



Zeise's dimer-catalyzed regioselective hydration of homopropargyl tertiary ether

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ABSTRACT

The regioselective hydroalkoxylation of homopropargyl tertiary ether catalyzed by Zeise's dimer was realized. The desired products were obtained in 61–95% yield with good regioselectivity. This methodology represents a valuable alternative to the aldol reaction or the oxa-Michael reaction to form prochiral tertiary β -hydroxy ketones.

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The β -hydroxy ketones are important building blocks and can be utilized in a variety of natural products.¹ The aldol reaction, acting as one of the most powerful tools to construct β -hydroxy carbonyl derivatives with high stereochemistry, has experienced an exponential growth in recent years.² Relatively, however, within the direct catalytic aldol realm, the reactions between unmodified ketones and aldehydes have been only scantily represented.³ The oxa-Michael reaction, which can be protonated to give β -hydroxy carbonyl compounds, has attracted increasing attention only in recent years.⁴ In view of this fact, several efficient strategies have been developed concerning the formation of β -hydroxy or β -alkoxy ketones, including the ruthenium-catalyzed regioselective hydrosilylation of propargyl alcohols, as well as an alkyne hydrosilylation-oxidation strategy to afford β -hydroxy ketone achieved by the Trost group.⁵ Other examples include catalytic peroxidation-hydrogenation of α , β -unsaturated ketones⁶ and reduction of Δ^2 -isoxazolines,⁷ etc.⁸ For the tactics with homopropargyl alcohol derivatives, the Shin group achieved an intramolecular hydroamination of homopropargyl trichloroacetimidates in 2006,⁹ and the Yanik group developed platinum-catalyzed intramolecular hydrosilylation of homopropargyl alcohols.¹⁰ In 2010, our laboratory developed an one-step, platinum-catalyzed hydration of internal homopropargyl ether,¹¹ which gives rise to β -alkoxy ketones regioselectively.

It is no doubt that the construction of tertiary β -hydroxy carbonyl is challenging in synthetic organic chemistry. To the best

of our knowledge, only a few of studies have been conducted on its direct building.¹² The Scheidt group synthesized tertiary β -hydroxy amides by enolate additions to acylsilanes,^{12a,12b} while the Panunzio group provided a general route to furnish 3,3-disubstituted β -hydroxy acids using *N*-trimethylsilylbenzaldimine and acetyl chloride as starting materials.^{12c} With this challenge in mind, we decided to expand our previous work to the hydration of homopropargyl tertiary ether. Herein, we would like to report our research results on this methodology.

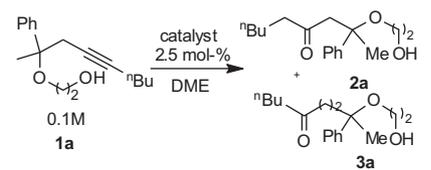
We began with the optimization studies on the hydration of substrate **1a**, relying on our previous findings.¹¹ Several different transition metals were examined with a catalyst loading of 2.5 mol %. Mercury triflate afforded an unfavorable regio-selectivity, preferring **3a** as the major product (0.6:1, **2a/3a**; Table 1, entry 1). Zeise's dimer and platinum chloride provided identical selectivity (3.3:1, *exo/endo*; Table 1, entries 2 and 3), while Zeise's dimer behaved better with relatively higher reactivity (4 h, 79% yield at 40 °C). However, when the cyclooctadiene coordinated with platinum, the catalyst turned inactive even at 60 °C (Table 1, entry 4). Other gold catalysts, such as sodium tetrachloroaurate(III) dihydrate, and gold(I) chloride combined with AgOTf or AgSbF₆, showed almost no activity (Table 1, entries 6–8), although Au(PPh₃)Cl/AgOTf afforded an unfavorable regioselectivity (Table 1, entry 5). So Zeise's dimer was the catalyst of choice for this particular reaction.

We then investigated different solvents at room temperature and found that the nature of the reaction medium significantly affected the catalytic reaction. The use of dimethoxyethane resulted in the best regioselectivity (*exo/endo*, 5:1); tetrahydrofuran,

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Table 1
Investigation of metal catalysts



| Entry | Catalyst | T (°C) | t (h) | Yield ^a (%) | 2a/3a ^b |
|-------|---|--------------------|-------|------------------------|--------------------|
| 1 | Hg(OTf) ₂ | 406 | 6 | 71 | 0.6:1 |
| 2 | Pt ₂ Cl ₄ (C ₂ H ₄) ₂ (Zeise's dimer) | 40 | 4 | 79 | 3.3:1 |
| 3 | PtCl ₂ | 40–60 ^c | 70 | 70 | 3.3:1 |
| 4 | PtCl ₂ (COD) | 40–60 ^c | | Trace | — |
| 5 | Au(PPh ₃)Cl/AgOTf ^d | 40–60 ^c | | 44(76) ^e | 0.5:1 |
| 6 | NaAuCl ₄ ·2H ₂ O | 40 | 24 | NR ^f | — |
| 7 | AuCl/AgOTf ^d | 40 | 24 | NR ^f | — |
| 8 | AuCl/AgSbF ₆ ^d | 40–60 ^c | | Trace | 3.3:1 |

^a Isolated yield combining **2a** and **3a**.

^b Determined by ¹H NMR spectroscopy of the mixture.

^c The catalytic reaction was stirred at 40 °C for 11 h and 60 °C for 8 h.

^d The ratio of the two metals is 1:1.

^e Based on the recovered starting material.

^f NR = No Reaction.

dioxane, and ether gave rise to the same moderate regioselectivity, that is, 3.3:1 (*exo/endo*); other solvent resulted in inferior regioselectivity. This is probably caused by the chelation between the oxygen atom in the solvent molecule and the metal catalyst. For the alkoxylation of **1a**, the triple bond required an intramolecular addition, other than the intermolecular addition, in which C4 behaves more electrophilic than C3 because of the chelation between the catalyst and the triple bond, as well as the ethereal oxygen (see Fig. 1). So the chelation effect with the dimethoxyethane molecule might compete with the above-mentioned chelation and benefit the intermolecular activation of the alkyne, thus resulting in the favorable regioselectivity.

Based on the solvent effect on regioselectivity, we thought about the introduction of a crown ether as the ligand to enhance the chelation with the metal catalyst. Fortunately, the results were gratifying as shown in Table 2.

It is obvious that notable increase on the ratio of **2a** to **3a** was obtained and the regioselectivity ranged from 7.1:1 to 14:1 when we used different size of crown ethers. Among them, 12-crown-4 acted as the best one. As we proposed in our previous communication,¹¹ the reason might be the incomplete enclosure of platinum by 12-crown-4 resulting in greater π acidity,¹³ which made the triple bond more electrophilic and led to the higher reactivity.

To clarify the scope of this hydroalkoxylation, a variety of substrates were examined (Table 3). On the whole, the results demonstrated great synthetic potential. When the substituent adjacent to the triple bond was switched from ethyl to propyl then to butyl, the ratios of **2** to **3** ranged from 7.7:1 to 14:1, showing satisfactory regioselectivity (Table 3, entries 1–3). When the homopropargyl substituent changed from methyl to ethyl or when the phenyl ring became substituted, the *exo/endo* selectivity could still maintain

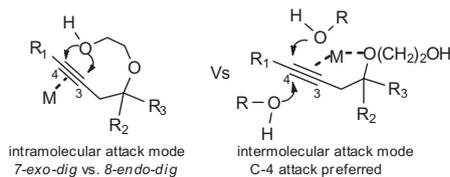
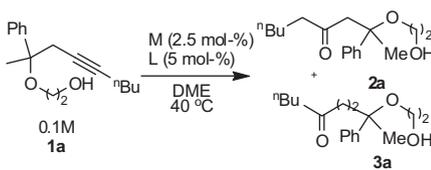


Figure 1. Two activation modes of the substrate by the metal catalyst.

Table 2
Beneficial effect of crown ether on the regioselectivity



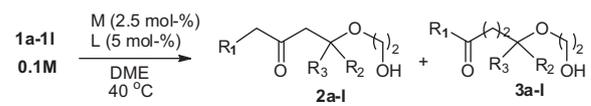
| Entry | Crown ether | t (h) | Yield ^a (%) | 2a/3a ^b |
|-------|-------------|-------|------------------------|--------------------|
| 1 | — | 4 | 79 | 3.3:1 |
| 2 | 12-C-4 | 1.5 | 79 | 14:1 |
| 3 | 15-C-5 | 6.5 | 71 | 8.3:1 |
| 4 | 18-C-6 | 3.5 | 82 | 7.7:1 |
| 5 | DCHI18-C-6 | 19 | 53(63) ^c | 7.1:1 |

^a Isolated yield combining **2a** and **3a**.

^b Determined by ¹H NMR spectroscopy of the mixture.

^c Based on the recovered starting material.

Table 3
Substrate scope of platinum-catalyzed hydration



| Entry | Substrate | Time (h) | Yield ^a (%) | 2/3 ^b |
|-------|-----------|----------|------------------------|------------------|
| 1 | 1a | 1.5 | 79 | 14:1 |
| 2 | 1b | 1.5 | 69 | 9.1:1 |
| 3 | 1c | 1.5 | 61 | 7.7:1 |
| 4 | 1d | 1.5 | 80 | >20:1 |
| 5 | 1e | 1.5 | 70 | 8.3:1 |
| 6 | 1f | 1.5 | 63 | 7.1:1 |
| 7 | 1g | 36 | 57(65) ^c | >20:1 |
| 8 | 1h | 36 | 43(74) ^c | >20:1 |
| 9 | 1i | 36 | 42(69) ^c | 3.6:1 |

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