Tetrahedron Letters 53 (2012) 4955–4958

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Ting Zhou[a], Guili Zhu[a], Xuan Huang[a], Bo Liu[a,b,*]

[a] Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 31 March 2012
Revised 24 June 2012
Accepted 3 July 2012
Available online 16 July 2012

Keywords:
Zeise's dimer
Homopropargyl tertiary ether
Regioselectivity
Tertiary β-alkoxy ketone

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.

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 scantly 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 ketones[6] 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 hydrosilation 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 $AgSbF_6$, showed almost no activity (Table 1, entries 6–8), although $Au(PPh_3)Cl$/AgOTf afforded an unfavorable regioselectivity (Table 1, entry 5). So Zeise's dimer was the catalyst of choice for this particular reaction.

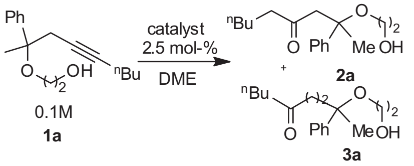
We then investigated different solvents at room temperature and found that the nature of the reaction medium significantly affected the catalytic reaction. The use of dimethoxyethane resulted in the best regioselectivity (*exo*/*endo*, 5:1); tetrahydrofuran,

---

* Corresponding author. Tel./fax: +86 28 8541 3712.
E-mail address: chembliu@scu.edu.cn (B. Liu).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.010

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	$Pt_2Cl_4(C_2H_4)_2$(Zeise's dimer)	40	4	79	3.3:1
3	$PtCl_2$	40–60[c]		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	$NaAuCl_4·2H_2O$	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 ^{1}H 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

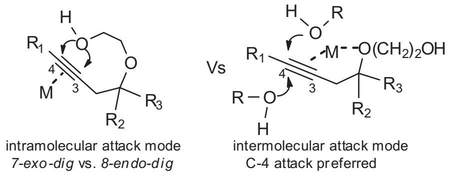
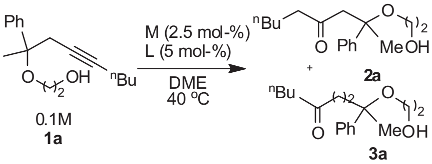


Figure 1. Two activation modes of the substrate by the metal catalyst.

Table 2
Beneficial effect of crown ether on the regioselectivity

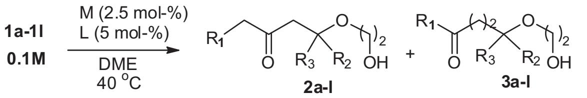


M: Zeise's dimer; L: 12-crown-4

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 ^{1}H NMR spectroscopy of the mixture.
[c] Based on the recovered starting material.

Table 3
Substrate scope of platinum-catalyzed hydration



M: Zeise's dimer; L: 12-crown-4

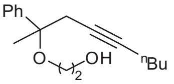
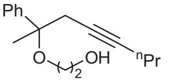
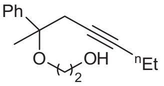
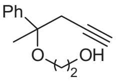
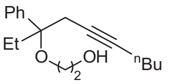
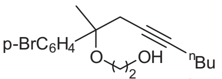
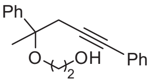
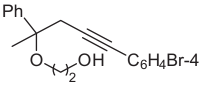
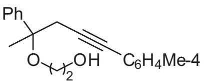
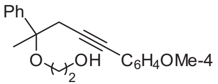
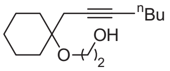
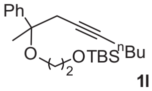
Entry	Substrate	Time (h)	Yield[a] (%)	2/3[b]
1	 **1a**	1.5	79	14:1
2	 **1b**	1.5	69	9.1:1
3	 **1c**	1.5	61	7.7:1
4	 **1d**	1.5	80	>20:1
5	 **1e**	1.5	70	8.3:1
6	 **1f**	1.5	63	7.1:1
7	 **1g**	36	57(65)[c]	>20:1
8	 **1h**	36	43(74) [c]	>20:1
9	 **1i**	36	42(69) [c]	3.6:1

Table 3 (*continued*)

Entry	Substrate	Time (h)	Yield[a] (%)	2/3[b]
10	 **1j**	36	46(63) [c]	3.3:1
11	 **1k**	1.5	95	16:1
12[d]	 **1l**	12	Mess	–

[a] Isolated yield combining **2a** and **3a**.

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

[c] Based on the recovered starting material.

[d] 3.0 equiv of water was added.

more than 7:1 (Table 3, entries 5 and 6). Undoubtedly, the terminal alkyne **1d** should adopt a *7-exo-dig* pathway after the coordination between the catalyst and the terminal alkyne (Table 3, entry 4). As for phenylacetylene-derived substrates, the regioselectivity proved to be sensitive to the substituent (Table 3, entries 7–10).When substituent on the phenyl ring turned more electrondonating, its ability to stabilize the positive charge at C4 position becomes stronger, making the C4 position more electrophilic, thus showing preferring the *8-endo-dig* product. In addition, the low reactivity derived from the bulk size of the aromatic ring led to the lower reactivity. The aliphatic substrate **1k**, to our delight, provided desired products in excellent yield with good ratio of 16:1 (*exo*/*endo*). However, under the same condition, the reaction of compound **1l** turned slow and messy, even though we used 3.0 equiv of water, which elucidates the hydroxyl in the substrate is essential to realize this transformation.

To illustrate the oxygen source, we did the $H_2{}^{18}O$ labeling experiment of substrate **1d**[14] (see Fig. 2). Besides the product **2d** due to the existence of the adventitious water in the reaction system, the product **2d′** containing the ^{18}O in carbonyl was also generated[15]; however, ^{18}O-labeled compound 2d″ was not detected. This experiment indicated that the oxygen source toward the carbonyl be provided by the nucleophilic water, not by the hydroxyl of the substrate (see Fig. 3).

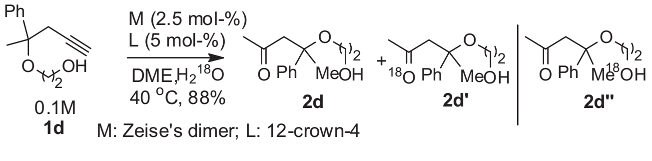


Figure 2. $H_2{}^{18}O$ labeling experiment of substrate **1d**.

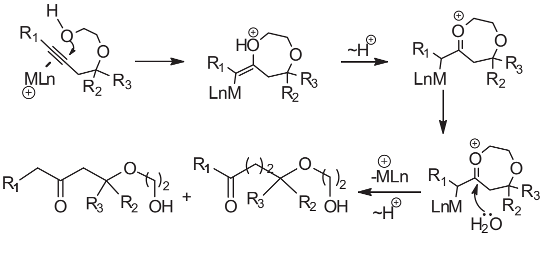


Figure 3. Mechanism of the hydration of the substrates.

In general, Zeise's dimer-catalyzed hydration of homopropargyl tertiary ether has been developed to afford tertiary β-hydroxy ketones. In addition, the chiral substrates of this reaction are facilely available since several elegant strategies have been developed on the asymmetric propargylation of prochiral aliphatic or aromatic ketones.[16] So it is worth considering for organic chemists to address chiral tertiary β-hydroxy ketones using our methodology, thus making it an attractive alternative to the asymmetric version of aldol reaction or the oxa-Michael reaction. The application of this methodology in the total synthesis of natural product is under way in our laboratory.

General procedure for the platinum-catalyzed hydration

A solution of Zeise's dimer (2.5 mol %, 2.3 mg) and 12-crown-4 (5 mol %, 1.4 mg) in dry DME (1.5 ml) was stirred at room temperature for 30 min, and then transferred to a tube containing the substrate (0.15 mmol) in a glove bag. The resulting mixture was stirred at 40 °C for the indicated time (for **1g–1j**: additional 2.3 mg of catalyst in 1.5 ml of DME was added after 12 h). Water (25 μL) was added, and the mixture was stirred for another 10 min. Subsequently, the reaction was quenched with triethylamine (50 μL). After evaporation of the solvent, the residue was purified by flash chromatography (SiO_2) to give the products.

Acknowledgments

We appreciate financial support from the National Natural Science Foundation of China (21021001, 21172154), and the Ministry of Science and Technology of China (2010CB833200). We also thank the Analytical & Testing Center of Sichuan University for recording the NMR spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.010.

References and notes

1. Scherer, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506–7525.
2. For recent reviews on aldol reaction, see: (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154; (b) Brovetto, M.; Gamenara, D.; Méndez, P. S.; Seoane, G. A. *Chem. Rev.* **2011**, *111*, 4346–4403; (c) Paradowska, J.; Pasternak, M.; Gut, B.; Gryzlo, B.; Mlynarski, J. *J. Org. Chem.* **2012**, *77*, 173–187.
3. (a) Reddy, B. V. S.; Bhavani, K.; Raju, A.; Yadav, J. S. *Tetrahedron: Asymmetry* **2011**, *22*, 881–886; (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575; (c) Li, H.; Da, C. S.; Xiao, Y. H.; Li, X.; Su, Y. N. *J. Org. Chem.* **2008**, *73*, 7398–7401; (d) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497–2500. and references cited therein.
4. (a) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218–1228; (b) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988–999; (c) Dong, C. G.; Henderson, J. A.; Kaburagi, Y.; Sasaki, T.; Kim, D. S.; Kim, J. T.; Urabe, D.; Guo, H. B.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15642–15646; (d) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46–48; (e) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141–2144.
5. (a) Trost, B. M.; Ball, Z. T.; Joge, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3415–3418; (b) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028–10038.
6. Lu, X. J.; Liu, Y.; Sun, B. F.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135.
7. Jiang, D. H.; Chen, Y. W. *J. Org. Chem.* **2008**, *73*, 9181–9183.
8. (a) Xu, H. J.; Liu, Y. C.; Fu, Y.; Wu, Y. D. *Org. Lett.* **2006**, *8*, 3449–3451; (b) Marion, N.; Carlqvist, P.; Gealageas, R.; Frémont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 6437–6451; (c) Corma, A.; Levva-pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657–1712.
9. (a) Kang, J. E.; Kim, H. B.; Lee, J. W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537–3540; (b) Kang, J. E.; Shin, S. *Synlett* **2006**, 717–720.
10. Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173–2175.
11. Yang, D. X.; Huang, J. F.; Liu, B. *Eur. J. Org. Chem.* **2010**, *22*, 4185–4188.

12. For the related examples, see: (a) Lettan, R. B., II; Reynolds, T. E.; Galliford, C. V.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15566–15567; (b) Lettan, R. B., II; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 8805–8814; (c) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Synlett* **1999**, 1735–1738.
13. For ring sizes of crown ethers, see: Hoiland, H.; Ringseth, J. A.; Burn, T. S. *J. Solution Chem.* **1979**, *8*, 779–792.
14. See Supplementary data.
15. See the ^{13}C NMR spectra of **2d** and **2d**′ in Supplementary data.
16. (a) Ding, C. H.; Hou, X. L. *Chem. Rev.* **2011**, *111*, 1914–1937; (b) Guo, L. N.; Gao, H. J.; Mayer, P.; Knochel, P. *Chem. Eur. J.* **2010**, *16*, 9829–9834; (c) Harper, K. C.; Sigman, M. S. *Science* **2011**, *333*, 1875–1878.