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Formal hydration of non-activated terminal olefins using tandem catalysts

Yongsheng Yang,^a Jiayi Guo^a, Huimin Ng^a, Zhiyong Chen^a, Peili Teo^{*a,b}

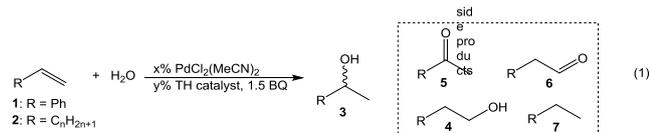
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The hydration of terminal olefins to secondary alcohols have been achieved using a Pd(II)/Ru(II) catalyst combination with high regioselectivity and yields. Both vinyl arenes and aliphatic olefins can be hydrated easily with the tandem catalyst system using low catalyst loadings of 1 mol%.

The addition of water across an olefin, commonly known as “olefin hydration”, is an important process for the synthesis of alcohols in both the laboratory and industry.¹⁻³ Olefin hydration is desirable in syntheses as the precursors are abundant and it is the most atom-economical method for alcohol production. Most hydration processes are multi-stepped in nature or acid-catalysed where strong acids are required. Functional groups that are sensitive to acids such as esters, hydroxyls and amines are not well-tolerated.⁴⁻⁶ In fact, among the various reported processes to hydrate an olefin, no process involving non-activated linear olefins has been reported.^{7, 8} Non-activated olefins are abundant and commonly used in the synthesis of commodity chemicals.⁹ In view of the importance of hydroxyl compounds to the research lab, pharmaceutical, material and specialty chemical industry, there remains a need to develop a mild and functional-group tolerant catalytic system for the production of alcohols from olefins. Herein, we report a highly regioselective tandem catalyst system for the production of secondary alcohols from non-activated terminal olefins, including styrene and 1-octene. A broad range of linear olefins have been studied using our catalytic system and found to give good yields on the secondary alcohol. The net outcome of the process is a formal hydration of the C=C double bond.

In a recent report by Grubbs *et al.*, a Pd/Ru catalyst combination was shown to be able to carry out anti-Markovnikov hydration of styrenes.^{1, 10} We envisioned that a similar strategy could be employed for Markovnikov hydration, given the higher propensity for the ketone product to be obtained in Wacker



oxidation, which is the first step of the reaction (eq 1). The selectivity of the tandem hydration system would be determined by the selectivity of the Wacker oxidation step in this case. We set out to screen various transfer hydrogenation (TH) catalysts that could be compatible with the Wacker oxidation catalyst, PdCl₂(MeCN)₂. Since the selectivity and yield of alcohol is dependent on the Wacker oxidation step, we first separated the oxidation and reduction steps in a single pot, by carrying out the reaction at 35 °C for 4 h, followed by stirring for another 30 h at 85 °C. Many TH catalysts require heat activation¹¹⁻¹⁵ so by separating the oxidation and reduction steps, we may optimize the

oxidation step first, in the presence of the TH catalyst. From the list of known TH catalysts screened, we found that only the Shvo's catalyst is compatible with PdCl₂(MeCN)₂ to result in alcohol formation (Table 1). All other TH catalysts were unable to reduce the carbonyls formed in the oxidation step of the reaction.

Table 1 Screening of TH catalysts for hydration of styrene^a

| TH catalyst | 3 | 4 | 5 | 6 | Total [O] | Selectivity/% ^c |
|-------------------------------|----|---|----|---|-----------|----------------------------|
| Shvo's catalyst ¹⁶ | 79 | 9 | 8 | 0 | 96 | 91 |
| R-Mac-H ¹⁷ | 0 | 0 | 89 | 1 | 90 | 98 |
| Funk's catalyst ¹² | 0 | 0 | 84 | 1 | 85 | > 99 |
| Milstein's PNN ¹³ | 0 | 0 | 78 | 1 | 79 | > 99 |
| Milstein's PNP ¹³ | 0 | 0 | 81 | 1 | 82 | > 99 |
| Ru-TsDPEN ^{b14} | 0 | 0 | 68 | 1 | 69 | > 99 |
| Ru-TSDENEB ^{b15} | 0 | 0 | 98 | 1 | 99 | > 99 |
| Ru-PNNP ^{b15} | 0 | 0 | 84 | 1 | 85 | 99 |

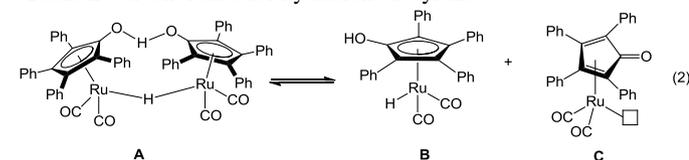
^aReaction conditions: 1% PdCl₂(MeCN)₂, 1% TH catalyst, 1.5 BQ, 0.083 M, 35 °C 4 h, 85 °C, 30 h, MeOH:IPA:H₂O 6:3:1; ^b35 °C 4 h, 60 °C 96 h, 1% MeONa added; ^cMarkovnikov selectivity = (3+5)/(4+6) x 100%; yields determined by GC using tridecane as internal standard.

From the TH catalyst screening results, it was observed that despite Shvo's catalyst being able to give the desired alcohol product, **3**, it resulted in the poorest selectivity. Upon identifying the right catalyst combination, we went on to optimize the conditions required for improving the selectivity for secondary alcohol. It was found that at high Shvo's catalyst loading of 10 mol%, a high ⁱPrOH content is required to solubilize Shvo's catalyst. When MeOH:ⁱPrOH was 2:1, yield of **3** was only 39%. However, when MeOH:ⁱPrOH was changed to 1:2, the yield increased to 74%. This however, was at the expense of selectivity. At high alcohol yields, selectivity was poorer (Table 2). However, when the amount of Shvo's catalyst was decreased to 1 mol%, a 2:1 ratio of MeOH/ⁱPrOH was able to give 80% 1-phenylethanol from styrene. This observation stems from the relatively poor solubility of Shvo's catalyst in MeOH and the addition of ⁱPrOH is required to solubilize the precatalyst, **A**. Shvo's catalyst in the active form, is the dissociated, monomeric Ru-H specie, **B**.¹⁶ In the heterogeneous form, most of the Shvo's catalyst remains in the non-activated **A** form. As such, when a large quantity of Shvo's catalyst (10 mol%) is used, much of it remains undissolved in solution, giving little **B** for reduction of **5** to **3**. However, when ⁱPrOH content is high for the solubilisation of **A**, more anti-Markovnikov product is being formed, due to the attack of the bulkier alcohol on the less hindered site of the terminal olefin to form a vinyl ether, that gets hydrolysed to primary alcohol, **4**.

A series of control experiments were also carried out and it was found that both MeOH and ⁱPrOH were required to give the

high product yield. In the absence of H₂O, small amounts of oxidized products were obtained, likely to be from trace amounts of moisture in the solvents. In the absence of BQ, the reaction did not proceed at all. In the absence of Shvo's catalyst or ⁱPrOH as hydrogen source, no alcohols could be obtained (Table 3).

Table 2 Solvent ratios for hydration of styrene^a



| MeOH: ⁱ PrOH:H ₂ O | 3 /% | 4 /% | 5 /% | 6 /% | Total [O] /% | Selectivity /% ^c |
|--|------|------|------|------|--------------|-----------------------------|
| 6 : 3 : 1 | 39 | 1 | 11 | 0 | 51 | 97 |
| 4.5 : 4.5 : 1 | 61 | 3 | 17 | 0 | 81 | 96 |
| 3 : 6 : 1 | 74 | 6 | 10 | 0 | 90 | 93 |
| 3.6 : 5.4 : 1 | 66 | 3 | 13 | 0 | 82 | 96 |
| 2 : 2 : 1 | 30 | 2 | 16 | 0 | 48 | 97 |
| 3 : 6 : 1 ^b | 80 | 5 | 6 | 0 | 91 | 94 |

^aReaction conditions: 1% PdCl₂(MeCN)₂, 10% Shvo's catalyst, 1.5 BQ, 0.083 M, 35 °C 4 h, 85 °C 30 h; ^b1% PdCl₂(MeCN)₂, 1% Shvo's catalyst; ^cMarkovnikov selectivity = (3+5)/(4+6) x 100%.

Table 3 Control experiments for hydration of styrene^a.

| Experiment | 3 /% | 4 /% | 5 /% | 6 /% | Total [O] /% | Selectivity /% ^c |
|----------------------|------|------|------|------|--------------|-----------------------------|
| No Pd | 0 | 0 | 0 | 0 | 0 | 0 |
| No Ru | 0 | 0 | 82 | 1 | 83 | 99 |
| No MeOH | 57 | 10 | 2 | 0 | 69 | 73 |
| No ⁱ PrOH | 0 | 0 | 84 | 0 | 84 | 100 |
| No H ₂ O | 12 | 1 | 5 | 0 | 18 | 51 |
| No BQ | 0 | 0 | 0 | 0 | 0 | 0 |

^aReaction conditions: 1% PdCl₂(MeCN)₂, 1% Shvo's catalyst, 1.5 BQ, 0.083 M, 35 °C 4 h, 85 °C 30 h, MeOH:IPA:H₂O 6:3:1. All other conditions remain the same except for reagent being omitted.

The reaction was also attempted on the bench to probe the effect of oxygen on the hydration system. However, it was found that the Shvo's catalyst is very sensitive to oxygen in our system, despite it being reported that Shvo's catalyst is stable in air.^{11, 16} This may be due to the acidity of our reaction system which tends to destabilize the active Ru hydride specie, **B**. The reaction mixture was observed to turn deep red rapidly, from yellow, when the reaction was carried out on the bench. A low alcohol yield of 24%, with 65% ketone was obtained in this case. The addition of CuCl₂ to the reaction as a reoxidant for the Pd(II) catalyst was also studied. However, in the presence of just 10% CuCl₂, Markovnikov selectivity decreased dramatically to 52%. As a result, *p*-benzoquinone (BQ) was employed as the only reoxidant for Pd(II) in the oxidation step. The optimum quantity of BQ was found to be 1.5 equivalents. Despite the reaction being non-catalytic with respect to BQ, BQ can easily be recovered from hydroquinone via facile aerobic oxidation.¹⁸

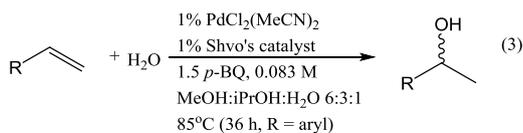


Table 4 Hydration of vinyl arenes

| Entry | Substrate | Yield of 3/ % ^a |
|-------|-----------|----------------------------|
| | | 66 |

| | | |
|----|-----------|--------------------------------------|
| 1 | 1a | 74 ^b |
| 2 | 1b | 68 |
| 3 | 1c | 54 |
| 4 | 1d | 59 (3) |
| 5 | 1e | 58 |
| 6 | 1f | 83 |
| 7 | 1g | 49 |
| 8 | 1h | 56 |
| 9 | 1i | 55 |
| 10 | 1j | 33 |
| 11 | 1k | 33 (3k) 51 (4k) |
| 12 | 1l | 24 (3l) 56 (4l) |
| 13 | 1m | 72 |

^aIsolated yield, 0.6 mmol reaction; ^bGC yield.

Upon developing a suitable system for hydrating non-activated olefins such as styrene, we went on to combine both oxidation steps and reduction steps into one single step by carrying out the entire tandem process at 85 °C. We also probed the functional group tolerance of the catalytic system (eq. 3). It was found that the reported tandem hydration system is tolerant of a wide variety of functional groups including esters, halides, alkyls, nitro, trifluoroalkyl and naphthyl. In particular, *p*-chlorostyrene, **1f**, resulted in a high yield of 83% 1-(4-chlorophenyl)ethanol. Acidic substrates such as 4-vinylbenzoic acid, **1j**, resulted in a poor yield of the corresponding alcohol, possibly due to premature degradation of active Shvo's catalyst **B**, in a highly acidic media. Highly electron-withdrawing substituents on phenyl ring such as nitro (**1k**) and bis(trifluoromethyl) (**1l**) tends to direct the selectivity toward anti-Markovnikov instead, to result in formation of 2-phenylethanol. This is due to the preferential coordination of Pd(II) to the alpha carbon when the aryl group is highly electron-deficient.

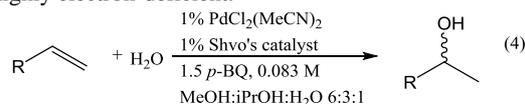
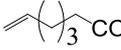
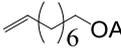
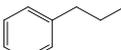
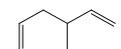
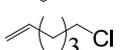
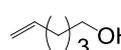
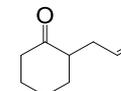
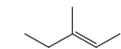


Table 5 Hydration of linear olefins^a

| Entry | Substrate | Yield of 3/ % ^a |
|-------|-----------|----------------------------|
|-------|-----------|----------------------------|

| | | | |
|----|---|-----------------------|--|
| 1 |  | 2a | 59 (71) ^b |
| 2 |  | 2b | 63 (69) ^c |
| 3 |  | 2c | 59 ^d |
| 4 |  | 2d | 85 |
| 5 |  | 2e | 82 |
| 6 |  | 2f^e | 64 |
| 7 |  | 2g | 42 |
| 8 |  | 2h | 9 (3hh) ^f 40 (4hh) |
| 9 |  | 2i | 52 |
| 10 |  | 2j | 58 |
| 11 |  | 2k | 34 ^g |
| 12 |  | 2l | - |
| 13 |  | 2m | - |

^aIsolated yield, 0.6 mmol reaction; ^bGC yield; ^c0.01 mol reaction, isolated yield; ^disolated as lactone, NMR yield; ^e2 mol% PdCl₂(MeCN)₂, 1 mol% Shvo's catalyst; ^fNMR yield; ^g2-(2-hydroxypropyl)cyclohexanol obtained.

Aliphatic olefins such as 1-octene (**2a**) and 4-phenyl-1-butene (**2f**) were also hydrated using the tandem hydration system developed (eq. 4). With 1-octene, much higher Markovnikov selectivity of > 99% could be obtained, with 2-octanol yield of 71 % using 1 mol% catalyst. Isolation of the alcohol was difficult, resulting in high loss of product after purification. Gram-scale synthesis of the 2-dodecanol was also attempted and 69% isolated yield could be obtained (1.29 g 2-dodecanol from 0.01 mol 1-dodecene). The system is also tolerant of functional groups on the olefin chain such as ester, hydroxyl and carboxylic acid, despite the mildly acidic reaction medium (Table 5). Esters in particular, such as ethyl-6-heptenoate (**2d**) and 8-nonyl acetate (**2e**) gave excellent isolated product yield of 85% and 82% respectively, with > 99% selectivity for the secondary alcohol. Unsaturated alcohols such as 3-buten-1-ol (**2i**) and 5-hexen-1-ol (**2j**) could be hydrated easily to give 1,3-butanediol and 1,5-pentanediol respectively, at modest yields of up to 58% using just 1 mol% catalyst. 1,3-butanediol is an important industrial solvent and monomer for polyurethane and polyester synthesis.^{19, 20} Chlorohexene on the other hand, resulted in little alcohol being formed, with significant amount of the product being unreduced ketone (40%). Ketone functionality on the olefin is not tolerated where the ketone gets reduced to alcohol in the transfer hydrogenation step to result in a diol (**2k**). Internal olefins could not be oxidized in our system as can be seen from substrates **2l** and **2m**.

We have presented here a tandem hydration system that is able to hydrate a broad range of olefins, including substituted styrenes and aliphatic olefins, with varying functional groups attached. As the catalyst used is achiral, we do not expect enantioselectivity in the secondary alcohols obtained. Nevertheless, the simplicity of the method makes it an attractive process for obtaining secondary alcohols from olefins. Current known asymmetric ketone reduction catalysts operate in multi-steps for obtainment of secondary alcohols from olefins. Efforts in our group are directed towards turning the asymmetric olefin hydration process into a single step system, based on the existing system. Catalyst modification to ensure enantioselectivity in the products is currently underway.

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Notes and references

^a Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore(117543). Tel: +65-65161377; E-mail: peiliteo@nus.edu.sg

^b Institute of Chemical & Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore(627833). Tel: +65 67998520.

† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, NMR data and spectra provided. See DOI: 10.1039/b000000x/

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