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Platinum-Catalyzed Regioselective Formation of β-Alkoxy Ketones from Internal Alkynes

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A catalytic amount of Zeise's dimer and 15-crown-5 were combined to effectively promote the regioselective formation of β-alkoxy ketones from 2-(homopropargyloxy)ethanols in dimethoxyethane. The desired products were obtained in 59–98 % yields with up to 17:1 *exo/endo* regioselectivity. The methodology allows access to β-hydroxy ketones as an aldol reaction alternative.

Introduction

Polyketides are ubiquitous in natural products or active pharmaceutical intermediates (APIs), most of which exhibit significant bioactivities. Undoubtedly, the aldol reaction acts as the most straightforward tool to construct polyketide motifs.[1] The application of an alkyne moiety as a latent functionality of a ketone in organic synthesis is appealing as a result of the relative insensitivity of alkynes and the facile accessibility of chiral homopropargyl alcohols.[2] Platinum and gold catalysts, enabling powerful atom-economic reactions to be effected, have initiated an explosion in their utilization in recent years.[3] Thus, it is beyond doubt that hydration or alkoxylation of alkynes catalyzed by transition metals should be a potentially powerful strategy to construct the β-hydroxy ketone motif, the iterative substructure of polyketides. However, to the best of our knowledge, whereas gold-catalyzed 5-*exo-dig* cyclizations of propargylic *tert*-butyl carbonates[4]and the Meyer–Schuster reaction have been explored already,[5] few successful examples of the metal-catalyzed formation of β-hydroxy ketones from propargyl alcohols have been reported.[6] The Trost group achieved a ruthenium-catalyzed regioselective hydrosilylation, followed by debenzylation and Fleming–Tamao oxidation to afford hydroxy ketones.[6a,6b] Other examples include the gold-catalyzed cyclization of 1,4-diynes (terminal alkynes) to seven-membered heterocycles[6c] and the cyclization of 1-alkynyl cyclopropyl *tert*-butyl carbonate,[6d] but both methods could only be applied to structurally special substrates. To illustrate the applicability with similar metal-catalyzed tactics in homopropargyl alcohols, several elegant strategies have also been developed that involve a regioselective metal-catalyzed process.[7] In 2006, the Shin group achieved an intramolecular hydroamination of homopropargyl trichloroacetimidates, which works well for both internal and terminal alkynes.[7a] In the same year, gold-catalyzed cyclization of *tert*-butyl carbonates of terminal alkynes was completed by the same group.[7b] In addition, platinum-catalyzed synthesis from homopropargylic alcohols of internal and terminal alkynes was achieved by intramolecular hydrosilation.[8] However, a one-step, metal-catalyzed synthesis of β-alkoxy ketones from homopropargyl alcohol derivatives of internal alkynes had not shown up yet. We envisioned that this kind of transformation might be realized through regioselective hydration with a homopropargyl directing group. Herein, we would like to present our research results on this methodology. Such regioselective results are easy to understand if one considers the unequal distribution of positive charges between C-3 and C-4 led by simultaneous coordination of the triple bond and the homopropargyl oxygen atom with the metal catalyst.

Results and Discussion

In a preliminary study, a variety of directing groups was evaluated with different transition metal catalysts in various solvents in the presence of water or methanol.[9] All these endeavors afforded substituted γ-hydroxy ketones as the major or sole product, which indicates that the π activation of the triple bond with metal catalysts, directed by the homopropargyl oxygen-containing functional groups, should facilitate attack at C-4 by the nucleophilic reagent.

Obstructed by the unfavorable selectivity of intermolecular hydration and hydroalkoxylation, we focused our attention on an intramolecular hydroalkoxylation tethered by a homopropargyl ether. With compound **1** as the test sub-

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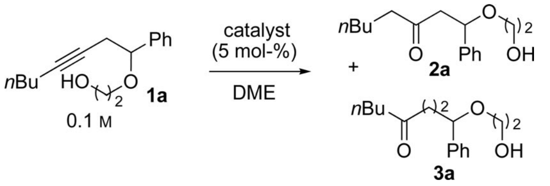
strate, the catalytic activity and regioselectivity of different transition metals were evaluated with a catalyst loading of 5 mol-%. In sharp contrast to the gold-catalyzed hydroalkoxylation of conjugated alkynoates reported recently,[10] simple gold catalysts, such as gold(I) chloride, gold(III) chloride, and sodium tetrachloroaurate(III) dihydrate, do not show any activity even at 60 °C, and Au(PPh_3)Cl/AgOTf afforded **3a** as the only detectable product (Table 1, Entries 1–4).[11] Mercury triflate displayed the same unfavorable regioselectivity, preferring an 8-*endo-dig* product (Table 1, Entry 5). The Nishizawa group reported a regioselective Hg($OTf)_2$-catalyzed hydration of undec-6-yn-1-ol in aqueous MeCN, favoring a 7-*exo-dig* product (3:1, 7-*exo*/8-*endo*);[12] however, when we treated compound **1a** under identical reaction conditions to those used by the Nishizawa group, ketone **3a** was obtained as the dominant 8-*endo-dig* product (1:5, **2a**/**3a**). This shows that the oxygen atom at the homopropargyl position in **1a** plays a very important role in the catalytic process. Interestingly, platinum chloride showed moderate selectivity (3.6:1, *exo*/*endo*; Table 1, Entry 6) in 61 % yield at 60 °C. Zeise's dimer behaved better, affording similar selectivity at 35 °C (Table 1, Entry 7). However, platinum catalysts with other ligand, such as PPh_3 or cyclooctadiene, proved totally inactive even at 60 °C (Table 1, Entries 8 and 9).

Table 1. Investigation of metal catalysts.



Entry	Catalyst	T [°C]	t [h]	Yield[a] [%]	**2a/3a**[b]
1	AuCl	60	6	NR	–
2	$AuCl_3$	60	6	NR	–
3	$NaAuCl_4·2H_2O$	60	6	NR	–
4	Au(PPh_3)Cl/AgOTf (1:1)	60	6	23	<1:20
5	Hg($OTf)_2$	35	4	44	<1:20
6	$PtCl_2$	60	6	61	3.6:1
7	$Pt_2Cl_4(C_2H_4)_2$ (Zeise's dimer)[c]	35	10	87	4:1
8	$PtCl_2(PPh_3)_2$	60	6	NR	–
9	$PtCl_2$(COD)	60	6	NR	–

[a] Isolated yield combining **2a** and **3a**. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] A catalyst loading of 2.5 mol-% was used.

For metal-catalyzed intramolecular alkoxylation of **1**, two activation modes of the triple bond with the metal, that is, *cis* activation and *trans* activation, are present in the reaction process, which complicate the regioselectivity of the reaction. As illustrated in Figure 1, for a *cis* activation case, homopropargylic oxygen directed intramolecular alkoxylation might strongly prefer 8-*endo-dig* selectivity, as an intramolecular version of the case illustrated in Scheme 1. Nevertheless, the inherent 7-*exo*/8-*endo* selectivity needs to be considered only in the *trans* activation mode. To simplify the possible reaction pathways and to probe the inherent *exo*/*endo* selectivity, a dominant *trans* activation mode was favorable. We speculated that application of ligands that are able to enclose a platinum atom might efficiently suppress the chelation between the substrate and the metal catalyst in a *cis* activation mode, and thus benefit *trans* activation of the alkyne, promoting, in principle, the *exo*/*endo* regioselectivity.[13]

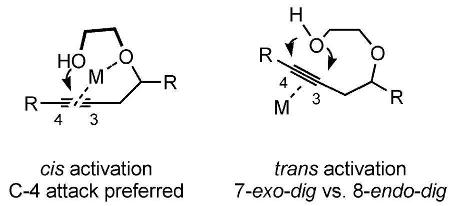
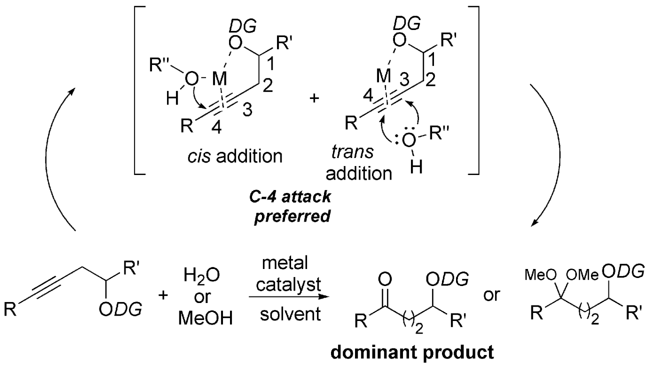
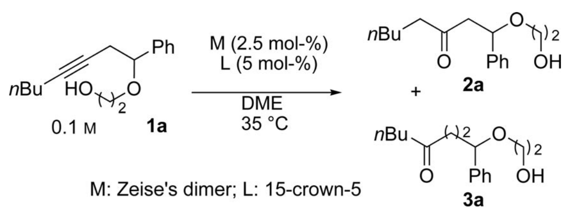


Figure 1. Two activation modes of the substrate by the metal catalyst.



Scheme 1. 1,4-Difuctionalization of homopropargyl alcohol derivatives catalyzed by transition metals; DG: directing group = Ac, Me, CONHBn, CH_2CO_2Et, etc.; metal cat.: Hg^{II}, Pt^{II}, Au^{I}, Au^{III}, Hg^{II}, etc.; solvent: DCM, THF, MeCN, etc.

Table 2. Beneficial effect of crown ether on the regioselectivity.

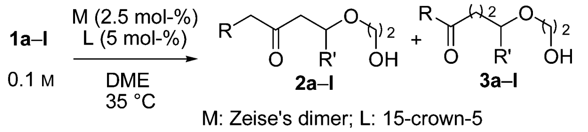


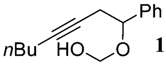
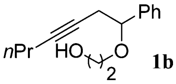
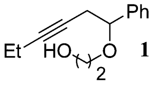
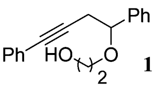
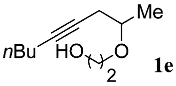
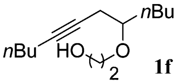
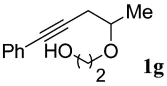
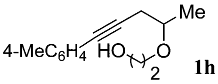
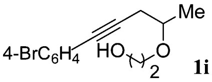
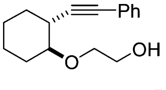
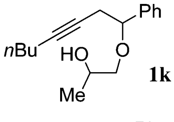
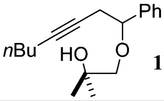
Entry	Crown ether	t [h]	Yield[a] [%]	**2a/3a**[b]
1	–	10	87	4:1
2	12-C-4	2	84	5.5:1
3	*15-C-5*	*2*	*98*	*12:1*
4	18-C-6	24	88	9:1
5	*DCH-18-C-6*	*10*	*92*	*12:1*
6[c]	–	4	73	10:1

[a] Isolated yield combining **2a** and **3a**. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Diglyme was used as the solvent and no crown ether was added. DCH-18-C-6: dicyclohexyl-18-crown-6.

To our delight, the introduction of a crown ether as the ligand did significantly promote the regioselectivity (Table 2). The ratio of **2a** to **3a** was as impressive as 12:1 when DCH-18-crown-6 and 15-crown-5 were used (Table 2, Entries 3–5). It deserves noting that the combination of Zeise's dimer with 15-crown-5 showed better catalytic activity, probably because the incomplete enclosure of platinum by 15-crown-5 resulted in greater π acidity,[14] which made the triple bond more electrophilic and led to a quicker reaction.

Table 3. Substrate scope of platinum-catalyzed alkoxylation.

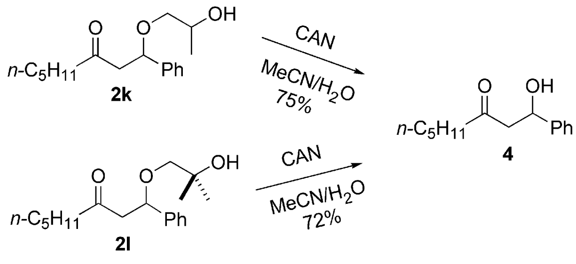


Entry	Substrate	Time [h]	Yield[a] [%]	**2/3**[b]
1	 **1a**	2	98	12:1
2	 **1b**	2	70	7:1
3	 **1c**	3	76	4:1
4	 **1d**	36	70	7:1
5	 **1e**	2.5	59	3:1
6	 **1f**	2.5	66	12:1
7	 **1g**	2.5	68	17:1
8	 **1h**	8	73	7:1
9	 **1i**	6	71	16:1
10	 **1j**	36	90	2.6:1
11[c]		36	71	4:1
12	 **1k**	4	96	7:1
13	 **1l**	4	81	6:1

[a] Isolated yield combining **2** and **3**. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] DCH-18-C-6 was employed instead of 15-C-5.

Actually, a platinum-catalyzed reaction in diglyme without crown ether gave an excellent 10:1 regioselectivity (Table 2, Entry 6), indicating that diglyme may be able to act as a multidentate ligand as well as a mimic for a crown ether.

To clarify the scope of this intramolecular hydroalkoxylation, a variety of substrates were examined (Table 3). The regioselectivity proved to be sensitive to the size of the substitution adjacent to the triple bond. When the substituent was switched from butyl to propyl then to ethyl, the ratios of **2** to **3** diminished from 12:1 to 7:1 to 4:1 (Table 3, Entries 1–3). As for a phenylacetylene-derived substrate, the regioselectivity could reach a ratio as good as 7:1 (Table 3, Entry 4). The substituent at the homopropargyl position also played an important role on the selectivity. When the phenyl group in **1a** was replaced by a methyl group, the *exo*/*endo* ratio dramatically decreased to 3:1 (Table 3, Entry 5). However, the ratio increased to 12:1 again once a substrate with a bulkier butyl group was tested (Table 3, Entry 6). The electronic effects showed an obvious impact on this reaction, which could be verified by varying the substituent on the phenyl ring. The results showed that substrates with electron-deficient aromatic acetylenes afforded more 7-*exo-dig* product, probably as a result of the lower degree of stabilization of the positive charge at C-4. This reaction could also be extended to 2-(phenylethylenyl)cyclohexanol (**1j**) with moderate 2.6:1 to 4:1 regioselectivity (Table 3, Entries 10 and 11). In addition, secondary and tertiary alcohols, **1k** and **1l**, also proved to be suitable substrates, showing good *exo*/*endo* selectivity. Major products **2k** and **2l** could be facilely transformed into β-hydroxy ketones (Scheme 2) according to a known method,[15] which reveals the potential application of this methodology.



Scheme 2. Conversion of the products into β-hydroxy ketones.

Conclusions

In general, we have developed an ether-tethered intramolecular regioselective alkoxylation to form useful β-alkoxy ketones in the presence of a catalytic amount of Zeise's dimer and a crown ether. Detailed mechanistic investigations and application of this methodology are underway in our laboratory.

Experimental Section

General Procedure for the Platinum-Catalyzed Reaction: Under an atmosphere of argon, a solution of Zeise's dimer (2.5 mol-%, 2.3 mg) and 15-crown-5 (5 mol-%, 1.6 mg) in dry DME (1.5 mL) was stirred at room temperature for 30 min. Then, working in a glove bag, the substrate (0.15 mmol) was added to the mixture. The resultant mixture was stirred at room temperature for the indicated time, H_2O (25 µL) was added, and the mixture was stirred for 10 min. Subsequently, triethylamine (50 µL) was added to quench the reaction. After evaporation of the solvent, the residue was purified by flash chromatography (SiO_2) to give the ketone products.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for the new compounds.

Acknowledgments

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[11] With these gold catalysts, the reactions in other solvents, such as DCM, DCE, THF, and toluene, afforded the same results.

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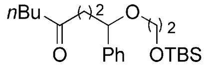
[13] When **1a** was protected with TBSCl, we obtained only product **3m** (yield: 50%) under the conditions of Table 3.



3m

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