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Feeding the Heck Reaction with Alcohol: One-Pot Synthesis of Stilbenes from Aryl Alcohols and Bromides

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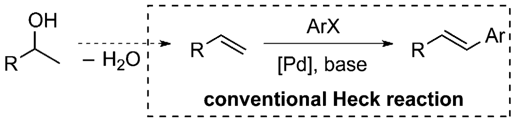
Abstract: Aryl alcohols are employed as feedstock for the Heck reaction. Keggin-type heteropolyacids catalyse the selective dehydration of the alcohols to styrenes, which, in one-pot, undergo palladium-catalysed Heck arylation with aryl bromides, affording broadly functionalised stilbenes. The choice of solvent is critical for the cascade dehydration–Heck reaction, with electron-rich aryl alcohols preferring a basic medium while electron-deficient ones demanding solvents of lower basicity.

Keywords: alcohols; dehydration; Heck reaction; olefination; palladium; polyoxometalates; stilbenes

The Heck reaction is one of the most widely used methods for the construction of carbon-carbon bonds in modern organic chemistry.[1] In a typical Heck reaction, an aryl halide couples with an olefin in the presence of a palladium catalyst and base, furnishing an arylated olefin (Scheme 1). In recent years, much effort has been focused on the dehydrogenative Heck reaction, which allows arene C–H bonds to be directly coupled to olefins, obviating the need for halogenation steps.[2] *The scope of the Heck reaction could be further widened if olefins could be easily generated, for example, in-situ*, as often the required olefins are not commercially available and may have poor stability.[3] For example, styrenes, which lead to stilbenes in the Heck reaction, are not commercially available in most cases and those that are available often need to be stored at low temperatures to prevent self-polymerisation. Consequently, only a few styrenes have appeared in the Heck reaction ever since the reaction was invented,[1] although stilbenes are found in many natural sources, show a number of pharmacological activities and are widely used as industrial dyes.[4]



Scheme 1. Alcohols as pseudo-olefins for the Heck reaction.

Realising that secondary aryl alcohols can be dehydrated to give styrenes, we thought it might be possible to replace the latter with the former in the Heck reaction (Scheme 1). We report herein that one-pot Heck coupling of aryl alcohols with ArBr is indeed possible, affording various stilbenes, in which the alcohol is *in-situ* dehydrated by a green, solid acid catalyst.[5] While this work was in progress, a similar approach using aryl iodides was reported by Sinha and co-workers.[6] A drawback of this interesting method is the need for heating (≥150 °C) under microwave irradiation and the use of a specific ionic liquid as solvent, in addition to limited substrate scope regarding the aryl alcohols.

Before attempting the one-pot synthesis of stilbenes, we needed to develop a general and efficient catalytic method for the dehydration of secondary aryl alcohols to the corresponding styrenes. The catalytic dehydration of secondary aryl alcohols is well precedented; but unfortunately all current methods have their own problems.[7] Strong Brønsted acids, such as sulfuric acid and *p*-toluenesulfonic acid, are commonly employed but suffer from low selectivity and low functional group tolerance.[8] Transition metal catalysts have proven capable of this transformation, although the cost associated with the use of precious metals is not desirable.[9] Heteropolyacids (HPAs), safe, easy-to-handle and economic solid catalysts,[10] have proven to be excellent in terms of activity; but dimerisation of the product styrene is a major drawback to their use.[11] To the best of our knowledge, no general catalytic method for the production of func-

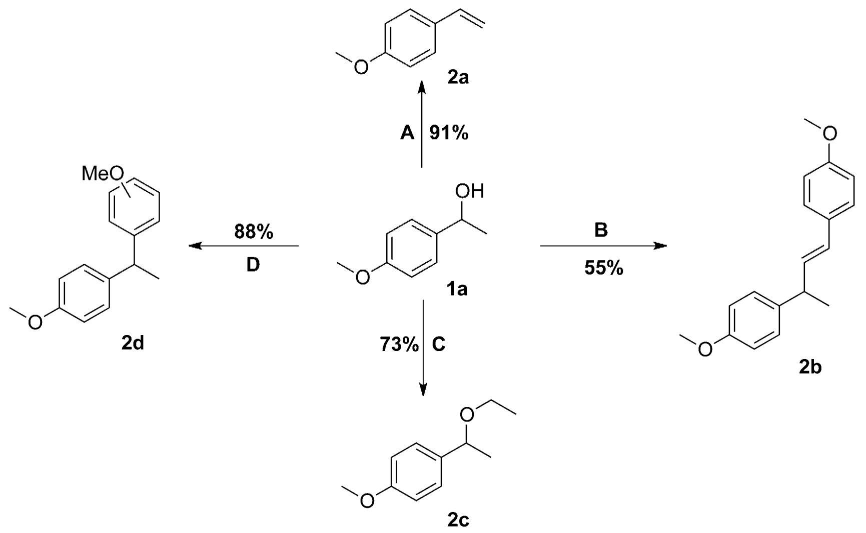


Figure 1. Effect of solvent on the product distribution of HPA-catalysed reactions of 1-(4-methoxyphenyl)ethanol **1a**. Reactions were carried out on a 1.0-mmol scale in 2 mL solvent using $H_3PW_{12}O_{40}$ (17 mg) as catalyst. **A** = DMSO, 100 °C, 1 h. **B** = diglyme, 100 °C, 1 h. **C** = ethanol, 100 °C, 1 h. **D** = anisole, 130 °C, 1 h.

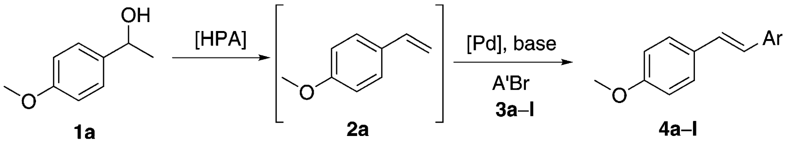
tionalised styrenes from secondary aryl alcohols has ever been reported.

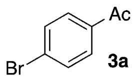
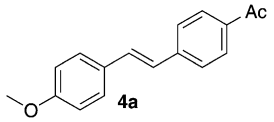
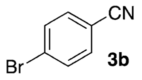
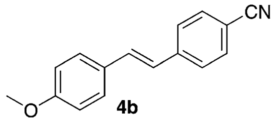
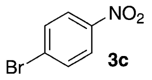
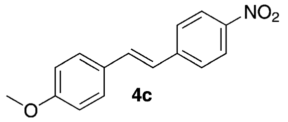
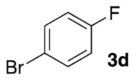
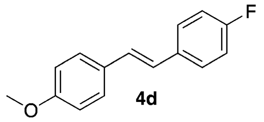
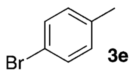
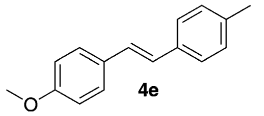
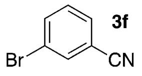
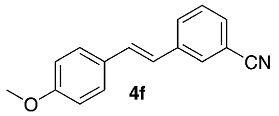
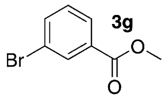
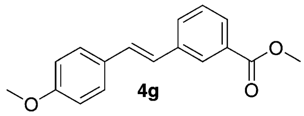
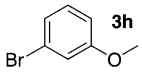
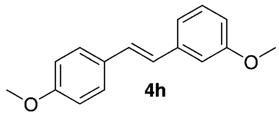
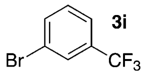
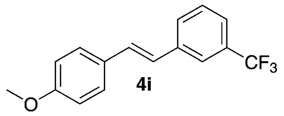
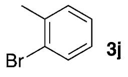
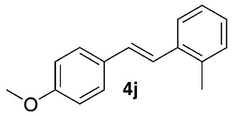
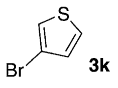
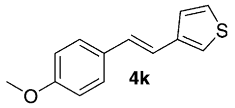
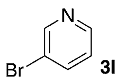
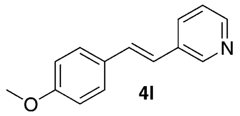
Given the benign features of HPAs, we set out to find conditions for their use in catalytic dehydration. As it has already been reported that the solvent plays a key role in the product distribution of the HPA-catalysed dimerisation of α-methylstyrene,[12] examining the effect of solvents seemed to be a good starting point. We began by subjecting 1-(4-methoxyphenyl)ethanol **1a** to thermal activation in the presence of a catalytic amount of the Keggin type HPA, $H_3PW_{12}O_{40}$, in a wide variety of solvents (Figure 1). Somewhat surprisingly, we observed that both the catalytic activity and product selectivity were strongly affected by the solvent. In the solvents DMF, DMA and MeCN, no reaction was observed. The reactions in hexane and sulfolane were rapid but non-selective. The reaction in ethanol led to an ether product **2c** in 73% isolated yield, which most likely results from nucleophilic interception of a cationic intermediate formed by protonation of the benzylic alcohol by the acid catalyst (Figure 1, **C**).[13] In a similar way, a Friedel–Crafts type reaction occurred when anisole was used as the solvent (Figure 1, **D**, 88% isolated yield of **2d**; 10:1 *para*/*ortho* regioselectivity).[14] When diglyme was used as the solvent, the desired dehydration occurred; however, the resultant styrene had been completely dimerised, leading to a 55% isolated yield of (*E*)-4,4′-(but-1-ene-1,3-diyl)bis(methoxybenzene) (**2b**) (Figure 1, **B**). Remarkably, the dimerisation was completely suppressed when the reaction was carried out in DMSO, yielding the desired styrene **2a** in 91% isolated yield (Figure 1, **A**).

Having found suitable conditions for the desired dehydration reaction, we turned our attention to the development of a one-pot dehydration–Heck procedure for the synthesis of stilbenes. Our initial attempts to have the HPA and components necessary for the Heck reaction in one-pot at the same time were unsuccessful, as the presence of a base needed for the Heck arylation neutralised the HPA, inhibiting the dehydration reaction. We therefore decided to develop a one-pot, two-step procedure consisting of initial dehydration of the secondary aryl alcohol in the presence of the HPA, followed by addition of a base, palladium catalyst and an aryl bromide coupling partner. A mixture of **1a** and HPA in DMSO was stirred at 100 °C for 1 h, at which point a mixture of aryl bromide **3a**, NEt_3, $Pd(dba)_2$ and $P(t\text{-}Bu)_3{\cdot}HBF_4$[15] in DMF was added and the resultant mixture was stirred for a further 4 h. To our delight, this resulted in efficient formation of the desired stilbene product **4a**, with an isolated yield of 82% (Table 1). A number of aryl bromides was then examined. As can be seen from Table 1, this cascade reaction sequence proved tolerant of a wide range of functionality incorporated on the aryl bromide, yielding functionalised stilbenes in good yields. Both electron-rich and electron-deficient aryl bromides were successful, with substitution at the *ortho*, *meta* and *para* positions posing no problem. Furthermore, heterocyclic substrates were also shown to be viable (entries 11 and 12).

If this newly developed protocol is truly general, it must work for a variety of secondary aryl alcohols. Therefore, we subjected a wide range of secondary aryl alcohols to the dehydration–Heck arylation sequence (Table 2). After attempting a small number of aryl alcohol substrates with varying electronic properties, it quickly became apparent that the current dehydration conditions were only suitable to electron-rich

Table 1. Dehydration–Heck arylation of benzylic alcohol **1a** with aryl bromides **3a–l**.[a]



Entry	ArBr	Product	Yield [%][b]
1	 **3a**	 **4a**	82
2	 **3b**	 **4b**	74
3	 **3c**	 **4c**	76
4	 **3d**	 **4d**	85
5	 **3e**	 **4e**	69
6	 **3f**	 **4f**	66
7	 **3g**	 **4g**	71
8	 **3h**	 **4h**	83
9	 **3i**	 **4i**	71
10	 **3j**	 **4j**	80
11	 **3k**	 **4k**	74
12	 **3l**	 **4l**	72

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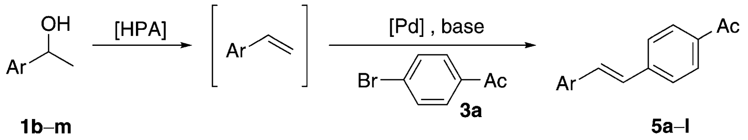
[a] *General conditions:* reactions carried out with **1a** (457 mg, 3.0 mmol) and $H_3PW_{12}O_{40}$ (50 mg) in 3 mL of DMSO at 100 °C for 1 h, followed by addition of Et_3N (304 mg, 3.0 mmol), aryl bromide **3** (2.0 mmol), $Pd(dba)_2$ (23 mg, 2 mol%), P(*t*-Bu)$_3$·HBF_4 (35 mg, 6 mol%) and DMF (3 mL) at 100 °C for 4 h.

[b] Yield of isolated product.

aryl alcohols. For electron-neutral aryl alcohols, a change from DMSO to diglyme was necessary, which allowed the alcohols to dehydrate to the corresponding styrene, with only small levels of the undesired dimerisation reaction.[16] In the case of the electron-deficient aryl alcohol **1c**, use of 1,2-dichloroethane as solvent allowed successful dehydration to occur. It thus appears that solvent basicity plays an important role, with lower basicity needed for the generation of less stable carbocations. As a result, careful solvent selection meant that a wide range of aryl alcohol substrates could be successfully employed, affording good to excellent yields of stilbenes (Table 2). Of particular note is that electron-rich heterocyclic aryl alcohols proved to be excellent substrates, giving access to interesting stilbene products (entries 10–12). In addition, non-terminal olefin intermediates could also be generated and were able to

Table 2. Dehydration–Heck arylation of alcohols **1b–m** with 4-bromoacetophenone **3a**.[a]



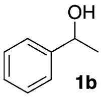
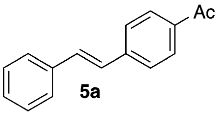
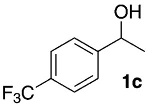
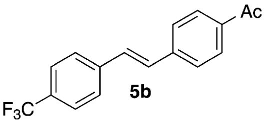
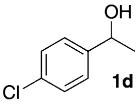
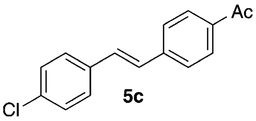
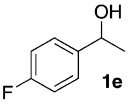
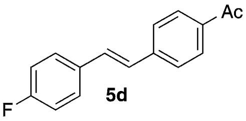
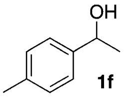
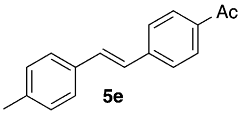
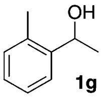
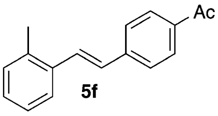
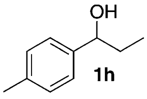
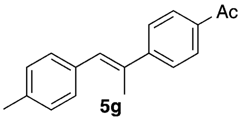
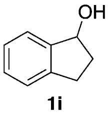
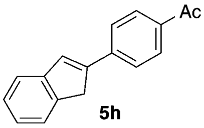
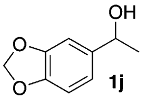
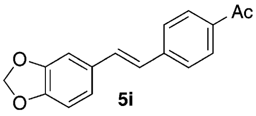
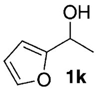
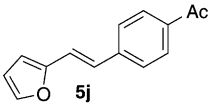
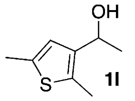
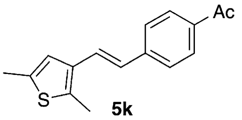
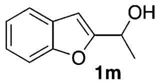
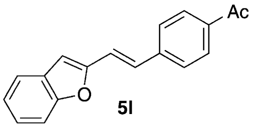
Entry	Aryl alcohol	Product	Yield [%][b]
1	 **1b**	 **5a**	70[c,d]
2	 **1c**	 **5b**	51[e]
3	 **1d**	 **5c**	80[c,d,f]
4	 **1e**	 **5d**	51[c,d,f]
5	 **1f**	 **5e**	68[g]
6	 **1g**	 **5f**	76[c]
7	 **1h**	 **5g**	72[c,f]
8	 **1i**	 **5h**	89[c,f,h]
9	 **1j**	 **5i**	91
10	 **1k**	 **5j**	66

Table 2. (Continued)

Entry	Aryl alcohol	Product	Yield [%][b]
11	 **1l**	 **5k**	74
12	 **1m**	 **5l**	68[i]

[a] *General conditions:* reactions were carried out with alcohol **1b–m** (3.0 mmol) and $H_3PW_{12}O_{40}$ (50 mg) in 3 mL of DMSO at 100 °C for 1 h, followed by addition of Et_3N (304 mg, 3 mmol), **3a** (398 mg, 2.0 mmol), $Pd(dba)_2$ (23 mg, 2 mol%), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (35 mg, 6 mol%) and DMF (3 mL) at 100 °C for 4 h.

[b] Yield of isolated product.

[c] Diglyme as initial solvent.

[d] 4 mmol of alcohol were used.

[e] 1,2-Dichloroethane as initial solvent.

[f] 18 h for arylation.

[g] Dehydration at 130 °C for 2 h.

[h] 10 min. for dehydration.

[i] 2 h for dehydration.

undergo the Heck arylation reaction, with very good isolated yields of the product stilbenes (entries 7 and 8). This cascade dehydration–arylation protocol tolerates the chloride substituent in **1** in the coupling with 4-bromoacetophenone **3a**, producing the chloride-substituted stilbene **5c** in 80% isolated yield; however, aryl chlorides can be used to couple with **1** as well. Thus, **5i** was also obtained when **3a** was replaced with 4-chloroacetophenone, albeit in a lower yield of 82% and a longer time of 18 h. Disappointingly, strongly electron-deficient aryl alcohols, such as 1-(4-nitrophenyl)ethanol, failed to undergo the desired dehydration reaction.

In conclusion, a one-pot protocol has been developed, which allows functionalised stilbenes to be easily synthesised from readily available, economic and green alcohols. The HPA-catalysed dehydration of secondary aryl alcohols first leads to the formation of styrenes which, under the intervention of a palladium catalyst, undergo regioselective Heck arylation with aryl bromides. This methodology eliminates the need for isolated styrenes, which are prone to polymerisation and often commercially not available.

We have also demonstrated that, with careful choice of solvent, HPA catalysis allows a range of useful products, including styrenes, to be selectively produced from aryl alcohols. Development of a single catalyst system that is effective for a wider range of aryl alcohols, particularly those that are electron-deficient, as well as extension of the methods into other alcohols will be the focus of future work.

Experimental Section

Representative Procedure for the Synthesis of Stilbene 4a

An oven-dried carousel tube containing a stirrer bar was charged with $H_3PW_{12}O_{40}{\cdot}xH_2O$ (50 mg). After degassing three times with nitrogen, 1-(4-methoxyphenyl)ethanol (**1a)** (457 mg, 3.0 mmol) and DMSO (3 mL) were injected and the reaction mixture was stirred at 100 °C for 1 h. Et_3N (304 mg, 3 mmol) was injected before injection of a preformed mixture of 4-bromoacetophenone (**3a**) (398 mg, 2.0 mmol), $Pd(dba)_2$ (23 mg, 2 mol%), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (35 mg, 6 mol%) and DMF (3 mL), and the resultant mixture was stirred at 100 °C for 4 h. After cooling down to room temperature, a saturated aqueous solution of $NaHCO_3$ (150 mL) was added and the product was extracted with toluene (5×20 mL). The organic washes were combined and concentrated under vacuum to yield the crude product, which was purified by recrystallisation in hexane/EtOAc. The desired stilbene product **4a** was obtained in 82% yield.

Acknowledgements

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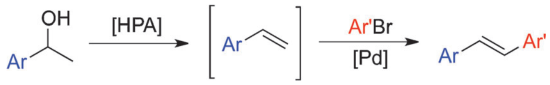
[16] Reaction time can be critical either to ensure complete consumption of the alcohol or to prevent dimerisation of the intermediate styrene.

COMMUNICATIONS

Feeding the Heck Reaction with Alcohol: One-Pot Synthesis of Stilbenes from Aryl Alcohols and Bromides



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