Chemo-, regio-, and stereoselective Heck–Matsuda arylation of allylic alcohols under mild conditions†

Tohasib Yusub Chaudhari, Asik Hossian, Manash Kumar Manna and Ranjan Jana*

Heck arylation with allylic alcohol is extremely challenging due to chemo-, regio-, and stereochemical scrambling. Here we report a mild protocol for the alcohol selective α- and β-arylation of allylic and cinnamyl alcohols respectively with aryldiazonium salts. The steric and electronic parameters of the alkene play a prominent role in the regioselectivity.

Since its discovery, significant effort has been dedicated to the development of highly efficient and selective Heck–Mizoroki reaction for the arylation of alkenes.1 Consequently, it has been recognized as one of the most powerful synthetic tools for C–C bond formation.2 The extent of research on the Heck reaction over the past few decades has inculcated the false notion that Heck chemistry is now a mature area. However, the mechanistic understanding of subtle changes that dictate regioselectivity and β-hydride elimination is still limited.3 Despite its robustness and efficiency, the Heck reaction involving aryl halides and triflates is mainly limited to the activated olefins such as acrylates, styrenes etc. In contrast, Heck arylation of electronically nonbiased olefin is still challenging due to sluggish alkene insertion and non-specific β-hydride elimination.4 Similarly, Heck arylation of allylic alcohol is extremely challenging due to chemo-, regio-, and stereochemical scrambling and double bond isomerization (Scheme 1).5

Mechanistically, after oxidative addition of palladium(0) to the allyl electrophile, a migratory β-alkene insertion occurs to generate an unstable σ-allyl-Pd species. Subsequently, random β-hydride elimination (either Hα or Hβ, Scheme 1) leads to the formation of a mixture of products, which limits its synthetic utility. Therefore, a mild reaction protocol that controls β-hydride elimination is extremely useful in regio- and chemoselective arylation of allylic alcohols. In general, oxidative addition to the allyl electrophiles such as aryl halides, triflates etc. is the rate limiting step, which requires high temperature, ligands, bases etc.6 The harsh reaction conditions lead to the non-specific arylation, β-hydride elimination, and double bond isomerizations. After the first report by Matsuda and co-workers in 1977, arenediazonium salts have been exploited as reactive aryl halide surrogates in Pd-catalyzed cross-coupling reactions.7 The Sengupta,8 Genêt,9 Correia,10 Felpin11 and other groups12 have contributed substantially to the Heck–Matsuda arylation of olefins. Recently, the Sigman group has accomplished styrenyl selective arylation of electronically non-biased olefins with aryldiazonium salts.13 Due to the facile oxidative addition to the aryldiazonium salts, the cross-coupling took place under mild reaction conditions, without any additional ligands or bases. Therefore, we decided to optimize Heck–Matsuda arylation of allylic alcohols with aryldiazonium salts. Although, there are few reports of Heck arylation with allyl or crotyl alcohol,14 most of them provide a mixture of aldehyde(or ketone) and alcohol. In addition, Heck–Matsuda arylation with β-substituted alkenes especially cinnamyl alcohols is underexplored.15 Heck arylation of cinnamyl alcohol with expensive aryl iodide has been reported by the Cacchi group.16 However, a high reaction temperature, a stoichiometric base, and a longer reaction time were required to afford only a low to moderate yield of the desired products. Here we report an alcohol selective, β- and α-arylation of allyl and cinnamyl alcohols respectively using aryldiazonium salts (Scheme 2). From the systematic study, we have observed that besides steric factors, electronic parameters of the alkene also play an important role in regioselectivity.

To begin, we tested simple allyl alcohol and phenyldiazonium salt with a catalytic amount of Pd2dba3. A rapid effervescence:

Scheme 1 Chemoselectivity in Heck arylation with allylic alcohol.
Regioselective arylation with aryldiazonium salts.

A homoallylic alcohol also underwent the Heck–Matsuda reaction affording moderate yield of the arylation product (2h, Table 1). Interestingly, protected allyl alcohols such as allyl acetate (2i, Table 1) and allyl carbonate (2j, Table 1) underwent smooth arylation providing β-arylation in high yields. In general, these substrates are unstable under Pd(0)-catalysis e.g. Tsuji–Trost conditions. This demonstrates the mild nature of these reaction conditions.

Next we turned our attention to the arylation of cinnamyl alcohol derivatives. From our previous experience with allyl alcohol we realized that cinnamyl alcohol may lead to the α-arylation due to steric hindrance with the terminal phenyl group. That said, we investigated the analogous Heck–Matsuda reaction with cinnamyl alcohol and arenediazonium tetrafluoroborate. Gratifyingly, a good yield of the arylation product was obtained simply by changing the solvent to DMA. As anticipated, the α-arylation was obtained exclusively to afford (Z)-2-3-diarylallylic alcohol. The stereochemistry of the arylation product was assigned by NOESY experiment and comparison with literature reports (see the ESI†).

A number of cinnamyl alcohol derivatives and arenediazonium salts were examined for the coupling reaction, and a wide range of functional groups such as methoxy (3b, 3d, 3m, 3n, 3r, Table 2), nitro (3c, 3e, 3f, 3m, 3o, Table 2), ester (3k, Table 2), bromo (3f, 3h, 3p, Table 2), chloro (3i, 3j, Table 2), and even iodo (3l, Table 2), were compatible under the reaction conditions. However, reaction with p-iodophenyl diazonium (3l) also gave ~10% of the corresponding aldehyde via double bond isomerization. These halogen substituents are useful for further cross-couplings. Gratifyingly, a sterically hindered mesitylenediazonium salt provided excellent yield of the arylation products (3n–3r, Table 2). Interestingly, no arylation was observed with cinnamyl acetate which indicates that besides steric effects the free hydroxyl group also may have a role in regioselectivity through coordination with the metal center.

Finally, we carried out a sequential Heck–Matsuda arylation to afford (Z)-2-3-diarylallylic alcohol. Since allyl alcohol provided low yield, we took allyl acetate for the β-arylation followed by hydrolysis to provide cinnamyl alcohol derivative, 4. The subsequent α-arylation provided 3f in 76% yield (Scheme 3a). Since halogens are compatible with our reaction conditions, we have demonstrated a sequential Heck/Suzuki coupling reaction. Initially, the Heck reaction was performed with 3-butene-2-ol and 4-bromo-phenyldiazonium salt to give 2e. The product was further cross-coupled with phenyl boronic acid to yield 5 (Scheme 3b). We have also showed that synthetically useful β,β- and β,α-diarylallylic alcohols can easily be accessed through the Heck–Matsuda reactions. The arylation of cinnamic ester occurs at the β-position selectively, and the

Table 1 Substrate scope with allylic alcohols

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>Yield (%)</th>
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<tr>
<td>H</td>
<td>2-Chlorophenyl</td>
<td>68</td>
</tr>
<tr>
<td>H</td>
<td>2-BrPh</td>
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<tr>
<td>H</td>
<td>2-OMePh</td>
<td>75</td>
</tr>
<tr>
<td>H</td>
<td>4-NO2Ph</td>
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<td>4-ClPh</td>
<td>60</td>
</tr>
<tr>
<td>H</td>
<td>3-NO2Ph</td>
<td>82</td>
</tr>
<tr>
<td>2-Chlorophenyl</td>
<td>2-OMePh</td>
<td>67</td>
</tr>
</tbody>
</table>

a The reaction was performed on a 0.2 mmol scale. b Yield refers to the isolated pure product.
ester is reduced to the corresponding alcohol with DIBAL-H, whereas, in this present protocol cinnamyl alcohol leads to the α-arylation product selectively (Scheme 3c). This phenomenon demonstrates that besides steric parameters, electronic nature of the alkene also plays an important role in regioselective arylation.

**Conclusions**

We have developed a mild protocol for the alcohol-selective Heck–Matsuda arylation of allylic alcohols in a highly regio- and stereoselective manner. In sharp contrast to the allylic alcohols, a selective α-arylation of the cinnamyl alcohols was observed to afford (Z)-2,3-diarylallylic alcohol. Taking advantage of mild reaction conditions, we have also demonstrated the sequential diarylation and Heck/Suzuki coupling. From
the systematic study, we observed that besides steric factors, electronic parameters also play an important role in regioselectivity. Therefore, selective β,β'- and β,α-diaryl allylic alcohols have been synthesized from cinnamic ester and cinnamyl alcohol respectively.

Acknowledgements

This work was supported by DST, award no. SR/S2/RJN-97/2012, Govt. of India and NIPER, Kolkata. AH and MKM thank CSIR, and UGC respectively for their fellowships.

Notes and references


