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Ligand-Free Pd-Catalyzed Reductive Mizoroki-Heck Reaction Strategy for the One-Pot Synthesis of Functionalized Oxygen Heterocycles in Deep Eutectic Solvents

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Dedicated to Professor Francesco Naso on the occasion of his 85th birthday

A Deep Eutectic Solvent, choline chloride/glycerol (1 : 2 mol mol^{-1}), proved to be an effective and sustainable reaction medium to promote telescoped, one-pot Mizoroki-Heck cross-coupling/reduction processes between 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran and several (hetero)aryl halides to easily access valuable 2-(hetero)aryl tetrahydrofuran (THF) or tetrahydropyran derivatives in up to 95% yield. Notably, the whole transformation takes place under aerobic conditions, in the absence of additional ligands, and with a good substrate scope. The practicability of the method is also exemplified by the sustainable synthesis of two key THF derivatives, which are side chains of pharmacologically relevant inhibitors of Kv1.2 channel.

Introduction

Oxygen-bearing heterocycles, like tetrahydrofuran (THF) and tetrahydropyran (THP) rings, are common structural motifs in many natural products, pharmaceuticals, and biologically active compounds.[1] In addition, they are privileged molecular structures amenable of further functionalization, for example, by oxygen-facilitated α-lithiation or *ortho*-lithiation reactions, with the oxygenated ring acting as a direct metalation group, followed by trapping reactions with various electrophiles.[2] Thus, the development of novel methodologies for the preparation of oxygen heterocycles is an ongoing synthetic endeavor. Classical procedures rely on a base-promoted halohydrins cyclization,[3] acid-catalyzed intramolecular cyclization of diols,[4] and the intramolecular hydroalkoxylation of alkenylalcohols.[5] However, these methods often require harsh reaction conditions such as elevated temperatures, and strongly acidic or basic reaction media.[6] Recent examples also include intramolecular dehydrative substitution of benzylic alcohols catalyzed by pentafluorophenylboronic acid,[7] light-induced intramolecular C–O bond formation of aryl alcohols,[8] and photoredox C–H arylation of cyclic ethers.[9]

As part of our ongoing drive to develop more safe and sustainable technologies and practices, aimed at reducing or eliminating pollution sources by replacing traditionally toxic, petroleum-based volatile organic compounds (VOCs) with "greener" solvents, we recently embarked on a program directed towards the synthesis of heterocycles,[10] and bio-,[11] metal-catalyzed, and metal-mediated organic transformations[12] in environmentally responsible solvents like water and deep eutectic solvents (DESs).[13] Building upon these findings, we envisioned the development of a reductive Mizoroki-Heck (MH) reaction based on a tandem coupling-hydrogenation sequence process[14,15] as a means to obtain more functionalized THF and THP derivatives, thereby forging new bonds between selected (hetero)aryl halides and the corresponding 2,3-dihydrofuran (DHF) or 3,4-dihydro-2*H*-pyran (DHP) precursors. Due to its versatility, high chemoselectivity and low toxicity and cost of the reagents, MH reaction has been widely used in the synthesis of agrochemical, pharmaceutical, and biologically active products.[16] All these studies, however, often involve VOCs as privileged reaction media jointly with the use of phosphine ligands.[17] MH couplings in an aqueous environment have proven to be one of the most challenging to pursue, thereby leading to various original developments in catalyst design, including homogeneous and immobilized catalysts.[18a] One notable example is represented by the use of nanoparticles containing *t*-Bu$_3$P-ligated Pd, which promoted MH couplings under aqueous micellar catalysis conditions.[18b] Other examples include (a) the Pd-catalyzed Matsuda-Heck reaction between arenediazonium tosylates and activated alkene,[18c] and (b) the mono- and double Pd-catalyzed MH couplings between dialkyl

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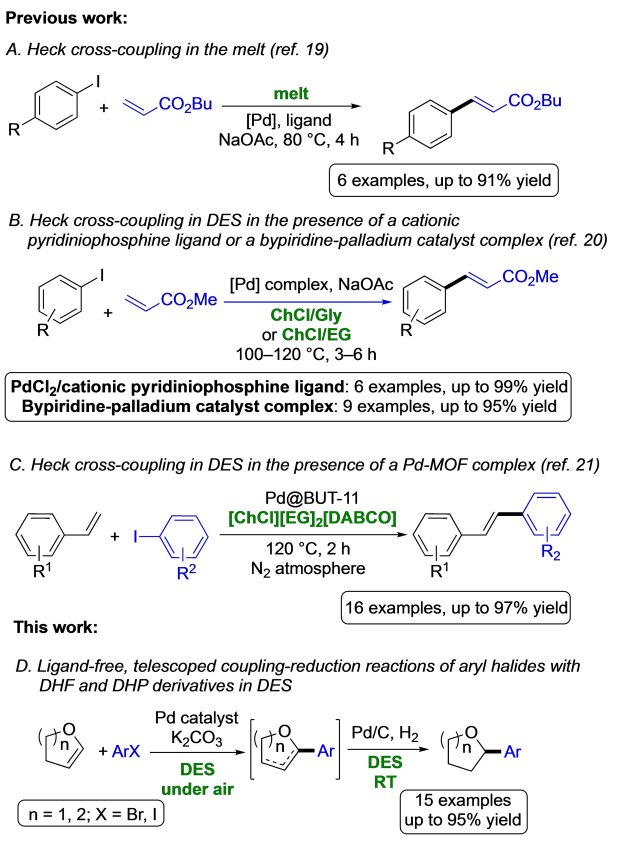
vinylphosphonates and aryl halides.[18d] There have also been reported very few examples of MH reactions run in DESs. After pioneering studies by König and co-workers on the coupling of iodoarenes with acrylates in the melt D-mannose/DMU (3:7 wt/wt), working under homogeneous conditions and in the presence of ligands (Scheme 1A),[19] Ramón and co-workers later described the coupling of aryl iodides with methyl acrylate in ChCl-based eutectic mixtures using $PdCl_2$ in the presence of a cationic pyridiniophosphine ligand or a bipyridine-palladium catalyst complex (Scheme 1B).[20] A palladium-incorporated metal-organic framework (MOF) (Pd@BUT-11) has also been used as an effective and recyclable catalytic system to promote the coupling reaction between aryl iodides and styrenes in a choline chloride (ChCl)-ethylene glycol (EG) eutectic mixture, in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base, at 120 °C, and under a nitrogen atmosphere (Scheme 1C).[21]

Herein, we report that 2-aryl-substituted saturated oxygen heterocycles can straightforwardly be synthesized by combining a Pd-catalyzed cross-coupling reaction between (hetero)aryl halides and DHF or DHP followed by an *in situ* reduction reaction of the corresponding unsaturated educts in DESs. We showcase that these reactions work well *i*) under aerobic conditions (warming up to 90 °C), *ii*) in the absence of additional ligands, and *iii*) with a good substrate scope (15 examples) with the desired educts isolated in up to 95% yield (Scheme 1D). Moreover, the practicability of the method has been exemplified by the sustainable synthesis in DES of two key intermediates *en route* to pharmacologically relevant inhibitors of Kv1.2 channel.[22]

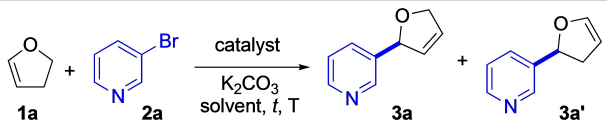


Scheme 1. (A) Pd-catalyzed MH coupling in the melt for the synthesis of cinnamic esters. (B) Ligand-based MH coupling in DES for the synthesis of cinnamic esters. (C) Pd@MOF-catalyzed MH coupling in DES for the synthesis of stilbenes. (D) Ligand-free reductive MH coupling in DES, under aerobic conditions, for the synthesis of 2-(hetero)aryl THF and THP derivatives. RT = room temperature, 25 °C.

Results and Discussion

As a bench reaction, we screened the cross-coupling reaction between DHF (**1a**, 3 equiv) and 3-bromopyridine (**2a**, 0.5 mmol) in a prototypical ChCl/glycerol (Gly) (1:2 mol mol^{-1}) eutectic mixture in the presence of K_2CO_3 (1 equiv) as a base, $Pd(OAc)_2$ (10 mol%) as a catalyst, and Ph_3P (40 mol%) as a ligand. After 6 h heating at 60 °C, a regioisomeric mixture of educts **3a**,**a**′ was isolated in 60% yield, the **3a**/**3a**′ ratio being 82:18 (Table 1, entry 1). A similar yield (62%) was achieved in the absence of Ph_3P, although the reaction became less regioselective (**3a**/**3a**′ ratio: 55/45, Table 1, entry 2). Bearing in mind that the next step is the reduction of alkene, we further optimized these last conditions. Lower yields in **3a**,**a**′ (up to 25%) where recorded when either the DHF or the K_2CO_3 stoichiometry was

Table 1. Screening of conditions for the MH reaction in unconventional solvents.[a]



1a **2a** **3a** **3a'**

Entry	Solvent	Catalyst [mol%]	T [°C]	*t* [h]	**3a**,**a**′ yield [%][b] (ratio **3a**:**3a**′)
1	ChCl/Gly	$Pd(OAc)_2$ (10)	60	6	60 (82:18) [c]
2	ChCl/Gly	$Pd(OAc)_2$ (10)	60	6	62 (55:45)
3	ChCl/Gly	$Pd(OAc)_2$ (10)	60	6	12[d,e]
4	ChCl/Gly	$Pd(OAc)_2$ (10)	60	6	25[d,f]
5	ChCl/Gly	$Pd(OAc)_2$ (10)	60	6	40 (55:45)[g]
6	ChCl/Gly	$Pd(OAc)_2$ (10)	90	6	98 (55:45)
7	MA/ChCl	$Pd(OAc)_2$ (10)	90	6	10[d]
8	ChCl/urea	$Pd(OAc)_2$ (10)	90	6	10[d]
9	ChCl/EG	$Pd(OAc)_2$ (10)	90	6	42
10	Gly	$Pd(OAc)_2$ (10)	90	6	25 (55:45)
11	**ChCl/Gly**	**$Pd(OAc)_2$ (3)**	**90**	**6**	**98 (55:45)**
12	ChCl/Gly	$Pd(OAc)_2$ (1)	90	6	65 (55:45)
13	ChCl/Gly	$Pd(OAc)_2$ (1)	120	9	98 (55:45)
14	ChCl/Gly	$PdCl_2$ (10)	90	12	50 (55:45)
15	ChCl/Gly	Pd/C (10)	90	12	5[d]
16	ChCl/Gly	CuO (10)	90	12	NR[h]
17	ChCl/Gly	$Cu(OAc)_2$ (10)	90	12	NR[h]
18	ChCl/Gly	CuI (10)	90	12	NR[h]
19	THF	$Pd(OAc)_2$ (10)	66	24	10[c,d]
20	DMF	$Pd(OAc)_2$ (10)	70	24	17[c,d,i]

[a] Typical conditions: 1.0 g of solvent per 0.5 mmol of **2a**, 1.5 mmol of **1a** and 0.5 mmol of K_2CO_3; DES: ChCl/Gly (1:2 mol mol^{-1}); malonic acid (MA)/ChCl (1:1 mol mol^{-1}); ChCl/urea (1:2 mol mol^{-1}); ChCl/ethylene glycol (EG) (1:2 mol mol^{-1}). [b] The yields reported are for products isolated and purified by column chromatography unless otherwise stated. [c] In the presence of 40 mol% of Ph_3P. [d] Yield determined by ^{1}H NMR using dibromomethane as an internal standard; ratio **3a**/**3a**′ not calculated. [e] **1a**: 1 equiv. [f] K_2CO_3: 0.5 equiv. [g] K_2CO_3 was replaced by NaOH (1 equiv). [h] NR: no reaction. [i] 40% yield after heating under microwave irradiation at 220 °C for 12 min.

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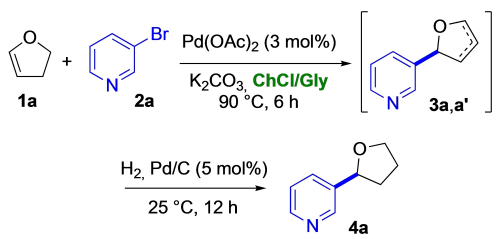
reduced from 3 to 1 and from 1 to 0.5 equiv, respectively (Table 1, entries 3,4). The replacement of K_2CO_3 by NaOH was similarly ineffective (**3a**,**a**′: 40% yield) (Table 1, entry 5). However, when the reaction temperature was elevated to 90 °C, the overall yield of **3a**,**a**′ became almost quantitative (98%) after 6 h reaction time (Table 1, entry 6).

Notably, the employment of either more acidic (malonic acid/ChCl 1:1 mol mol^{-1}) or more basic (ChCl/urea 1:2 mol mol^{-1}) eutectic mixtures, as well as switching ChCl/Gly for ChCl/EG (1:2 mol mol^{-1}) or Gly, caused a drastic decrease of the reaction yield of **3a**,**a**′ to 10–42%, the remaining being starting material only (Table 1, entries 7–10).[23] Gratifyingly, the amount of the catalyst could be reduced to 3 mol%, which still afforded **3a**,**a**′ in 98% yield after 6 h at 90 °C (Table 1, entry 11). Conversely, when the catalyst loading was up to 1 mol%, it required up to 9 h heating at 120 °C for the quantitative conversion of the substrates (Table 1, entries 12,13). A catalyst screen identified $Pd(OAc)_2$ as the optimal choice among several Pd and Cu catalysts examined (Table 1, entries 14–18). By alternatively running the MH reaction in dry THF (66 °C, reflux) or in dry DMF (70 °C), in the presence of K_2CO_3 (0.5 mmol), $Pd(OAc)_2$ (10 mol%) and Ph_3P (40 mol%), the overall yield of **3a**/**3a**′ was 10 and 17% yield, respectively, after 24 h (ratio **3a**/**3a**′: 55:45). This yield could be increased to 40% after heating the above mixture in DMF under microwave irradiation, at 220 °C for 12 min (Table 1, entries 19,20).

We next focused on the following reduction step. Under the best conditions identified (Table 1, entry 11), the formation of the desired saturated educt **4a** was not observed upon directly subjecting the mixture resulting from the cross-coupling reaction to hydrogenation (6 atm H_2). On the other hand, such reduction proceeded smoothly, at 4 atm H_2, when working under heterogeneous conditions in the presence of Pd/C (5 mol%) as a catalyst, leading to the isolation of **4a** in 97% yield after 12 h stirring at room temperature (RT, 25 °C) (Scheme 2). By reacting **1a** with **2a** in the presence of the two catalytic systems since the beginning, that is, $Pd(OAc)_2$ (3 mol%) and Pd/C (5 mol%), for 6 h at 90 °C, and subjecting the resulting mixture to hydrogenation (4 atm H_2), educt **4a** was isolated in 20% yield only, 3,3′-bipyridine (the homocoupling product of **2a**) being isolated as a major by-product in 80% yield.

We also investigated the recycle/reuse of the solvent/catalyst. After extracting the product **4a** with cyclopentyl methyl ether (CPME), new fresh reagents (**1a** and **2a**) were added to the resulting eutectic mixture, and the two cross-coupling/reduction steps were repeated. Unfortunately, the yield of **4a** dropped down to 61% just after the 1st cycle.



Scheme 2. One-pot reductive MH reaction in DES.

The recycle of the solvent/catalyst was similarly ineffective even if performed soon after the MH reaction. After extracting the products **3a**,**a**′ with CPME (98% yield), the addition of **1a** and **2a** furnished educts **3a**,**a**′ in 50% and 20% yield after the 1st and the 2nd recycle, respectively. We noticed that, in both cases, the viscosity of the system increased considerably, and a precipitation of Pd-black also occurred, which indicated modification of the catalyst(s). Thus, we decided not to investigate further this process.

With these conditions in hands, we then investigated the generality of this one-pot tandem cross-coupling-reduction process by reacting several (hetero)aryl halides (**2b**–**h**) with DHF **1a** (Scheme 3). 2-PhenylTHF (**4b**) could straightforwardly be isolated in 95% yield starting from iodobenzene (**2b**). Assorted aryl derivatives with electron-donating (4-MeO, 4-NH_2, 2-CH_2OH) (**2c**–**e**) or electron-withdrawing (2-CHO, 3-CN) (**2f**,**g**) groups were also good substrates, affording the educts **4c**–**g** in 85–92% yield. Chlorobenzene was unreactive with **1a**. An electron-rich five-membered heterocycle, such as 2-iodothiophene (**2h**), proved to be a competent partner as well, delivering educt **4h** in 83% yield, whereas 2-bromothiophene gave the corresponding homocoupling product. Other heterocycles like 2,3-dihydropyrrole did not react under the above conditions.

To further explore the utility of this new protocol for Pd-catalyzed reductive MH reactions using eutectic mixtures, we then investigated the synthesis of 2-(hetero)aryl THP derivatives **5**. As shown in Scheme 3, telescoped, one-pot cross-coupling/reduction processes between DHP **1b** and iodobenzene (**2b**) as well as electron-deficient (**2a**) or electron-rich (**2c**,**d**,**h**) (hetero)aryl halides proceeded uneventfully, affording the desired educts **5a**–**e** in moderate to good yields though (42–66%). The latter could not be improved at longer reaction times or at a higher catalyst loading, the remaining being either unreacted (hetero)aryl halides or homocoupling side products. Most probably, the greater flexibility of the six-membered cycle, compared to the five-membered one, makes the two steps of syn-addition and syn-β-hydride elimination, related to the MH reaction, more challenging. Finally, we embarked on the synthesis of THF derivatives **4i**,**j**, which are key intermediates for the preparation of organic skeletons **7**, on a 2-gram scale. The latter are known to be strong inhibitors of Kv1.2 channel, and have been proposed for stroke treatment, as antidepressant and for their lipid-lowering activity (Scheme 4c).[22] Following the afore-mentioned conditions, DHF **1a** (26.1 mmol) was first cross-coupled with 3-iodobenzonitrile (**2g**, 1.993 g) in a ChCl/Gly eutectic mixture. The resulting mixture of the two regioisomers **3g**,**g**′ (^{1}H NMR analysis: 86% yield, 55:45 molar ratio) was directly hydrogenated at RT in the presence of Pd/C (5 mol%) (H_2: 4 atm) for 12 h, and finally reacted in the same pot with $LiAlH_4$ to reduce the nitrile group, thereby providing the benzylamine derivative **4i** in 81% yield (1.25 g) (Scheme 4a). As for the synthesis of the secondary amine **4j**, the mixture of regioisomers **3g**,**g**′ was first extracted with CPME, and the resulting ethereal solution was treated with a solution

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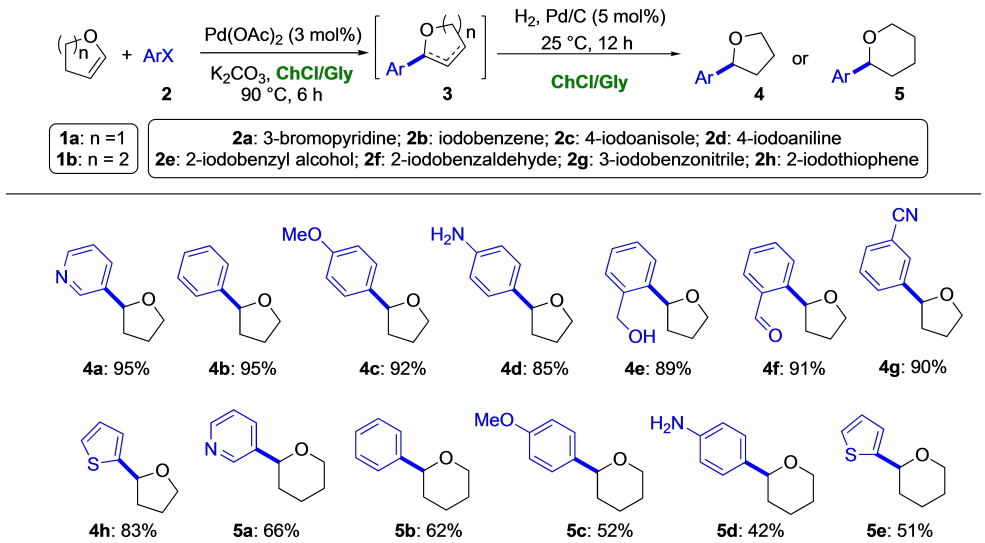
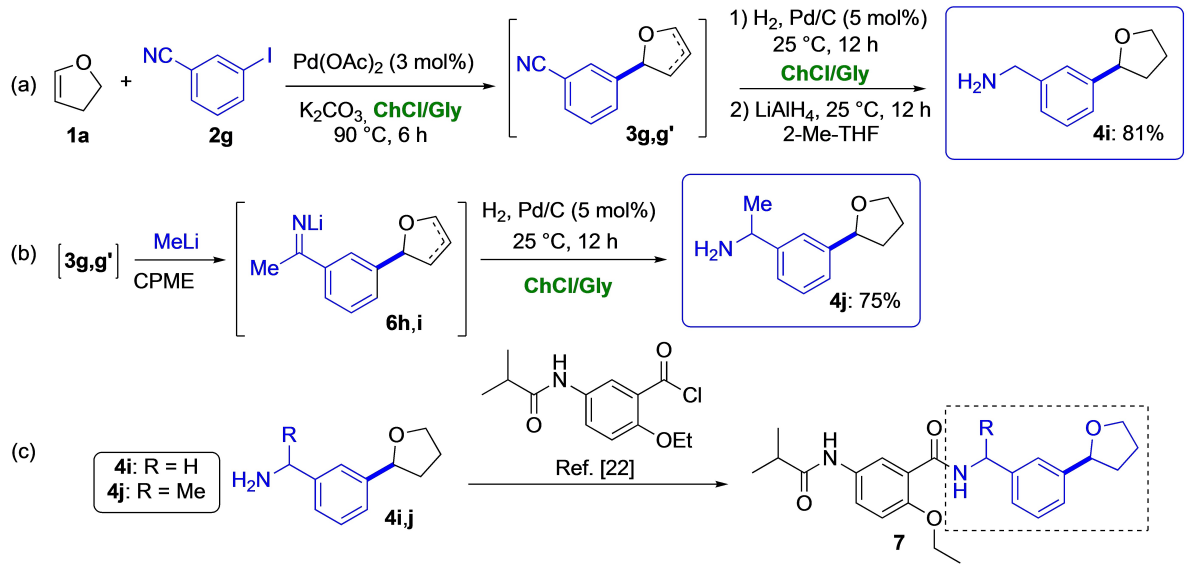


Scheme 3. Scope of the reductive MH reaction in the synthesis of 2-(hetero)aryl THF **4** and 2-(hetero)aryl THP **5** derivatives.



Scheme 4. Synthesis of THF derivatives **4i,j** (side chains of pharmacologically active compounds **7**) via reductive MH reactions in DES.

of MeLi (1.5 M, 1.5 equiv). The solution of the putative lithiated ketimines **6h,i** was subsequently subjected to hydrogenation in a ChCl/Gly eutectic mixture in the presence of Pd/C (5 mol%), thereby providing **4j** in 75% yield (1.245 g) as a mixture of two separable diastereomers (1.3:1 molar ratio by ^{1}H NMR analysis) (for details, see ESI) (Scheme 4b).

Conclusion

In summary, we have shown that telescoped, one-pot reductive MH reactions between DHF or DHP and several electron-rich and electron-deficient (hetero)aryl halides can regioselectively be carried out using a ChCl/Gly eutectic mixture as an environmentally responsible reaction medium. These reactions, which are of great value to minimize chemical waste,[24] 1) allow for the straightforward synthesis of valuable functionalized 2-(hetero)aryl THF and THP derivatives in up to 95% yield, 2) proceed without any halfway isolation/purification step, 3) are feasible working under aerobic conditions, and 4) do not require additional ligands. The usefulness of the methodology was demonstrated by the sustainable preparation of two key side chains THF derivatives of pharmaceutically relevant molecules. Further applications of DESs as green and sustainable reaction media for the preparation of other functionalized heterocycles are underway and will be reported in due course.

Experimental Section

General procedure for the synthesis of 2-(hetero)aryl THF or 2-(hetero)aryl THP derivatives in DESs

In a 10 mL round-bottom flask, aryl halide **2** (0.5 mmol), 2,3-dihydrofuran **1 a** (1.5 mmol) or 3,4-dihydro-2*H*-pyran **1 b** (1.5 mmol), K_2CO_3 (0.5 mmol, 69 mg) and ChCl/Gly (1.0 g), were sequentially added. The mixture was stirred until it was homogeneous. Then, $Pd(OAc)_2$ (3.0 mol%, 0.015 mmol, 3 mg) was added to the mixture at 25 °C, and the flask was closed with a glass stopper to prevent the evaporation of **1 a** or **1 b**. The reaction was stirred for 6 h at 90 °C. After this time, the reaction mixture was cooled down to room temperature, and 2.0 g of ChCl/Gly and Pd/C 10% (5 mol%, 0.025 mmol, 27 mg) were sequentially added. The hydrogenation was run under stirring at room temperature in a stainless steel autoclave at 4 atm for 12 h. Finally, the reaction mixture was extracted with CPME (3×3 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered through a celite pad, and evaporated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (hexane/EtOAc 9:1 ÷ 6:4) to produce the desired reduction product **4** or **5**.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Deep eutectic solvents · Mizoroki-Heck reaction · Oxygen heterocycles · Tetrahydrofurans · Tetrahydropyrans

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