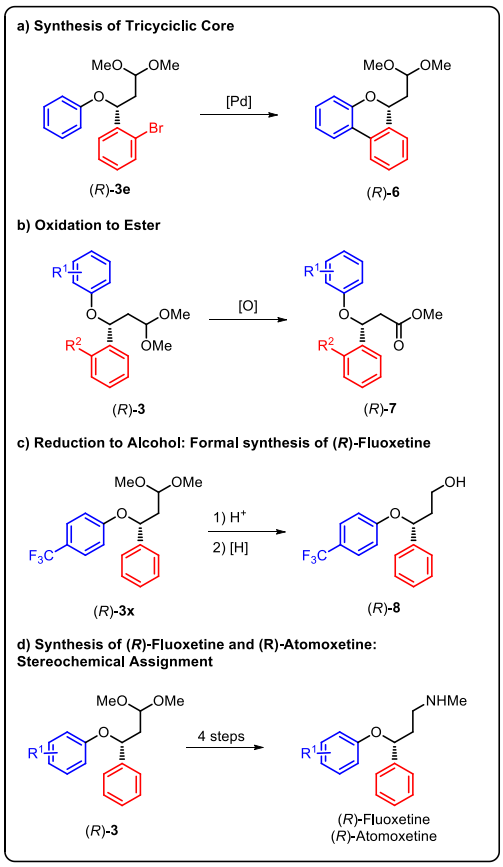


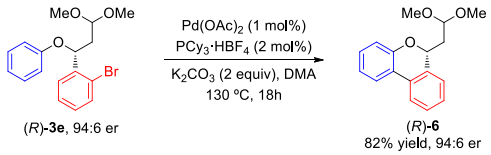
Scheme 2. Enantioselective Heck reactions of (*E*)-**4** and (*Z*)-**4**.

The results obtained above allowed us to envision the synthetic potential of the method toward complex frameworks and pharmacologically active molecules of interest, as summarised in Scheme 3.



Scheme 3. Synthetic application for the Heck arylated product (*R*)-**3**.

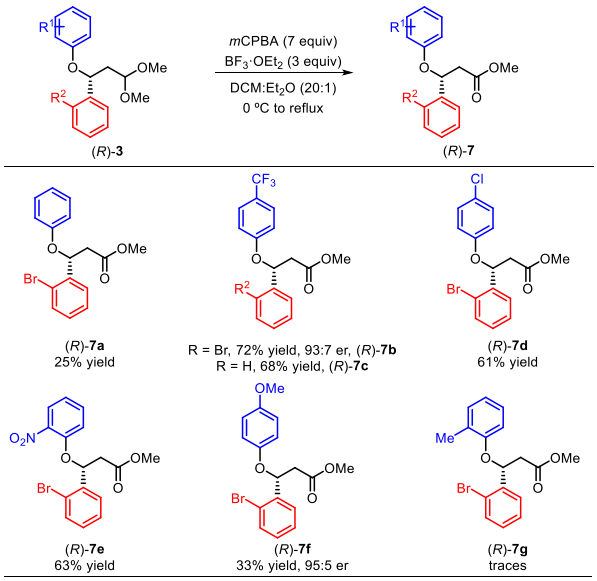
First, we subjected compound (*R*)-**3e** to the method described by Fagnou and collaborators for the intramolecular cyclization by C−H activation.[43] As shown in Scheme 4, the direct intramolecular arylation of (*R*)-**3e** led to compound (*R*)-**6** containing the 6*H*-benzo[*c*]chromene core in excellent yield without any signs of erosion of the enantiomeric ratio.[44,45] It is worth mentioning that this core structure is present in a number of biologically active compounds, such as the cannabinols.[46]



Scheme 4. Synthetic application for the Heck arylated product (*R*)-**3e**.

Next, the dimethyl acetals were converted into the synthetically valuable methyl esters using *m*CPBA/BF_3·OEt_2 (Table 5).[47] For the specific case of our Heck products **3**, this was a challenging transformation due to the liability of *β*–aryloxy esters under Lewis acid conditions. Oxidation of compound **3e** with *m*CPBA led to the corresponding ester **7a** in a modest 25% yield. However, for substrates bearing an electron-deficient aryloxy group, there was a significant increase in yields. Therefore, esters **7b**, **7c**, **7d**, and **7e** bearing a *para*-trifluoromethyl group, *para*-chloro, and an *ortho*-nitro group, good yields of the respective esters were obtained. As expected, the yield dropped significantly for ester **7f** containing a *para*-methoxy group in the aryloxy ring. Ester **7g**, containing an ortho-methyl group in the aryloxy ring was obtained only in trace amounts, together with other by-products. Preparative TLC of the crude reaction mixture allowed us to obtain an analytical sample of ester **7g** for structural characterization. The e.r. of esters **7b** and **7f** were compared to those of the dimethyl acetal substrates and confirmed that this oxidation method did not affect the stereogenic centre formed in the Heck reaction.

Table 5. Oxidation of dimethyl acetals (*R*)-**3** to the corresponding methyl esters (*R*)-**7**.



The lower yields of methyl esters **7** from the dimethyl acetals possessing electron-rich *β*-aryloxy groups is not totally surprising. These groups could easily compete with the dimethyl acetals for the BF_3 Lewis acid during the reaction, leading to *β*-aryloxy elimination and other by-products. The complexity and sensibility of this transformation are clearly demonstrated by the isolation and structure elucidation of its main side product. This was the case for the oxidation of dimethyl acetals **3e** and **3p**. The major side-products of the oxidation of these dimethyl acetals were identified as their 3,4-dihydro-

2*H*-1,5-benzodioxepin-2-one derivatives (*R*)-**7a'** and (*R*)-**7g'** (Figure 1). We postulate that compounds (*R*)-**7a'** and (*R*)-**7g'** are formed from a Friedel-Crafts/Baeyer-Villiger sequence as illustrated in the rationale presented in the SI.

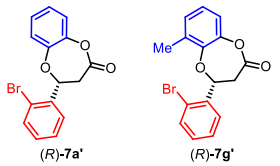
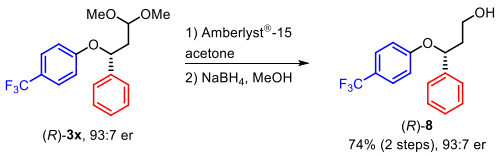


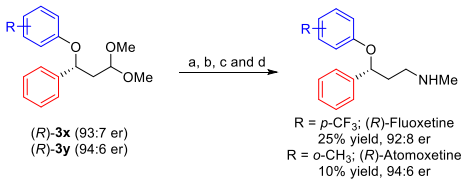
Figure 1. The main side-products formed by the oxidation of acetals **3e** and **3p** into their respective esters using *m*CPBA/BF_3·OEt_2.

As stated previously, the free aldehydes are susceptible to *β*-aryloxy elimination (Table 1). Nonetheless, we reasoned that the use of a mild proton source could avoid the decomposition pathway and allow access to this versatile intermediate. We decided to test our hypothesis with compounds (*R*)-**3x** and (*R*)-**3y** - prepared via C−Br bond hydrogenolysis of compounds (*R*)-**3l** and (*R*)-**3p** (see SI). Although compounds (*R*)-**3x** and (*R*)-**3y** could be prepared by the direct Heck-Matsuda arylation of allylic alcohol (*Z*)-**1** using benzenediazonium tetrafluoroborate, we found out that this particular reaction leads to a lower yield of the desired Heck product. On the other hand, the reaction using the benzenediazonium salt allowed us to isolate and characterise the regioisomer formed from arylation on the *α*-position (see SI). To our delight, the use of Amberlyst®-15, a mild proton source proved effective for the hydrolysis of the dimethylacetals to provide the respective aldehydes. For example, acetal (*R*)-**3x** was hydrolyzed with Amberlyst®-15 followed by a subsequent reduction with $NaBH_4$ affording the alcohol (*R*)-**8** in high yield and er (Scheme 5). The arylated alcohol (*R*)-**8** constitutes an advanced intermediate in the total synthesis of fluoxetine as described by Trost and co-workers.[48]



Scheme 5. Reduction of acetal (*R*)-**3x** to alcohol (*R*)-**8**.

To further demonstrate the synthetic potential of the developed method, and to ascertain our stereochemical assignments, we also employed the advanced intermediates dimethylacetals (*R*)-**3x** and (*R*)-**3y** in the total synthesis of fluoxetine and atomoxetine respectively (Scheme 6). The synthesis of (*R*)-fluoxetine and (*R*)-atomoxetine were completed in 4 steps from intermediates (*R*)-**3x** and (*R*)-**3y** in reasonably good overall yields as indicated in Scheme 6. The comparison of their optical rotation values with the corresponding ones reported in the literature allowed us to assign the absolute configuration of our Heck products as indicated (see SI for details).[49] We extended the configuration determined by this method to all the compounds synthesized in this study.



Scheme 6. Synthesis of (*R*)-fluoxetine and (*R*)-atomoxetine and stereochemical assignments. Reaction conditions: a) Amberlyst®-15, acetone. b) NaH_2PO_4, $NaClO_2$, amylene, ^{t}BuOH/H_2O. c) $MeNH_2$·HCl, EDC·HCl, HOBt, DIPEA, DCM. d) BH_3·Me_2S, THF, then HCl, reflux and then NaOH. For more information see SI.

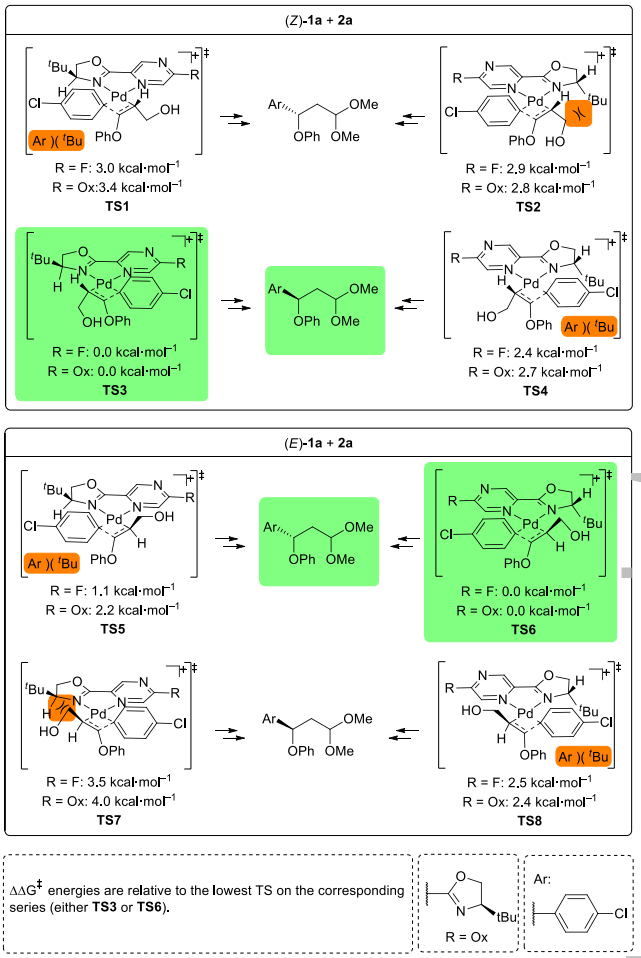
To get further insights about these challenging Heck-Matsuda arylations, we also decided to investigate the enantioselectivity of these reactions through DFT studies. The analysis of the aryl palladium migratory insertion into the alkene has shown to be crucial to rationalize the stereochemical outcome of the Heck reactions on many occasions.[14,27–29,50–52] Our investigation took into account the four permutations between the orientations of different substrate components for both (*Z*)-**1a** and (*E*)-**1a** (Scheme 7). Therefore, we investigated the enantioselectivity of the reaction (i.e.: arylation at either the *Re* or *Si* face of a given alkene carbon), and the relative orientation of the ligands during the migratory insertion (i.e.: alkene *cis* or *trans* to the oxazoline at the stage of the corresponding *σ*-arylpalladium). For comparison, we also investigated a less computationally demanding model ligand in which one of the oxazolines was replaced by a fluorine substituent.

As in previous investigations, we assumed that Curtin-Hammett conditions apply to the migratory insertion and, that the redox relay is efficient at converting the migratory insertion products, alkyl palladium complexes, into the reaction products (aldehydes or ketones).[14,50–52] The redox relay process was previously investigated by Sigman and coworkers and, in general, it is an efficient process with both PyOx and PyraBox ligands.[15,52] In essence, this transformation consists of a series of *syn β*-hydride eliminations and palladium hydride migratory insertions. Under these assumptions, the product distribution should be determined by the difference in free energy of activation of the corresponding migratory insertion transition states. The computational method employed was M06-L/def2-TZVP//M06-L/set1, in which set1 is a basis set composed of 6-31G(d,p) for H, C, N, O, F and Cl atoms and LANL2DZ pseudopotential with its associated basis set for Pd. Solvent effects were included both during the optimization and at single point calculations by the SMD model (more information about the method as well as the xyz

coordinates for the transition states are described in the SI).

Both for (*Z*)-**1a** and (*E*)-**1a**, the lowest energy transition states found do correlate with the absolute stereochemistry of the corresponding products (Scheme 7). In addition, given the 2.8 kcal·mol^{-1} free energy difference between **TS3** and **TS2**, high levels of enantio-induction are expected for this reaction. Indeed, this observation agrees qualitatively with high experimental enantioselectivity obtained for this transformation (er: 95:5, $\Delta\Delta G^{\ddagger} \approx 1.84$ kcal·mol^{-1} estimated from: $\Delta\Delta G^{\ddagger} = -RT \ln(e.r.)$). Similarly, the 2.4 kcal·mol^{-1} free energy difference between **TS6** and **TS8** also qualitatively agrees with the experimental enantioselectivity (e.r.: 92:8, $\Delta\Delta G^{\ddagger} \approx 1.52$ kcal·mol^{-1}).

The reaction enantioselectivity can be understood once one recognizes that the chiral palladium complex differentiates prochiral alkenes' faces depending upon their substitution at the *β*-aryloxy position. This differentiation is based primarily on steric hindrance between the allylic hydrogens and the bulky substituent at the oxazoline moiety. Arylation proceeds at the *α*-aryloxy position and thus the stereoisomer formed depends upon the double bond geometry. The preference for transition states in which the aryl group is proximal to the pyrazine moiety can be understood both in terms of steric hindrance between ^{t}Bu group and aryl group and in terms of a favourable C-H···π interaction between the pyrazine C-H bond (**TS3** and **TS6**).[50,51]



Scheme 7. Relative free energies for migratory insertion on the (*Z*)-**1a** and (*E*)-**1a**.

Conclusion

In summary, we have developed an efficient enantioselective Heck-Matsuda arylation of acyclic enol ethers. The arylated products were prepared in moderate to good yields and in high enantiomeric ratios. Competing *β*-aryloxy eliminations were avoided in most cases via in situ methanol ketalization of the intermediate *β*-aryloxyaldehydes. The dimethyl acetals obtained can be effectively transformed into their corresponding methyl esters by mild oxidation with *m*CPBA/BF_3·OEt_2 or to the primary alcohols by a two-step sequence involving hydrolysis with Amberlyst®-15 and immediate reduction with $NaBH_4$. The method demonstrated its synthetic potential by the synthesis of enantioenriched bioactive compounds and valuable core structures, like (*R*)-fluoxetine, (*R*)-atomoxetine, and a functionalized benzo[*c*]chromene. The relative free energies of activation of the carbopalladation step were calculated with DFT and are in good agreement with the product distribution of the Heck-Matsuda reaction. The enantiodivergent nature of the arylation, regarding the *E* and *Z* enol ethers, could be also understood as a natural consequence of the transition states these olefins go through.

Experimental Section

General Procedure for Enantioselective Heck-Matsuda Reactions: $Pd(TFA)_2$ (4.99 mg, 5 mol%, 0.015 mmol), ligand (*S*)-PyraBox **L1** (5.95 mg, 6 mol%, 0.018 mmol), and methanol (1.5 mL or 0.75 mL) were added to a 4 mL screw-top vial containing a magnetic stirrer. The resulting light-orange solution was then stirred at 40°C for 15 min to form the catalyst complex. In another 4 mL vial, was added the olefin (*Z*)-1a (0.30 mmol), $CaCO_3$ (0.33 mmol, 33.0 mg, 1.1 equiv) or $ZnCO_3$ (0.30 mmol, 37.6 mg, 1 equiv), diazonium salt (0.60 mmol, 2 equiv) and the solution of catalyst complex, rinsing the vial containing the catalyst solution with MeOH (1.5 mL or 0.75 mL). The vial was then capped and stirred for 1-8 h. (Caution! Pressure might develop inside the reaction flask due to the N_2 released by the reaction). The reaction vessel was then cooled to room temperature, carefully opened and the reaction mixture was poured onto a pad of silica gel (230–400 mesh; column height ~3 cm; diameter ~2 cm) previously washed with a 50% mixture of EtOAc/hexanes. The silica pad was then washed with about 50 mL of the same eluent. The solvent was removed with a rotary evaporator and the resulting mixture was purified by column chromatography on silica gel with ethyl acetate and hexanes as the eluent.

Acknowledgements

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References

[1] A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945–2964.
[2] D. Mc Cartney, P. J. Guiry, *Chem. Soc. Rev.* **2011**, *40*, 5122–5150.
[3] M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533–1552.
[4] M. Oestreich, *The Mizoroki-Heck Reaction*, John Wiley & Sons, **2009**.
[5] M. Oestreich, *Angew. Chem., Int. Ed. Engl.* **2014**, *53*, 2282–2285.
[6] X. Wu, J. (Steve) Zhou, *Chem. Commun.* **2013**, *49*, 4794–4796.
[7] R. C. Carmona, O. D. Köster, C. R. D. Correia, *Angew. Chem., Int. Ed. Engl.* **2018**, *57*, 12067–12070.
[8] C. M. Avila, J. S. Patel, Y. Reddi, M. Saito, H. M. Nelson, H. P. Shunatona, M. S. Sigman, R. B. Sunoj, F. D. Toste, *Angew. Chem., Int. Ed. Engl.* **2017**, *56*, 5806–5811.
[9] Y. Reddi, C.-C. Tsai, C. M. Avila, F. D. Toste, R. B. Sunoj, *J. Am. Chem. Soc.* **2019**, *141*, 998–1009.
[10] G. Yue, K. Lei, H. Hirao, J. (Steve) Zhou, *Angew. Chem., Int. Ed. Engl.* **2015**, *54*, 6531–6535.
[11] J. A. Carmona, V. Hornillos, P. Ramírez-López, A. Ros, J. Iglesias-Sigüenza, E. Gómez-Bengoa, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2018**, *140*, 11067–11075.
[12] Z.-M. Chen, M. J. Hilton, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 11461–11464.
[13] H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 14226–14229.
[14] C. Zhang, B. Tutkowski, R. J. DeLuca, L. A. Joyce, O. Wiest, M. S. Sigman, *Chem. Sci.* **2017**, *8*, 2277–2282.
[15] C. C. Oliveira, A. Pfaltz, C. R. D. Correia, *Angew. Chem., Int. Ed. Engl.* **2015**, *54*, 14036–14039.
[16] T. Y. Chaudhari, A. Hossian, M. K. Manna, R. Jana, *Org. Biomol. Chem.* **2015**, *13*, 4841–4845.
[17] W. Khodja, A. Leclair, J. Rull-Barrull, F. Zammattio, K. V. Kutonova, M. E. Trusova, F.-X. Felpin, M. Rodriguez-Zubiri, *New J. Chem.* **2016**, *40*, 8855–8862.
[18] D. Cortés-Borda, K. V. Kutonova, C. Jamet, M. E. Trusova, F. Zammattio, C. Truchet, M. Rodriguez-Zubiri, F.-X. Felpin, *Org. Process Res. Dev.* **2016**, *20*, 1979–1987.
[19] H. Nakamura, K. Yasui, Y. Kanda, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 1494–1497.
[20] N. J. Race, Q. Yuan, M. S. Sigman, *Chem. Eur. J.* **2019**, *25*, 512–515.
[21] Z.-M. Chen, C. S. Nervig, R. J. DeLuca, M. S. Sigman, *Angew. Chem., Int. Ed. Engl.* **2017**, *56*, 6651–6654.
[22] C. Zhang, C. B. Santiago, J. M. Crawford, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 15668–15671.
[23] E. W. Werner, T.-S. Mei, A. J. Burckle, M. S. Sigman, *Science* **2012**, *338*, 1455.
[24] C. Frota, E. C. Polo, H. Esteves, C. R. D. Correia, *J. Org. Chem.* **2018**, *83*, 2198–2209.
[25] C. C. Oliveira, R. A. Angnes, C. R. D. Correia, *J. Org. Chem.* **2013**, *78*, 4373–4385.
[26] R. A. Angnes, J. M. Oliveira, C. C. Oliveira, N. C. Martins, C. R. D. Correia, *Chem. Eur. J.* **2014**, *20*, 13117–13121.
[27] J. de Oliveira Silva, R. A. Angnes, V. H. Menezes da Silva, B. M. Servilha, M. Adeel, A. A. C. Braga, A. Aponick, C. R. D. Correia, *J. Org. Chem.* **2016**, *81*, 2010–2018.
[28] F. de Azambuja, R. C. Carmona, T. H. D. Chorro, G. Heerdt, C. R. D. Correia, *Chem. Eur. J.* **2016**, *22*, 11205–11209.
[29] S. Kattela, G. Heerdt, C. R. D. Correia, *Adv. Synth. Catal.* **2017**, *359*, 260–267.
[30] J. M. de Oliveira, R. A. Angnes, I. U. Khan, E. C. Polo, G. Heerdt, B. M. Servilha, V. H. Menezes da Silva, A. A. C. Braga, C. R. D. Correia, *Chem. Eur. J.* **2018**, *24*, 11738–11747.
[31] R. A. Angnes, L. M. Thompson, M. S. Mashuta, C. R. D. Correia, G. B. Hammond, *Adv. Synth. Catal.* **2018**, *360*, 3760–3767.
[32] G. M. Borrajo-Calleja, V. Bizet, T. Bürgi, C. Mazet, *Chem. Sci.* **2015**, *6*, 4807–4811.

[33] C. Wu, J. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 650–652.
[34] J. Hu, Y. Lu, Y. Li, J. (Steve) Zhou, *Chem. Commun.* **2013**, *49*, 9425–9427.
[35] Q. Yuan, M. S. Sigman, *J. Am. Chem. Soc.* **2018**, *140*, 6527–6530.
[36] S. Kattela, E. C. de Lucca Jr., C. R. D. Correia, *Chem. Eur. J.* **2018**, *24*, 17691–17696.
[37] Z.-Z. Jiang, Y.-J. Jiang, J. Du, D. Chen, C.-H. Ding, B. Xu, X.-L. Hou, *Synthesis* **2019**, s-0037-1610712.
[38] H. H. Patel, M. B. Prater, S. O. Squire, M. S. Sigman, *J. Am. Chem. Soc.* **2018**, *140*, 5895–5898.
[39] M. B. Prater, M. S. Sigman, *Israel Journal of Chemistry* **2019**, *0*, DOI 10.1002/ijch.201900077.
[40] J. G. Taylor, A. V. Moro, C. R. D. Correia, *Eur. J. Org. Chem.* **2011**, *2011*, 1403–1428.
[41] A. Roglans, A. Pla-Quintana, M. Moreno-Mañas, *Chem. Rev.* **2006**, *106*, 4622–4643.
[42] F.-X. Felpin, L. Nassar-Hardy, F. Le Callonnec, E. Fouquet, *Tetrahedron* **2011**, *67*, 2815–2831.
[43] L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590.
[44] D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.
[45] D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.
[46] L. Qi, N. Yamamoto, M. M. Meijler, L. J. Altobell, G. F. Koob, P. Wirsching, K. D. Janda, *J. Med. Chem.* **2005**, *48*, 7389–7399.
[47] E. J. Corey, W. G. Su, *J. Am. Chem. Soc.* **1987**, *109*, 7534–7536.
[48] B. M. Trost, P. L. Fraisse, Z. T. Ball, *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1059–1061.
[49] Y. Li, Z. Wang, K. Ding, *Chem. Eur. J.* **2015**, *21*, 16387–16390.
[50] Y. Dang, S. Qu, Z.-X. Wang, X. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 986–998.
[51] L. Xu, M. J. Hilton, X. Zhang, P.-O. Norrby, Y.-D. Wu, M. S. Sigman, O. Wiest, *J. Am. Chem. Soc.* **2014**, *136*, 1960–1967.
[52] M. J. Hilton, L.-P. Xu, P.-O. Norrby, Y.-D. Wu, O. Wiest, M. S. Sigman, *J. Org. Chem.* **2014**, *79*, 11841–11850.

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FULL PAPER

Enantioselective Heck Arylation of Acyclic Alkenol Aryl Ethers: Synthetic Applications and DFT Investigation of the Stereoselectivity

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