CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201804958

Link to VoR: http://dx.doi.org/10.1002/chem.201804958

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Enantioselective Synthesis of Phthalides and Isochromanones *via*Heck–Matsuda Arylation of Dihydrofurans

Shivashankar Kattela,[a] Emilio C. de Lucca Jr.,[a] and Carlos Roque D. Correia*[a]

Abstract: In this communication, we describe the enantioselective synthesis of phthalides and isochromanones through a new palladium-catalyzed Heck–Matsuda arylation/$NaBH_4$-reduction/lactonization sequenceof 2,3- and 2,5-dihydrofurans in good overall yields and excellent enantioselectivities (up to 98:2 er). Thisexpeditious synthesis of chiral Heck lactol intermediates allowed thediversification of the strategy to obtain medicinally relevant chiral lactones, amines, and olefins. The natural product 3-butylphthalide was obtained in 3 steps with an overall yield of 33% yield in 98:2 er.

Chiral phthalide and isochromanone motifs are found in a wide variety of natural products possessing a broad spectrum of biological activities.[1] For example,3-butylphthalide (**1**) is a commercial antiplatelet drug,[2] fuscinarin (**2**) has anti-amnesia activity,[3] and AI-77-B(**3**) displays considerable anti-inflammatory activity (Figure 1).[4]

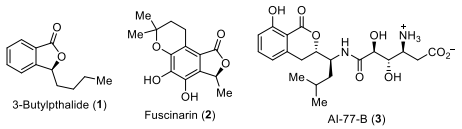
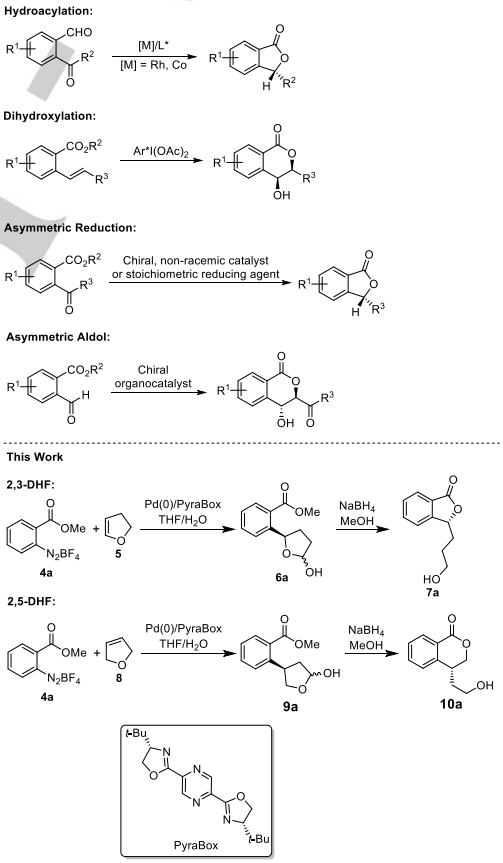


Figure 1. Representative chiral phthalides and isochromanone.

In view of their multiple biological activities, several methodologies have been developed for the synthesis of phthalides and isochromanones, in particular some enantioselective processes, such as intramolecular hydroacylation,[5] dihydroxylation of alkenes,[6] asymmetric reduction,[7] *ortho*-lithiation,[8] and addition to carbonyls[9] (Scheme 1).

Despite the efficiency of these methods, strategies based on an enantioselective metal-catalyzed C—C bond formation are very rare.[10] In view of our ongoing research on metal catalyzed arylations,[11] we envisioned that a Heck–Matsuda reaction between the functionalized arenediazonium salt **4a** and the 2,3-dihydrofuran (**5**) allied to a sequential $NaBH_4$-reduction and *in situ* lactonization could provide effective access to these important scaffolds. Isochromanones would be accessible by a similar sequence starting with 2,5-dihydrofuran (**8**).

2,3-Dihydrofuran is a cheap and readily available starting material for a variety of chemical transformations in classical total synthesis of complex molecules and metal catalyzed reactions. Particularly, in natural product synthesis,dihydrofurans are key substrates to access various functional groups and ring systems. In metal catalysis, 2,3-DHF is often explored as a model substrate to evaluate the regio- and enantioselectivity of new chiral ligands in the presence of various catalysts.[12] However, in most of these cases, the dihydrofuran moiety is maintained in the final products. Additionally, the regioselective Heck arylation of 2,3-dihydrofurans show considerable limitations due to the double bond migration resulting from uncontrolled migratory insertion and *β*-hydride eliminations, thus leading to the formation of kinetic and thermodynamic products in many occasions (Scheme 2).



Scheme 1. Proposed strategy.

Herein, we report an operationally simple, open air, regio- and enantioselective Heck–Matsuda arylation of 2,3- and 2,5-dihydrofuransfor rapid access to chiral phthalides and isochromanonesin which the dihydrofuran moiety functions a complementary source of functionalities and the point of creation of the new stereogenic center.

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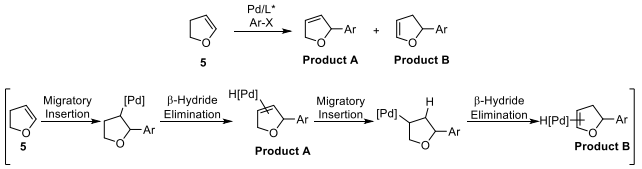
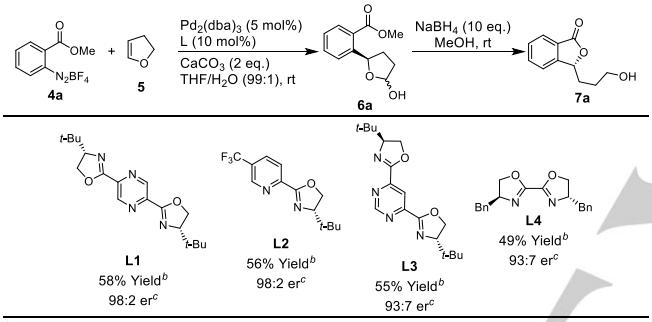
10.1002/chem.201804958



Scheme 2. Heck arylation of 2,3-DHF.

Based on our previous report,[11i] we started the optimization of the reaction conditions for the Heck–Matsuda/reduction sequence using $Pd_2(dba)_3$, the pyrazine bisoxazoline (**L1**, PyraBox), $CaCO_3$, and THF/H_2O as a solvent for the Heck reaction, followed by $NaBH_4$ in MeOH for the reduction/lactonization steps (Table 1). To our delight, the phthalide **7a** was obtained in 58% yield over the three steps in 98:2er. Evaluation of other ligands, such as pyridine oxazoline **L2**, pyrimidine oxazoline **L3**, and bisoxazoline **L4**, did not improve the yield or the enantiomeric ratio.

Table 1. Ligand evaluation.[a]



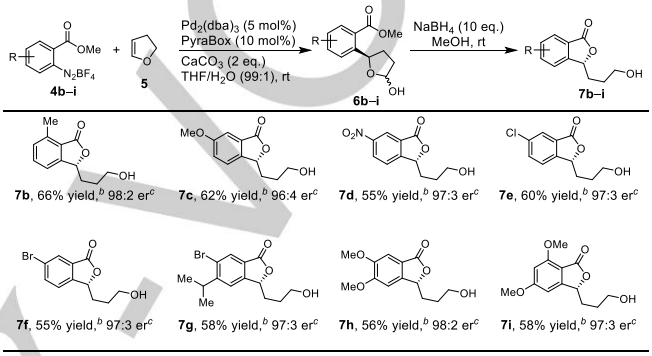
[a] Reaction Condition: $Pd_2(dba)_3$ (5 mol%), **L** (10 mol%), **4a** (0.10 mmol), **5** (0.30 mmol), $CaCO_3$ (0.20 mmol), (THF/H_2O). [b] Yields were determined by ^1H NMR analysis. [c]Enantiomeric ratios were determined by HPLC analysis.

With the optimized condition in hand, we evaluated the scope of the sequential reactions(Table 2). The presence of electron-donating groups, such as methyl (**4b**), methoxy (**4c**) and dimethoxy (**4h** and **4i**), provided the corresponding phthalides in good yields and excellent levels of enantioselectivity. Following the same trend, the electron-withdrawing groups nitro (**4d**), chlorine (**4e**), and bromide (**4f**) delivered the desired products in good yields and er. It is worth emphasizing that in all cases the reported yields displayed in Table 2 correspond to isolated yields after silica gel chromatography purification after the arylation/reduction/lactonization sequence. In order to determine the efficiency of the Heck arylationstep, we determined the ^1H NMR yield after the arylation (60% to 68%),and concluded that the isolated yield after the 3-steps sequence (arylation, reduction and lactonization) is very representative of the Heck–Matsuda arylation (see Supporting Information for full details).

Interestingly, in some initial experiments,the main product isolated when using the bromo substrate **4f**in the arylation-reduction sequence was the debrominated phthalide **7a**. This result was curious since the Heck–Matsuda hemiacetal product **6f** could be obtained in a good61% yield. Thus, we hypothesized that some remaining palladium from the Heck–Matsuda reaction in the presence of $NaBH_4$ could be responsible for the debromination event.[14a] Gratifyingly, the use of the MP-TMT resin to remove the palladium after the Heck–Matsuda step proved to be an efficient strategy, furnishing the brominated phthalide **7f** in good yield and excellent level of enantiomeric ratio after the reduction step (52%, 97:3er).[14b]

The influence of polysubstituted arenediazonium salts was also investigated. As previously observed, the brominated substrate **4g** afforded a debrominated side product. As in the case of brominated phthalide **7f**, removal of the residual palladium by the MP-TMT resin, allowed the synthesis of phthalide **7g** in 58% yield (3 steps) and 97:3er.

Table 2. Phthalide synthesis: scope.[a]

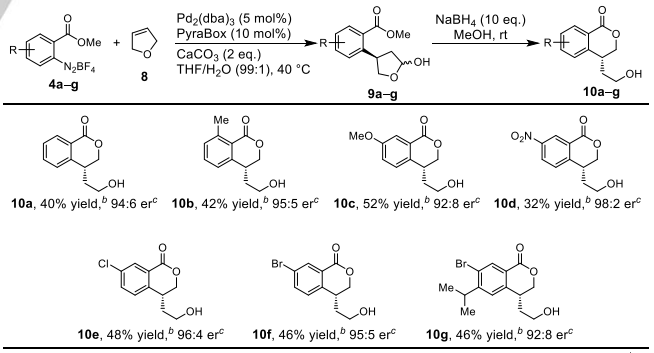


[a] Reaction Condition: $Pd_2(dba)_3$ (5 mol%), **L1** (10 mol%), **4b–i** (0.10 mmol), **5** (0.30 mmol), $CaCO_3$ (0.20 mmol), (THF/H_2O). [b] ^1H NMR yields were calculated for Heck–Matsuda arylation (See Supporting Information). Isolated yields after the 2-steps sequence. [c]Enantiomeric ratios were determined by HPLC analysis.

These encouraging results prompted us to extend the developed strategyto the synthesis of isochromanones using 2,5-dihydrofuran (**8**) (Table 3).

After some optimization, we found out that increasing the Heck–Matsuda reaction temperature to 40˚C was necessary to maintain a good balance between good yields and excellent levels of enantioselectivity.

Table 3. Isochromanone synthesis: scope.[a]



[a] Reaction Condition: $Pd_2(dba)_3$ (5 mol%), **L1** (10 mol%), **4a–g** (0.10 mmol), **8** (0.30 mmol), $CaCO_3$ (0.20 mmol), (THF/H_2O). [b] ^1H NMR yields were calculated for Heck–Matsuda arylation (See Supporting Information). Isolated yields after the 2-steps sequence. [c]Enantiomeric ratios were determined by HPLC analysis.

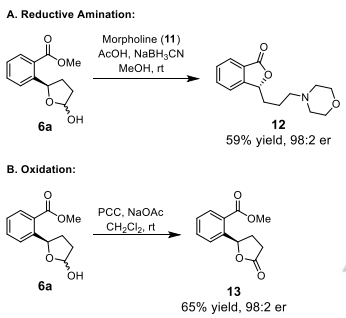
To our satisfaction, the Heck–Matsuda reaction between the functionalized arenediazonium salt **4a** and 2,5-DHF (**8**) followed by the $NaBH_4$-reduction/lactonization delivered the more challenging isochromanone **10a** in an overall yield of40% and 94:6 er. Interestingly, the ^1H NMR yield for the Heck–Matsuda arylation step was shown to be superior to the

reduction/lactonization steps in the sequence (See Supporting Information).

The reactions involving substrates with the electron-donating methyl (**4b**) and methoxy (**4c**) groups provided the corresponding isochromanones in good yields and excellent levels of enantioselectivity. Likewise, substrates containing the electron-withdrawing nitro (**4d**) and chlorine (**4e**) groups gave the desired products in good yields and er. Again, the use of the MP-TMT resin was necessary to ensure reproducibility with arenediazonium salts **4f** and **4g**.

The versatility of this Heck/reduction/lactonization strategy was also demonstrated by some additional transformations employing the end products or the intermediates (Schemes 3 and 4).

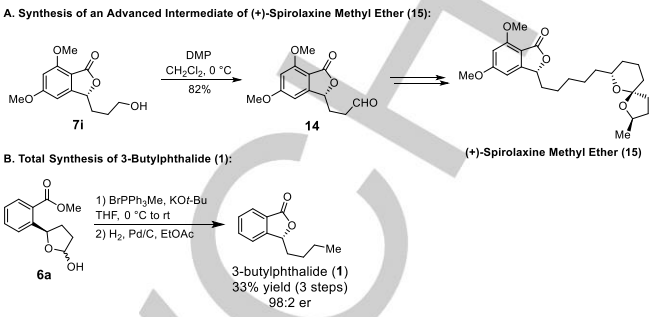
Nitrogen-containing molecules are ubiquitous in medicinally-relevant compounds.[15] Therefore, the reductive amination between the hemiacetal **6a** and morpholine (**11**) provided compound **12** in 59% yield and 98:2er (Scheme 3A). Alternatively, hemiacetal **6a** was oxidized under PCC conditions to afford the lactone **13**, a structure present in many natural products,[16] in moderate yield and excellent enantioselectivity (65%, 98:2 er, Scheme 3B). It is worth mentioning that the Heck–Matsuda arylation/oxidation sequence represents a complementary strategy to our previously developed synthesis of β-aryl lactones.[11b]



Scheme 3. Synthetic application of lactol intermediates.

The synthetic value of this new strategy can be evaluated considering that compound **7i** corresponds to an advanced intermediate in the total synthesis of (+)-spirolaxine methyl ether (**15**), an anti-*Helicobacter pyroli* agent.[17] While compound **7i** was obtained in 5 steps (24% overall yield)[16a] or 11 steps (14% overall yield)[16d], we were able to synthesize compound **7i** in only 3 steps and 53% overall yield starting from the corresponding commercially available aniline (See Supporting Information). Furthermore, the specific rotation of phthalide**7i** matched that previously reported indicating that the absolute stereochemistry of the compound **7i** prepared in this work is *R* (**7i**: $[\alpha]_D$ +28 (*c* 0.5, $CHCl_3$), lit:[16d] $[\alpha]_D$ +14 (*c* 1.03, $CHCl_3$)). The DMP oxidation of the alcohol group of phthalide**7i** delivered the corresponding aldehyde **14** in 82% yield (Scheme 4A).

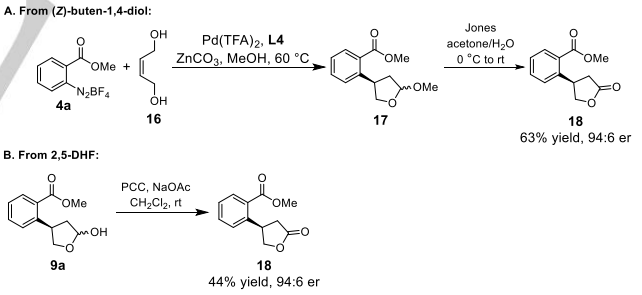
The robustness of this protocol was also tested in the total synthesis of the natural product 3-butylphthalide (**1**, Scheme 4B). Rewardingly, the Wittig reaction involving hemiacetal **6a** followed by a catalytic hydrogenation furnished 3-butylphthalide (**1**) in 33% yield and 98:2 er (over 3 steps), which corresponds to an average yield of 69% per step. The absolute configuration of compound **1** was determined to be *R* by comparison with a previously reported optical rotation value (**1**: $[\alpha]_D$+59 (*c*1.1, $CHCl_3$), lit for the *S* enantiomer: $[\alpha]_D$–66.2 (*c* 1.1.08, $CHCl_3$)).[18]



Scheme 4. Applications in formal and total synthesis.

We also envisioned that the Heck/oxidation protocol could be applicable to determine the absolute configuration of the isochromanones synthesized by the Heck/reduction/lactonization sequence protocol involving 2,5-DHF (**8**) (Table 3).

The Heck–Matsuda reaction between arenediazonium salt **4a** and (*Z*)-buten-1,4-diol (**16**) using bisoxazoline **L4** – which is known to deliver the *R* enantiomer of β-aryl lactones,[11b] furnished acetal **17** in 75% (Scheme 5). Jones oxidation of methyl lactol **17** afforded lactone *R*-**18** in 63% isolated yield and 94:6 er ($[\alpha]_D$–52 (*c*1.0, $CHCl_3$)). Similarly, PCC-oxidation of compound **9a** synthesized by Heck arylation of 2,5-DHF (Table 3) furnished the corresponding lactone **18** in 44% isolated yield and 94:6 er, favouring the *R* enantiomer ($[\alpha]_D$–54 (*c*1.1, $CHCl_3$)).

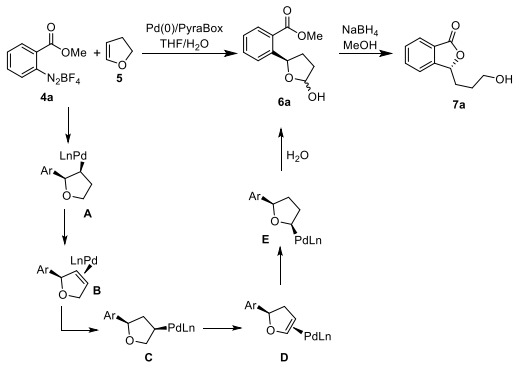


Scheme 5. Synthesis of lactone **18**.

Based on the observed products, a mechanistic insight is proposed. An initial regioselective arylation of 2,3-dihydrofuran (2,3-DHF) **5** would afford intermediate **A**, which by a series of β-hydride elimination/migratory insertions would deliver intermediate **E** (Scheme 6). A H_2O-based aliphatic nucleophilic substitution would lead to the formation of compound **6a**. Finally, a $NaBH_4$-reduction should provide phthalide **7a**.

In summary, we have developed an operationally simple, open air, regio- and enantioselective Heck arylation/$NaBH_4$ reduction/lactonization sequence of 2,3- and 2,5-dihydrofurans to afford phthalides and isochromanones in good yields and excellent enantioselectivity ratio. The versatility of this strategy allowed us to couple the Heck–Matsuda arylation with other transformations to access relevant structures, such as amines,

lactones, and the total synthesis of 3-butylphthalide (**1**). Further investigations to extend the mechanistic understanding and substrate variability are ongoing in our laboratory and will be reported in due course.



Scheme 6: Mechanistic proposal.

Experimental Section

A 4mL vial equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (4.58 mg, 5.00 µmol, 5 mol%), (*S*)-PyraBox**L1** (3.30 mg, 10.0 µmol, 10 mol%), and THF:H_2O99:1 (1.5 mL). The vial was capped and the mixture was stirred at 60°C for 10 minutes to form the precatalyst. Next, the vial was cooled to room temperature and charged with 2,3-DHF (**5**) (22.7 µL, 0.30 mmol, 3 eq.), $CaCO_3$ (20.0 mg, 0.20 mmol, 2 eq.), and the appropriate arenediazonium salt (0.10 mmol, 1 eq.). The vial was closed and then the reaction was stirred at room temperature until complete consumption of the arenediazonium salt (β-naphthol test, approx. 5–10 minutes). Next, the reaction was filtered through a short pad of silica gel and washed with EtOAc (3 x 15 mL) and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (2.0 mL) and $NaBH_4$ (38 mg, 1.00 mmol, 10 eq.) was added at room temperature. After 15 minutes, the reaction was concentrated under reduced pressure and the residue was purified by flash chromatography to afford pure samples of the corresponding Heck–Matsuda products.

Acknowledgements

We thank the financial support of the São Paulo Research Foundation (FAPESP grants: 2014/25770-6 and 2013/07600-3 [CRDC.]; 2014/05407-4[SK]; 2017/18023-8 [ECLJr]), and the Brazilian National Research Council (CNPq grant: 457027/2014-2).

Keywords:*N,N*-ligands•Palladium catalysis•Enantioselective Heck–Matsuda•Arenediazonium salts

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Layout 1:

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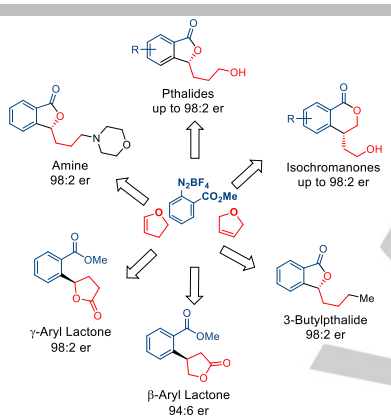
TRANSFORMER:A new palladium-catalyzed Heck–Matsuda arylation of dihydrofurans coupled with $NaBH_4$-reduction/lactonization furnished phthalides and isochromanones in good overall yields and excellent enantioselectivity (up to 98:2 er). The DHF moiety functions as a complementary source of functionalities and the point of creation of the new stereogenic center.



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Page No. – Page No.

Enantioselective Synthesis of Phthalides and Isochromanones *via* Heck–Matsuda Arylation of Dihydrofurans

Layout 2:

COMMUNICATION