In Tandem Enantioselective Intramolecular Heck-Matsuda Reactions directly from anilines.

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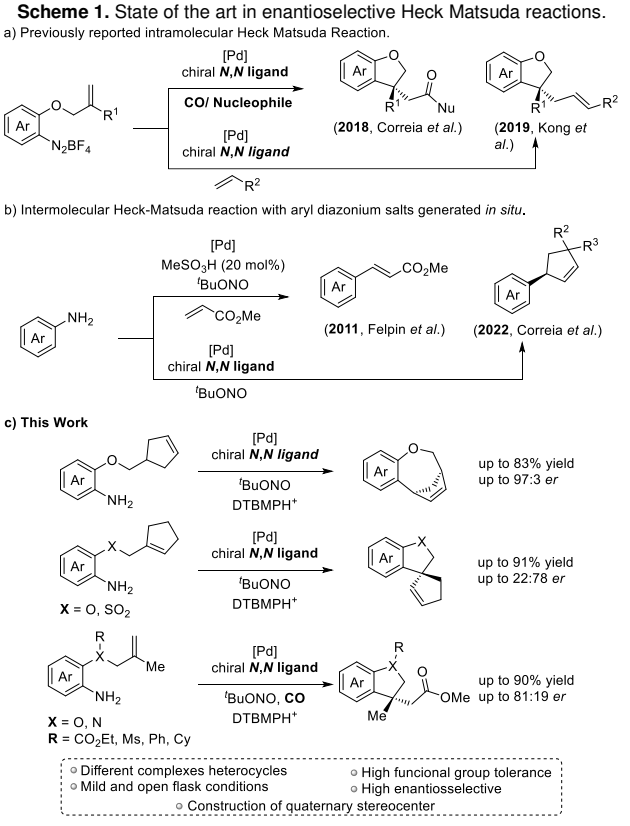
Abstract: A new enantioselective intramolecular strategy for the synthesis of enantioenriched bridged benzoxacines, unsaturated spirobenzofurans, methyl-2,3-dihydrobenzofuran acetates, and methyl-2,3-indoline acetate scaffolds in a tandem-like diazotization/Heck Matsuda process directly from anilines has been developed. The process combines the *in situ* diazotization of the aniline, followed by the intramolecular Heck-Matsuda reaction, thus skipping the isolation and purification of unstable or hard-to-synthesize aryldiazonium salts. The practicality and robustness of the sequence were demonstrated by the synthesis of 26 examples of complex structural motifs with yields up to 91% and enantiomeric ratio (*er*) up to 97:3, including quaternary stereocenters. The in-tandem processes from anilines were compared to conventional Heck Matsuda reactions using pre-synthesized aryldiazonium salts. With few exceptions, the reactions starting directly from the anilines afforded better overall yields and *er*, demonstrating the efficiency of this method.

Homogeneous metal catalysis stands as a reliable tool for the construction of C–C bonds which are critical in the synthesis of complex molecules.[1] In this regard, the palladium-catalyzed reactions hold a prominent place with the enantioselective intramolecular Heck arylation standing as a hallmark due to its versatility and outstanding synthetic potential. [2–5] Despite the undeniable success of the palladium-catalyzed enantioselective Heck reactions using aryl halides and aryl tosylates/triflates with chiral phosphines, in the last few years the enantioselective Heck-Matsuda reactions using aryldiazonium tetrafluoroborates and *N,N*-ligands appeared as a valuable alternative to the Heck arylations.[6a-g] Aryldiazonium salts have been applied as useful tools since their discovery in 1858 by Peter Griess,[7] and a clear advantage of the aryldiazonium salts in the Heck and cross-coupling reactions is their higher reactivity when compared to aryl halides/tosylates/triflates.[8]

Although the intermolecular version of the enantioselective Heck-Matsuda reaction has been extensively explored by us and others, its enantioselective intramolecular version is still underexplored.[9a-e] There are a few reasons for it. The synthesis of aryldiazonium salts from more complex anilines is rather challenging since it usually requires strong acidic conditions. Moreover, very often these aryldiazonium salts are thermally unstable and/or hard to synthesize in good yields and acceptable purity. To the best of our knowledge, there are only a few examples in the literature of the enantioselective intramolecular Heck-Matsuda reaction. In 2018, we reported the first enantioselective intramolecular *exo*-carbonylative Heck-Matsuda reaction, employing chiral *N,N* ligands (Scheme 1a).[10] In line with this work, Kong and co-workers reported the enantioselective double Heck reaction,[11] an intramolecular Heck-Matsuda reaction followed by an intermolecular Heck using the same substrate previously reported by us (Scheme 1a).

Scheme 1. State of the art in enantioselective Heck Matsuda reactions.



Another potential reason for the slow development of the Heck-Matsuda reactions is a general perception, to some extent reasonable, that arenediazonium salts are potentially hazardous compounds for use in organic synthesis, especially on a large scale, although tetrafluoroborates, tosylates, and hexafluorophosphates diazonium salts are usually thermally stable compounds.[34] To avoid the isolation and purification of particularly unstable aryldiazonium salts, their *in situ* generation has emerged as an efficient and attractive synthetic strategy.[13–16]

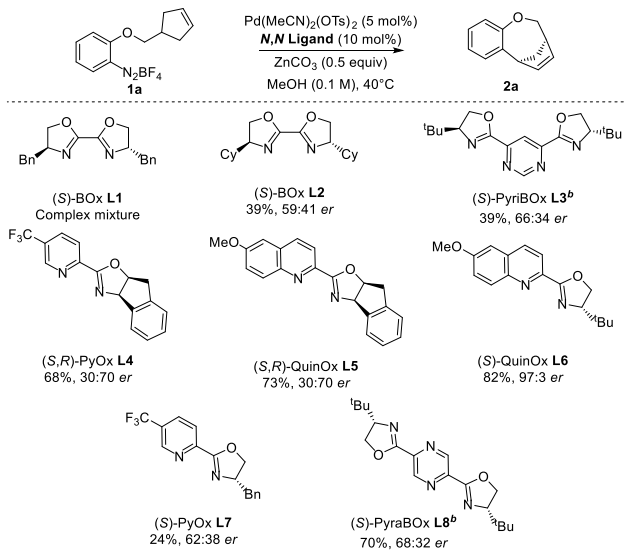
In 2011, Felpin and co-workers reported the intermolecular arylation of acrylates through a Heck-Matsuda reaction with *in situ* generation of aryldiazonium salts from anilines (Scheme 1b) using catalytic amounts of methanesulfonic acid.[17] Recently, we have reported an in tandem enantioselective Heck-Matsuda arylation of non-activated cyclopentenes, and 1,4-butendiol which can be carried out in almost neutral conditions (Scheme 1b).[18] The endogenous acid produced *in situ* during the Heck reaction was capable of driving the diazotization of the aniline sequentially.

Inspired by these previous results, we envisioned the development of a strategy for the intramolecular enantioselective one-pot Heck-Matsuda reaction directly from functionalized anilines. Herein, we report the first examples of this strategy to access different enantioenriched bridged benzoxacines, unsaturated spirobenzofurans, methyl-2,3-dihydrobenzofuran acetates, and methyl-2,3-indoline acetate scaffolds in good overall yields.

The reaction conditions needed for the *in situ* diazotization followed by the sequential enantioselective Heck-Matsuda reaction posed a few challenges, including (1) a precise synchronization between the diazotization step and the catalytic Heck cycle; (2) adequate acidic conditions to promote the diazotization of the starting aniline, avoiding interferences with the chiral *N,N*- ligand,[19] (3) compatibility of the starting unsaturated anilines with the nitrating agents, and the acidic conditions of the medium, and (4) control of a potential triazene-diazonium equilibrium.[20–21]

Our studies started testing the feasibility of the intramolecular enantioselective Heck-Matsuda reaction regarding chemical yield and enantioselectivity. For these first experiments, we employed the preformed aryldiazonium salt **1a** as model substrate using a mixture of **1a**, $ZnCO_3$ as a base, 5 mol% of $Pd(MeCN)_2(OTs)_2$, 10 mol% of the selected *N,N*-ligands and MeOH as solvent at 40°C under open flask conditions until total consumption of the starting material (Table 1).

Table 1. Ligand evaluated in this study

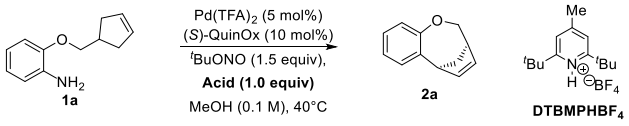


[a] Reactions were conducted on 0.1 mmol scale and yields were determined by ^{1}H NMR analysis using 3,5-bis(trifluoromethyl)bromobenzene as an internal standard in the crude reaction. The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [b] Ligand 6 mol%.

Gratifyingly, the *N,N*-ligand QuinOx **L6** provided the desired product **2a** in a very good yield of 82%, and an excellent enantiomeric ratio (*er*) of 97:3. Other *N,N*-ligands tested gave lower *er*, although some reactions led to the formation of the Heck product **2a** in good yields, such as **L5** and **L8**. After some experimentation, we found that $Pd(MeCN)_2(OTs)_2$ palladium source could be replaced by the commercially available $Pd(TFA)_2$ without losses in yield or *er*.

After these initial tests, we then examined the one-pot Heck Matsuda reaction based on our previous report of the intermolecular enantioselective Heck-Matsuda using the unsaturated aniline **1b**.[18] In agreement with our previous results, the Heck-Matsuda reaction conducted without external acid demonstrated the viability of the intramolecular Heck-Matsuda reaction from the starting aniline, furnishing the desired tricyclic Heck product **2a**, however, in only 28% yield in an excellent 97:3 *er* (Table 2, Entry 1). Since some acidic conditions are essential for the critical *in situ* formation of the aryldiazonium salt, we hypothesized that the addition of an external acid could provide the necessary conditions to form the aryldiazonium salt and start the sequential processes. Therefore, in an attempt to increase the yield, different acids were evaluated employing the model substrate **1a** (Table 2).

Table 2. Acid evaluation



Entry	Acid (%)	Yield (%)[a]	*er*[b]
1	None	28	97:3
2	AcOH	20	95:5
3	HCl	0	-
4	Ascorbic acid	0	-
5	Methanesulfonic acid	65	67:33
6	*p*-Toluenesulfonic acid	63	70:30
7	HBF_4	58	80:20
8	TFA	53	96:4
9[c]	$DTBMPHBF_4$	66	94:6
10[d]	$DTBMPHBF_4$	70	95:5

[a] Reactions were conducted on 0.1 mmol scale, and yields were determined by ^{1}H NMR analysis using 3,5-bis(trifluoromethyl)bromobenzene as an internal standard in the crude reaction. [b] The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [c] 2,6-*tert*-butyl-4-methyl-pyridinium tetrafluoroborate ($DTBMPHBF_4$), [d] 60 °C and MeOH (0.03 M).

The use of HCl led to complex mixtures (entry 2). The use of milder acid such as ascorbic acid (entry 3) led to the recovery of the starting materials, whereas AcOH (entry 4) gave the Heck product **2a** in a low yield of 20% and 95:5 *er*. The stronger methanesulfonic and *p*-toluenesulfonic acids (entries 5 and 6) furnished the Heck product **2a** in moderate yields of 65% and 63%, but with a significant drop in the *er*, to

67:33 and 70:30, respectively. Tetrafluoroboric acid also gave the Heck product **2a** in a reasonable yield of 58% and an improved *er* of 80:20, whereas trifluoroacetic acid led to a slight decrease in the chemical yield, but a much improved 96:4 *er*.

Because HBF_4 responded reasonably well regarding the enantioselectivity and chemical yield, we decided to mix it with 2,6-di-*tert*-butyl-4-metylpyridine (DTBMP), a base extensively used by us in the Heck-Matsuda reactions, and that is fully compatible with aryldiazonium salts. [6e, 9c, 9e] The acidic 2,6-di-*tert*-butyl-4-metylpyridinium tetrafluoroborate salt ($DTBMPHBF_4$) was then easily prepared and applied in the next Heck arylations directly from the aniline. To our satisfaction, the desired product **2a** could be obtained in an improved 66% yield and excellent 94:6 *er* (Table 2, entry 9). After some optimization regarding the reaction concentration, temperature, stoichiometry of ^{t}BuONO, and the amount of the acidic pyridinium salt, the Heck product **2a** could be obtained in 70% yield and 95:5 *er* (Entry 10). The option to carry out the reaction with the corresponding 2,6-di-*tert*-butyl-4-metylpyridinium trifluoroacetic salt was frustrated by the difficulties in preparing this compound.[22]

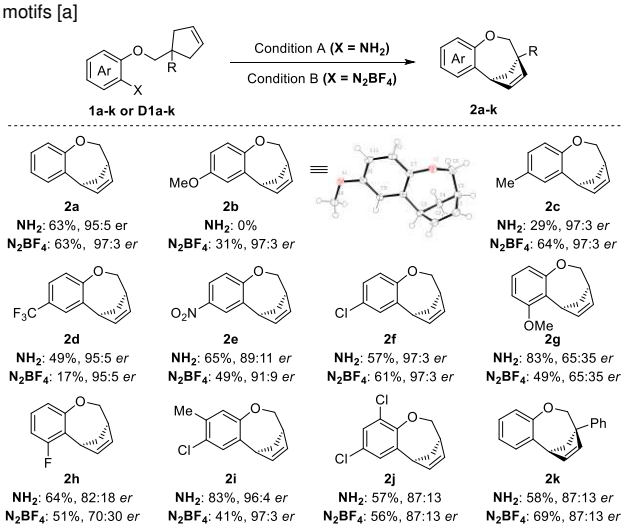
With the optimal reaction conditions in hand, we then examined the scope of the method and its functional group tolerance. Additionally, we also carried out the enantioselective Heck reactions using preformed aryldiazonium salts to compare the efficiency of the present protocol (Table 3). For Heck-Matsuda reactions carried out with the preformed and purified aryldiazonium salts, the yields shown in Table 3 correspond to two steps: aryldiazonium salt synthesis and its intramolecular Heck-Matsuda reaction.

As shown in Table 3, a wide range of electronic distinct anilines is well tolerated. Anilines bearing electron-donating and electron-withdrawing substituents including methyl, nitro, trifluoromethyl, and chlorine at the 5-position of the aryl moiety were well tolerated, affording the corresponding products **2c**–**2f** in moderate to good yields and good to excellent *er* (89:11-97:3). Somewhat surprisingly, the 5-methoxy aniline **1b** did not lead to the formation of the corresponding product **2b**, although this reaction worked reasonably well with the isolated aryldiazonium salt providing the corresponding Heck product **2b** in 31% overall yield and *er* of 97:3 (over 2 steps). We speculate that this particular electron-rich aniline undergoes decomposition under the oxidizing conditions of the reaction before *in situ* diazotization.

Next, we investigated the substrates where the substituent was located at the 6-position of the aryl moiety (**1g**-**1h**). The results showed that methoxy, and fluoride substituents at those positions are well-tolerated affording the desired product **2g** and **2h** in 83% and 64% yields, respectively. However, a decrease in the *er* was observed when compared to 5-substituted anilines. The same trend was observed with the pre-formed aryldiazonium salt in these cases. The 4-methyl-5-chloro disubstituted aniline **1i** led to the corresponding product **2i** in 83% and 96:4 *er*, whereas the 3,5-dichloro aniline **1j** afforded the corresponding product **2j** in 57% yield and 87:13 *er*. Overall, these results indicate not only some complementarity between the two protocols, but, more importantly, that in several instances, the Heck-Matsuda reaction carried out directly from the anilines outperformed the two-step processes requiring the previous synthesis of the aryldiazonium salts. The intramolecular enantioselective Heck-Matsuda arylations directly from the anilines are also more practical, as they do not involve the handling of oftentimes unstable aryldiazonium salts, especially in intramolecular cases.

To further evaluate the capability of this strategy, we investigated the formation of chiral quaternary centers by using the unsaturated aniline **1k**, carrying a phenyl cyclopentene moiety. The corresponding product **2k** was obtained in 58% yield and 87:13 *er*. The absolute stereochemistry of the tricyclic products was determined by the single crystal X-ray crystallographic analysis of the Heck product **2b** (see SI for details). The absolute configuration of **2b** was further confirmed as (3*R*,6*S*) by vibrational circular dichroism (VCD)[45] spectroscopy (see SI for details). The stereochemistry of the remaining tricyclic products was inferred by analogy to the one determined to the tricyclic adduct **2b**, and by the single crystal X-ray of derivatives of the Heck product **2a**, as described in Scheme 2 below.

Table 3. Reaction scope for the synthesis of methanobenzo[*b*]oxocine motifs [a]



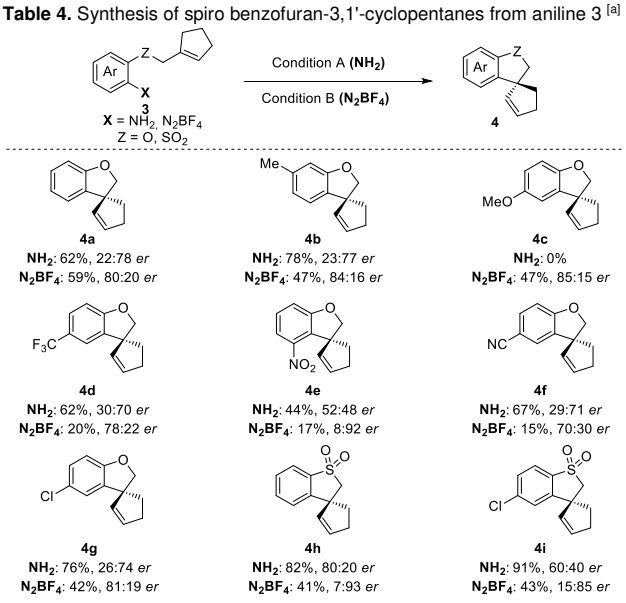
[a] Isolated yields were calculated from an average of two runs at 0.3 mmol scale. The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. The yields for the aryldiazonium salt entries are the overall yield: the aryldiazonium synthesis and the Heck-Matsuda reaction employing aryldiazonium salt. **Condition A:** $Pd(TFA)_2$ (5 mol%), **L6** (10 mol%), aniline (1.0 equiv), ^{t}BuONO (1.5 equiv), $DTBMPHBF_4$ (1.0 equiv), MeOH (0.03 M), 60 °C; **Condition B:** $Pd(OAc)_2$ (5 mol%), **L6** (10 mol%), aryldiazonium salt (1.0 equiv), $ZnCO_3$ (0.5 equiv), MeOH (0.1 M), 40°C.

These encouraging results with the desymmetrization of aniline **1** motivated us to synthesize the spiro[benzofuran-3,1'-cyclopentan] scaffolds **4** using the isomeric unsaturated aniline **3** (Table 4). We started with the same reaction conditions employed for substrate **1**. Our first experiments provided the expected Heck product **4a** in a very good yield of 82%, but in a somewhat low 22:78 *er*, leading us to evaluate other *N,N*-ligands (see SI for details). After some experimentation, we found out that **L2** (Table 1) worked best for the Heck-Matsuda reaction using the preformed aryldiazonium salt, whereas **L5** proved to be a superior *N,N*-ligand when starting directly from aniline **3**.

With the preformed aryldiazonium salt and using ligand **L2**, the spiro Heck product **4a** was obtained in 59% yield and 80:20 *er*, providing the *R*)-enantiomer as the major product. The one-pot protocol starting directly from the aniline **3a** and ligand **L5** furnished comparable results (62% yield, and 22:78 *er*) with the (*S*)-enantiomer as the major product. Since **L2** and **L5** ligands showed similar performances, both were used for the reaction scope.

As shown in Table 4, several electronic different anilines were well tolerated in the reaction. In general, higher chemical yields were obtained starting directly from the anilines, although higher *er* were obtained starting from the preformed aryldiazonium salts. For example, the Heck product **4b** was obtained in a much better overall yield (78%) directly from the aniline **3b** than from the preformed aryldiazonium salt (47%), albeit in lower *er*. As observed previously, aniline **3c** bearing a 5-OMe substituent did not furnish the desired Heck product **4c**. However, it was obtained in a moderate yield of 47% in 85:15 *er* using the preformed diazonium salt. Anilines containing electron-withdrawing groups, such as -CF_3 (**3d**), -NO_2 (**3e**) and -CN (**3f**) furnished the spiro Heck products in much higher yields using *N,N*-ligand **L2** (condition B) than from the previously formed diazonium salts (condition A), although a significant drop in *er* was observed when starting from these anilines. Aniline **3g** yielded the Heck product **4g** in 76% (26:74 *er*). Finally, the unsaturated anilines-sulfones **3h** and **3i** provided the respective Heck products in excellent yields (82% and 91%, respectively), but in lower *er*. The tandem process involving aniline **3h** and **3i** provided the spiro Heck product **4h** and **4i** in 7:93 er (41% yield) and 15:85 *er* (43% yield) respectively. The products **4e** and **4h** obtained using **L2** were unambiguously assigned as *R* by means of VCD (see SI for details).

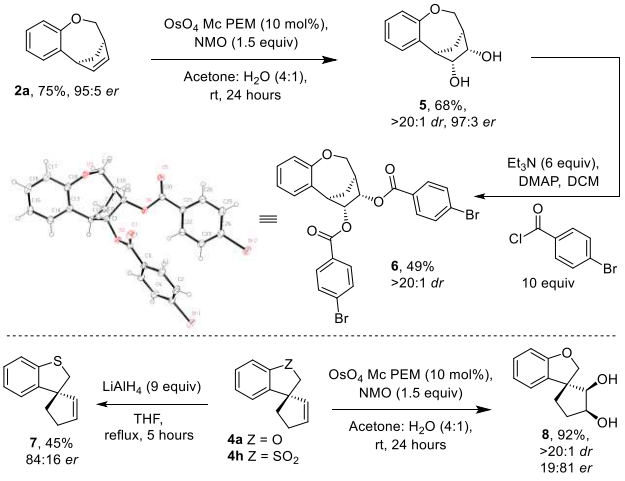
Table 4. Synthesis of spiro benzofuran-3,1'-cyclopentanes from aniline 3 [a]



[a] Isolated yields were calculated from an average of two runs at 0.3 mmol scale. The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. The yields for the aryldiazonium salt entries are overall yield: the aryldiazonium synthesis and the Heck-Matsuda reaction employing aryldiazonium salt. **Condition A:** Pd_2dba_3 (5 mol%), **L5** (11 mol%), aniline (1.0 equiv), ^{t}BuONO (1.5 equiv), $DTBMPHBF_4$ (2.0 equiv), MeOH (0.05 M), 40°C; **Condition B:** $Pd(OAc)_2$ (5 mol%), **L2** (10 mol%), aryldiazonium salt (1.0 equiv), $ZnCO_3$ (0.5 equiv), MeOH (0.1 M), 40°C.

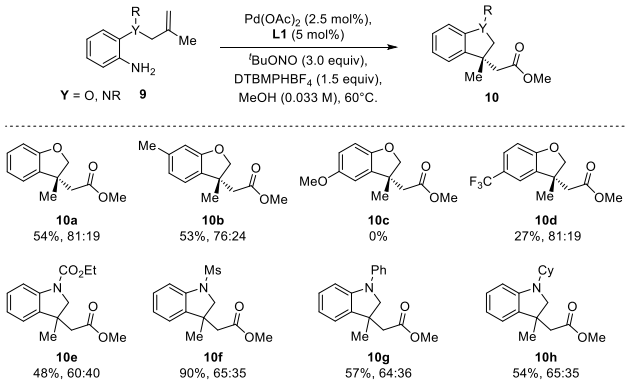
Both the enantioenriched methanobenzo[*b*]oxocine and the unsaturated spirobenzofurans compounds synthesized above have some potential for the construction of more complex structures. To evaluate their synthetic potential, some derivatizations were performed. The enantioenriched tricyclic Heck product **2a** was submitted to a dihydroxylation reaction with OsO_4 (Scheme 2a) to give the corresponding diol **5** in 68% yield in a >20:1 diastereoisomeric ratio. The diol **5** was then subjected to benzoylation with the 4-bromobenzoyl chloride to furnish dibenzoyl **6** in 49% as a crystalline compound, which by single crystal X-ray crystallographic analysis allowed the determination of the absolute stereochemistry of all 4 stereocenters as well as the diastereoselectivity of the dihydroxylation step. Moreover, the enantioenriched spirocyclic Heck products **4h** and **4a** were submitted to reduction of the sulfone followed by dihydroxylation (Scheme 2b) to afford the corresponding thioether **7** and diol **8** in 48% and 92% yield, respectively. Compound **8** was obtained as a single diastereoisomer (stereochemistry was determined by NOESY, see SI).

Scheme 2. Synthetic derivatizations of a) tricycle Heck product **2a** and b) spirocycle Heck product **4a**.



The successful results obtained with the in tandem enantioselective Heck-Matsuda reactions using the unsaturated anilines have motivated us to briefly reinvestigate the enantioselective carbonylative reactions disclosed in 2018,[10] including some anilines from which the respective aryldiazonium salt proved extremely difficult to synthesize. In this case, due to the quite distinct reaction conditions needed for efficient carbonylations, another optimization study was carried out (see SI). The best reaction conditions found consisted of using $Pd(OAc)_2$ as palladium source, (*S*)-Box **L1** as ligand, ^{t}BuONO (3 equiv), and MeOH as solvent (Table 5).

Table 5. Reaction scope for the synthesis of methyl-2-(3-methyl-2,3-dihydrobenzofuran-3-yl)acetate and methyl-2-(3-methyl-indolin-3-yl)acetate motifs [a]



[a] Isolated yields were calculated from an average of two runs at 0.3 mmol scale. The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase.

With the reaction conditions established, some unsaturated anilines were evaluated (Table 5). Heck products **10a, 10b,** were obtained in good yields and moderate enantiomeric ratios. As mentioned earlier, (Tables 3 and 4), the 5-methoxy substituted anilines were incompatible with the *in situ* diazotization procedure. Gratifyingly, substrates containing nitrogen (Y=NR) in the side chain furnished the privileged indoline nuclei in moderate to excellent yields, albeit in low *er*. Notably, the indoline Heck products **10f, 10g, 10h**, could only be obtained by using the *in situ* generation of the aryldiazonium salt, since they could not be prepared under the standard diazotization conditions.

In summary, we have developed the first intramolecular enantioselective Heck Matsuda reaction directly from unsaturated anilines in a tandem-like process. The one-pot enantioselective diazotization/Heck-Matsuda strategy proved to be efficient and very practical, showing broad scope as well as being a useful method for the creation of stereocenters, including quaternary ones. This novel methodology was applied to the synthesis of rather complex methanobenzo[*b*]oxocine, unsaturated spirobenzofurans, indolines, and benzofurans in a straightforward manner directly from the corresponding anilines, thus avoiding the synthesis and purification of often hard-to-synthesize and/or thermally unstable arenediazonium salts. Further studies and applications of this novel Heck-Matsuda strategy are ongoing and should be reported in due course.

Associated Content

CCDC-2194049 and CCDC-2194048 contains the supplementary crystallographic data for the compounds **2b** and **6**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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Keywords: Enantioselective Heck Matsuda reactions • One pot reactions • *In situ* aryldiazonium salt formation • Palladium • *N*,*N*-ligands.

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