Palladium-Catalysed Direct Regioselective Synthesis of Cyclic Ketals from Electron-Rich Olefins and Aryl Bromides in Ionic Liquids

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Abstract: The Heck reaction comprises one of the most important carbon-carbon coupling reactions in organic synthesis. The popularity of the reaction is attributable to the broad availability of aryl halides and to the tolerance of the reaction for a wide variety of functional groups. Reported herein is a direct method for the highly regioselective preparation of 5-membered and 7-membered cyclic ketals in respectable to good yields from aryl bromides (**1a–k**) and electron-rich olefins (**2a** and **b**). The reaction is performed with palladium catalysis using ionic liquid as solvent with no need for any halide scavengers, providing an alternative to the use of aryl triflates. The ionic liquid is found to direct the reaction pathway towards exclusive α-arylation *via* a cationic route.

Keywords: Heck reaction; ionic liquids; ketals; palladium; regioselectivity

Introduction

The formation of carbon-carbon bonds is one of the most significant reactions in synthetic chemistry. Among the many established methods for doing this, the palladium-catalysed arylation and vinylation of olefins by aryl and vinyl halides or their derivatives, known as the Heck reaction, is one of the most important.[1,2] The Heck reaction generally works well with olefins possessing electron-withdrawing substituents, such as $-CO_2R$ and $-CN$, i.e., electron-deficient olefins. When aryl halides are used, electron-rich olefins, such as acyclic enol ethers, silanes, and enol amides, often suffer from poor α/β-regioselectivity, producing a mixture of linear and branched regioisomer**s** (Scheme 1). This problem thus hampers the applicability in synthetic chemistry.

Whilst the use of electron-rich olefins in Heck arylation reactions is limited, progress made in this area thus far has enabled very regioselective arylation to be performed. Early research by Hallberg and Larhed and co-workers revealed that the regioselectivity of the palladium-catalysed arylation of enol ethers is sensitive to structure of the enol ether, the arylating agent used, and the reaction medium.[3] Control of these factors allows control of regioselectivity for arylation at the olefinic α- or β-carbons of the enol ether. It was also suggested that electron-rich aryl systems favour α-arylation whereas electron-poor aryls favour β-arylation. A significant advance was made by Cabri, recording α/β-regioselectivities of > 99/1 with acyclic enol ethers such as butyl vinyl ether in DMF; the key finding was to use bidentate ligands and stoichiometric amounts of silver or thallium salts as halide scavengers, or replace the arylating halides with triflates.[4,5] The chemistry has since been applied to a number of synthetic efforts.[1] A drawback to the chemistry is that triflates are base-sensitive, thermally labile, and are rarely commercially available, and the inorganic salt additives are costly and toxic. Hence, there is a need for an alternative route that allows for the use of aryl halides and circumvents the need for the halide scavengers, while maintaining regioselectivity.
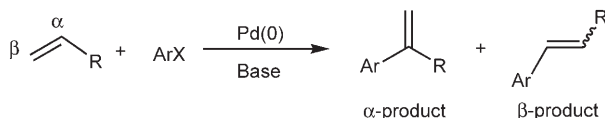
**Scheme 1.** Formation of regioisomers in the Heck reactions.

The regioselective reactions observed with triflates or halide scavengers can be rationalised by the mechanism shown in Scheme 2, in which two reaction pathways are suggested. Path A portrays the dissociation of one neutral ligand, while path B is characterised by the dissociation of halide anions generating a cationic Pd(II)-olefin complex, which is believed to be the key species that gives rise to the α-regioselectivity.[4,5] Triflates or halide scavengers are expected to facilitate the formation of the cationic palladium species and hence the α-arylated products. In our research into catalysis in ionic liquids,[6] we thought that the formation of such ionic species might also be promoted by ionic liquid as solvent because this would be favoured by electrostatic interactions.[6a] Indeed, we have found that several classes of electron-rich olefins can be arylated highly regioselectively in imidazolium ionic liquids by directly using aryl halides with no need for a halide scavenger.[6a–c,j] Similar results have also been reported by other groups by using ionic liquid solvents.[7] Herein, we report that the Heck arylation of hydroxyalkyl vinyl ethers by aryl bromides can be carried out in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]), leading to interesting cyclic ketal compounds in a highly selective manner. These ketals can be useful as intermediates in the synthesis of anti-HIV agents or as protected precursors for carbonyls.[8]

Hallberg and Larhed and co-workers were the first to report the highly regioselective arylation of hydroxyalkyl vinyl ethers to synthesise cyclic ketals, using aryl triflates in DMF.[9] Aryl bromides and iodides were also used; but these required the addition of TlOAc and tend to afford slow arylation.[9] When aryl halides are used without the halide scavenger, hydroxyalkyl vinyl ethers can be arylated highly regioselectively in DMF to give the β-arylated products by using a tetradentate phosphine-palladium catalyst as shown by Santelli and co-workers.[10] As will be seen, ionic liquids as solvent allow aryl bromides to be directly employed to give the α-products. Apart from this advantage, there is a growing need to replace toxic and/or volatile organic solvents with eco-friendly media. In this context, room temperature ionic liquids such as those based on imidazolium salts have been recognised as a promising alternative to hazardous organic solvents, due to the low vapour pressure and tuneable physiochemical properties.[11]

Results and Discussion

Following the successful arylation by aryl halides of vinyl ethers and other electron-rich olefins in the ionic liquid [bmim][BF$_4$],[6a–c,j] we were delighted to find that the hydroxyalkyl vinyl ether **2a** could also be arylated highly regioselectively, and the resulting products can cyclise to give cyclic ketals under the same conditions. To the best of our knowledge, this is the first time when a hydroxyalkyl vinyl ether is selectively α-arylated by an aryl bromide without recourse to a halide scavenger. The arylation of hydroxyalkyl vinyl ether **2a** was carried out with a variety of aryl bromides in [bmim][BF$_4$], with all the reactions affording the cyclic ketals that arise from the α-arylated **2a**. In a typical reaction, a mixture of **1**, **2a**, NEt$_3$, Pd(OAc)$_2$, and DPPP was heated in [bmim][BF$_4$] for a certain period of time under an inert atmosphere, and standard work-up afforded the product **3**. The results obtained are summarised in Table 1. All the reactions finished in > 99/1 regioselectivity in favour of the branched products with good to excellent yields. As can be seen, the reactions all completed within 24 h, regardless of the nature of the substituents on the aryl rings, e.g., compare entry 2 with entry 9. A notable example is the coupling of **1c**, which provides
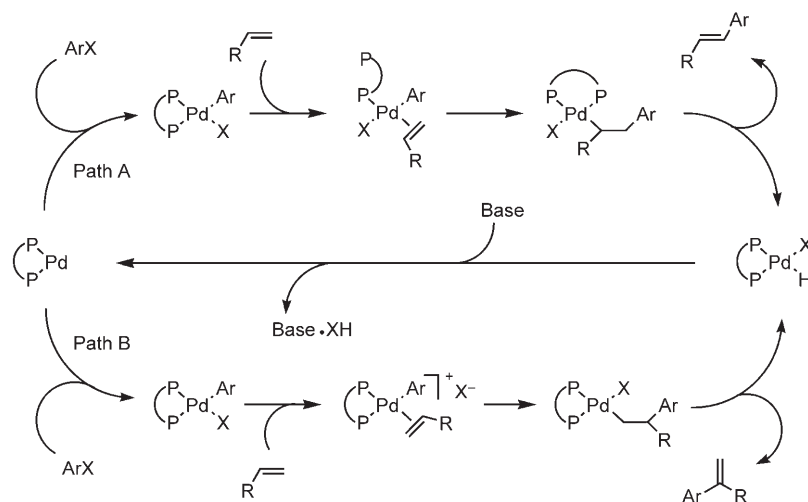
Scheme 2. The suggested neutral and cationic pathways of the Heck reaction.

Table 1. Regioselective arylation of hydroxy vinyl ether **2a**.[a]

Entry	ArBr		Product		t [h]	Yield [%]
1	MeOC—	**1a**	MeOC—	**3a**	22	86
2	NC—	**1b**	NC—	**3b**	24	94
3	OHC—	**1c**	OHC—	**3c**	18	63
4	F—	**1d**	F—	**3d**	24	86
5	F—	**1e**	F—	**3e**	24	86
6	F (ortho)	**1f**	F	**3f**	24	96
7		**1g**		**3g**	18	83
8	Me—	**1h**	Me—	**3h**	24	80
9	MeO—	**1i**	MeO—	**3i**	24	89
10	naphthalene	**1j**	naphthalene	**3j**	8	90
11	naphthalene	**1k**	naphthalene	**3k**	12	72

[a] *Reaction conditions:* 1.0 mmol **1**, 2.0 mmol **2a**, 3 mol % Pd(OAc)$_2$, 6 mol % DPPP, and 1.5 mmol NEt$_3$ in 2 mL [bmim] [BF$_4$] at 115 °C; 100 % conversion and > 99/1 regioselectivity for all, as determined by ^{1}H NMR; isolated yields.

a protected ketone and thus enables further elaboration on the more reactive aldehyde. As aforementioned, similar coupling of aryl halides has been shown to be feasible in DMF by Hallberg and Larhed and co-workers, but it requires stoichiometric TlOAc. In its absence, a mixture of α- and β-regioisomers was obtained.[9] In contrast, no halide scavenger is required here, and the reaction appears to be faster. It is also interesting to point out that the ionic liquid [bmim][BF$_4$] allows the internal arylated product to

cyclise to give **3** with no need for an acid to be added. HOAc is sometimes necessary for the reactions in conventional solvents.[9]

Under the same reaction conditions, the hydroxy-alkyl vinyl ether **2b** could also be arylated highly regioselectively, and the resulting products cyclise to give the 7-membered cyclic ketals **4**. The results obtained are summarised in Table 2. As can be seen, the reaction is completed within 32 h, affording the cyclic ketals in good isolated yields.

**Table 2.** Regioselective arylation of 1,4-butanediol vinyl ether **2b**.[a]

Entry	ArBr		Product		t [h]	Yield [%]
1	MeOC—C₆H₄—Br	**1a**		**4a**	24	77
2	NC—C₆H₄—Br	**1b**		**4b**	24	76
3	F—C₆H₄—Br	**1d**		**4d**	24	86
4	F—C₆H₄—Br	**1e**		**4e**	32	72
5	F—C₆H₄—Br	**1f**		**4f**	30	61
6	C₆H₅—Br	**1g**		**1g**	24	61
7	naphthyl—Br	**1j**		**4j**	24	71
8	naphthyl—Br	**1k**		**4k**	30	77

[a] *Reaction conditions:* 1.0 mmol **1**, 2.0 mmol **2b**, 3 mol% Pd(OAc)₂, 6 mol% DPPP, and 1.5 mmol NEt₃ in 2 mL [bmim][BF₄] at 115 °C; 100% conversion and > 99/1 regioselectivity for all, as determined by ^{1}H NMR; isolated yields.

The arylation of **2** presumably proceeds *via* the cationic pathway B (Scheme 2), and we believe that it is the unique ionic property of the ionic liquid that makes this possible. In accordance with the findings made by Hallberg and Larhed,[9] the reaction first leads to the arylation of **2**, giving rise to an α-arylated vinyl ether. This is followed by cyclisation to give the cyclic ketals **3** or **4** (Scheme 3). Unlike the reaction in DMF, however, no additional Brönsted acid is needed for the cyclisation in [bmim][BF₄]. In the latter, the reaction might be promoted by the ammonium salt HNEt₃⁺ generated in the Heck coupling step or by the Lewis acidic C2-H proton of the imidazolium cation. Hallberg and Larhed showed that NH₄Br promotes the cyclisation.[9] There may also exist a possibility of Pd(II)-catalysed cyclisation followed by protonolysis to release the ketal.
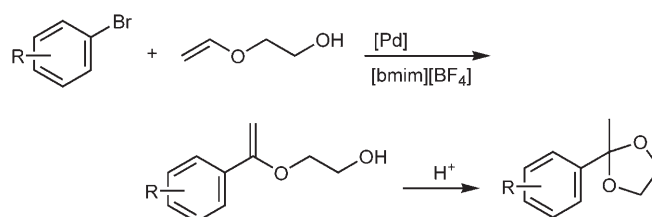
Scheme 3. A possible sequence leading to the cyclic ketals.

The regioselective Heck arylation of **2a** can also be performed in the ionic liquid [bmim][PF₆]. [bmim][PF₆] is known to readily form a triphasic system with water and non-polar solvents, which makes possible the recycle of catalyst.[12] As is shown in Scheme 4, when diethyl ether was used to extract the product
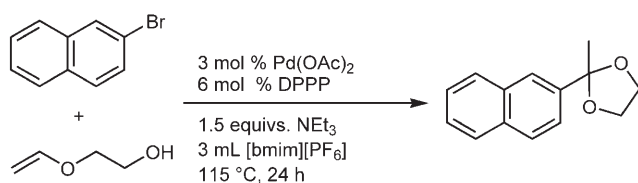
Run	1	2	3	4	5	6	7	8
Yield [%]	85	89	84	83	81	86	81	80

Scheme 4. Catalyst and ionic liquid recycle in the arylation of **2a**.

and water to extract the ammonium bromide salt, the catalyst and the ionic liquid [bmim][PF$_6$] can be recycled and reused for 8 times without significant loss of their catalytic effect under the chosen conditions.

Conclusions

In summary, we have developed an efficient method for the internal arylation of hydroxyalkyl vinyl ethers by aryl bromides by using Pd-DPPP catalysis in the ionic liquids [bmim][BF$_4$] and [bmim][PF$_6$]. The resulting products cyclise *in situ* to give cyclic ketals in good to excellent isolated yields, and the catalyst and ionic liquid can be recycled. Although the detailed reaction mechanism remains to be clarified, the Pd-DPPP catalysis described here is typical of the Heck reaction proceeding *via* the cationic pathway. As a solvent made entirely of ions, the ionic liquid promotes this pathway and hence renders the addition of halide scavengers totally unnecessary.

Experimental Section

General Procedure for the Heck Arylation in Ionic Liquid

An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl bromide **1** (1.0 mmol), Pd(OAc)$_2$ (0.03 mmol), DPPP (0.06 mmol), and [bmim][BF$_4$] (2 mL) under nitrogen at room temperature. Following degassing three times, a hydroxyalkyl vinyl ether **2** (2.0 mmol) and NEt$_3$ (1.5 mmol) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at 115 °C. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for NMR analysis. The rest of the mixture was extracted with CH$_2$Cl$_2$ (3×20 mL), and the combined organic layer was washed with water until neutrality, dried (Na$_2$SO$_4$), filtered, and concentrated under vacuum. The cyclic ketal derived from the arylated olefin was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl

acetate and hexane (5/95 to 30/70) containing 2% (in volume) triethylamine as eluant. The isolated yields of the products are given in Table 1 and Table 2, and the analytical details of the products are found in the Supporting Information.

Recycle of the Palladium Catalyst and Ionic Liquid in the Heck Arylation

An oven-dried, two-necked round-bottom flask containing a stir bar was charged with 2-bromonaphthalene **1j** (1.0 mmol), Pd(OAc)$_2$ (0.03 mmol), DPPP (0.06 mmol), and [bmim][PF$_6$] (3 mL) under nitrogen at room temperature. Following degassing three times, 2-hydroxy vinyl ether **2a** (2.0 mmol) and NEt$_3$ (1.5 mmol) were injected. The flask was placed in an oil bath, and the mixture was stirred and heated at 115 °C. After a reaction time of 24 h, the flask was removed from the oil bath and cooled to room temperature. The resulting mixture was extracted with diethyl ether (5× 10 mL), and the rest of the mixture was washed with water (3×10 mL). The recovered catalyst and ionic liquid were ready for a next run. The diethyl ether was then washed with water until neutrality, dried (Na$_2$SO$_4$), filtered, and concentrated under vacuum. The cyclic ketal **3j** was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (10/90) containing 2% (in volume) triethylamine as eluant. The isolated yields of the products are given in Scheme 4.

Acknowledgements

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