Regioselective synthesis of halohydrin esters from epoxides: reaction with acyl halides and rhodium-catalyzed three-component coupling reaction with alkyl halides and carbon monoxide†‡

Koji Nakano, Shunsuke Kodama, Yessi Permana and Kyoko Nozaki*

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Regioselective synthesis of halohydrin esters was achieved by (1) the reaction of acyl halides with epoxides and (2) the rhodium-catalyzed three-component coupling reaction of alkyl halides, carbon monoxide, and epoxides.

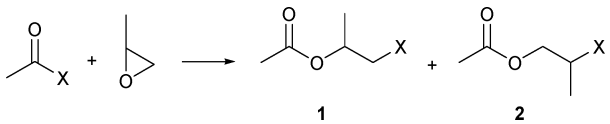
Halohydrin esters can be used as building blocks for the synthesis of lipids[1] and biologically active compounds.[2] One of the common synthetic strategies for them is the conversion of 1,2-diols.[3] Another class of powerful synthetic strategies includes using epoxides as a starting material. For example, epoxides can be transformed into halohydrin esters *via* a two-step procedure in one-pot: (i) the ring-opening by halogen nucleophiles and (ii) the subsequent *O*-acylation of the resulting halohydrin derivatives.[4] An alternative pathway to halohydrin esters from epoxides is the direct reaction with acyl halides.[5] In general, a mixture of regioisomers is obtained when using unsymmetrical 1,2-diols or epoxides in each synthetic strategy mentioned above. Accordingly, the achievement of high regioselectivity would ensure a method gains prominence as a useful synthetic transformation. Here we report the regioselective synthesis of halohydrin esters by using epoxides as one of the starting materials.

First, halohydrin-ester synthesis from acyl halides and epoxides was investigated. Simple mixing of acetyl chloride and propylene oxide provided regio-isomers **1a** and **2a** in 53/47 ratio in low yield (Table 1, entry 1). On the other hand, the addition of pyridine derivatives was found to be effective, giving higher yields and higher regioselectivities (entries 2 and 3).[6,7] The reaction of acetyl iodide also proceeded, while the yield and the regioselectivity were lower (entry 4).

Next, the transition-metal-catalyzed three-component coupling reaction of organic halides, carbon monoxide, and epoxides was investigated for halohydrin-ester synthesis.[8] Based on the well-known Monsanto process, we can expect that acid halides are generated from organic halides and carbon monoxide in the presence of carbonylation catalysts. Accordingly, the subsequent reaction of the resulting acid halides with epoxides would give the corresponding halohydrin esters. This type of catalytic transformation is attractive because three easily-available substrates can be incorporated into one molecule directly. Previously, Tanaka and co-workers reported the three-component coupling reaction using a palladium complex, while the proposed reaction mechanism did not involve the formation of acid halides.[9,10] This catalytic reaction can be applied to a variety of substrates. Unfortunately, however, a mixture of regio-isomers was formed when using propylene oxide.

Regioselective synthesis of halohydrin esters was successfully achieved by using $[PPN]^+[Rh(CO)_4]^-$ as a catalyst ($[PPN]^+$ = bis(triphenylphosphoranylidene)iminium). The reaction of benzyl bromide, carbon monoxide (6 MPa), and propylene oxide (2 equiv. to BnBr) in the presence of $[PPN]^+[Rh(CO)_4]^-$ (0.5 mol%) and 3-methoxypyridine (1 mol%) at 75 °C for 6 h gave 1-bromopropan-2-yl phenylacetate (**1c**) in 77% yield, with high regioselectivity (Table 2, entry 1). Only a small amount of the regio-isomer, 2-bromopropyl phenylacetate (**2c**) was observed (**1c**/**2c** = 97/3). Addition of pyridine derivatives is necessary for high yield: the reaction in the absence of 3-methoxypyridine for 12 h gave a much lower yield of 12% (entry 2), while high regioselectivity was maintained. Other pyridine derivatives such as pyridine and 4-(*N*,*N*-dimethylamino)pyridine were also effective, although

Table 1 Halohydrin-ester synthesis by the reaction of acetyl halides with propylene oxide[a]



Entry	X	Solvent	Additive (mol%)	Yield of **1** (%)[b]	**1**/**2**[c]
1	Cl	—	—	**1a**, 35	53/47
2	Cl	—	3-MeO-pyridine (1.0)	**1a**, 80	81/19
3	Cl	—	Pyridine (1.0)	**1a**, 57	82/18
4	I	CH_2Cl_2	Pyridine (30)	**1b**, 38	62/38

[a] Reaction conditions: acetyl chloride (5.6 mmol), propylene oxide (14 mmol), additive, 75 °C, 12 h (entries 1–3); acetyl iodide (4.4 mmol), propylene oxide (9.3 mmol), pyridine (1.24 mmol), CH_2Cl_2 (5.0 ml), −78 °C, 3 h (entry 4). In entry 4, acetyl iodide in CH_2Cl_2 was slowly added *via* syringe pump. [b] NMR yield. [c] Determined by ^1H NMR analysis of the reaction mixture.

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan. E-mail: nozaki@chembio.t.u-tokyo.ac.jp; Fax: +81 3 5841 7263; Tel: +81 3 5841 7261

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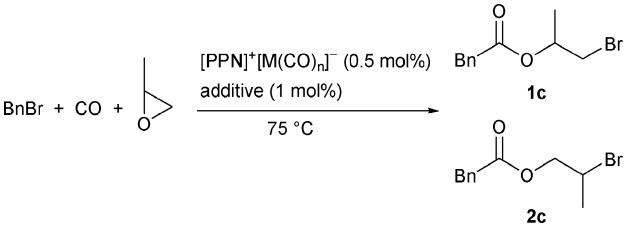
‡ Electronic supplementary information (ESI) available: Experimental section, ^1H and ^{13}C NMR spectra and plausible reaction pathways. See DOI: 10.1039/b912907c

Table 2 Rhodium-catalyzed halohydrin-ester synthesis from benzyl bromide, carbon monoxide, and propylene oxide[a]



Entry	$[PPN]^+[M(CO)_n]^-$	Additive	Yield of **1c** (%)[b]	**1c**/**2c**[c]
1	$[PPN]^+[Rh(CO)_4]^-$	3-MeO-pyridine	77	97/3
2	$[PPN]^+[Rh(CO)_4]^-$	—	12	93/7
3	$[PPN]^+[Rh(CO)_4]^-$	Pyridine	73	95/5
4	$[PPN]^+[Rh(CO)_4]^-$	4-Me_2N-pyridine	45	95/5
5[d]	$[PPN]^+[Co(CO)_4]^-$	3-MeO-pyridine	14	50/50
6	$[PPN]^+[Mn(CO)_5]^-$	3-MeO-pyridine	No reaction	—

[a] Reaction conditions: benzyl bromide (1 equiv.), CO (6 MPa), propylene oxide (2 equiv.), $[PPN]^+[M(CO)_n]^-$ (0.5 mol%), additive (1 mol%), 75 °C, 6 h (entries 1, 3, and 4) or 12 h (entries 2, 5, and 6). [b] NMR yield. [c] Determined by ^{1}H NMR analysis of the reaction mixture. [d] Ether **3c** (19%) and **4c** (23%) were also produced.

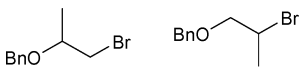
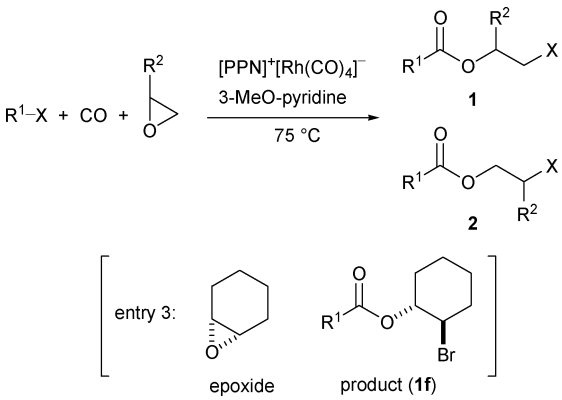


Table 3 Scope of alkyl halides and epoxides in rhodium-catalyzed halohydrin-ester synthesis[a]



Entry	Organic halide (R^1–X)	Epoxide (R^2)	Product, yield (%)[b]	**1**/**2**[c]
1	Bn–Br	–CH_2OBn	**1d**, 61 (70)	>99/<1
2	Bn–Br	–CH_2Br	**1e**, 67 (68)	>99/<1
3	Bn–Br	Cyclohexene oxide	**1f**, 89 (84)	—
4	Bn–Br	–CH_3 (*S*, >99% ee)	(*S*)-**1c**, 73 (71)	94/6
5	Me–I	–CH_3	**1b**, 50 (40)	92/8
6	Allyl–Br	–CH_3	**1g**, 66 (41)	97/3
7	MeOC(O)CH_2–Br	–CH_3	**1h**, 91 (70)[d]	92/8
8	Bn–Cl	–CH_3	**1i**, 22 (24)[d]	83/17

[a] Reaction conditions: alkyl halide (1 equiv.), CO (6 MPa), epoxide (2 equiv.), 75 °C. $[PPN]^+[Rh(CO)_4]^-$ (0.5 mol%), 3-methoxypyridine (1 mol%), 24 h (entries 1 and 3); $[PPN]^+[Rh(CO)_4]^-$ (1 mol%), 3-methoxypyridine (2 mol%), 12 h (entries 2 and 5, 6, and 8); $[PPN]^+[Rh(CO)_4]^-$ (0.5 mol%), 3-methoxypyridine (1 mol%), 12 h (entry 4); $[PPN]^+[Rh(CO)_4]^-$ (1 mol%), 3-methoxypyridine (2 mol%), 24 h (entry 7). [b] NMR yield (isolated yield). [c] Determined by ^{1}H NMR analysis of the reaction mixture. [d] A small amount of regioisomer could not be separated by column chromatography.

the yields were slightly lower than that with 3-methoxypyridine (entries 3 and 4).[11] When using $[PPN]^+[Co(CO)_4]^-$ as a catalyst, a significant amount of **2c** and ethers **3c** and **4c**, which were derived from benzyl bromide and propylene oxide without carbonylation, were produced along with **1c** (entry 5). The use of $[PPN]^+[Mn(CO)_5]^-$, which was reported to be more nucleophilic toward methyl iodide than $[PPN]^+[Co(CO)_4]^-$,[12] did not give any product (entry 6). Accordingly, $[PPN]^+[Rh(CO)_4]^-$ was found to catalyze the reaction efficiently with high regioselectivity.[13]

With the optimized conditions, we examined the scope of this transformation (Table 3). The reactions of benzyl glycidyl ether and 3-bromopropylene oxide with benzyl bromide and CO gave the corresponding halohydrin esters **1d** and **1e**, respectively, with extremely high regioselectivity (entries 1 and 2). Cyclohexene oxide, a representative alicyclic epoxide, was also applicable to this transformation (entry 3). The obtained halohydrin ester **1f** was found to be a *trans* isomer. The reaction of (*S*)-propylene oxide (>99% ee) gave (*S*)-**1c** without a loss of enantiopurity (entry 4). The scope of alkyl halides was also examined by using propylene oxide as a coupling partner. Methyl iodide, allyl bromide, and methyl bromoacetate were transformed into halohydrin esters **1b**, **1g**, and **1h**, respectively, in moderate yields (entries 5–7). Benzyl chloride was also employable (entry 8), while the reaction was slower than that with benzyl bromide (Table 2, entry 1). When *normal*- and *secondary*-butyl bromides were used, the starting materials were recovered. Such inertness of unactivated alkyl halides is a key point for the successful formation of the desired halohydrin esters since the produced halohydrin esters **1** themselves are alkyl halides, potential substrates for the present transformation. The reaction with *tert*-butyl bromide gave a complex mixture without the desired halohydrin ester.[14] Employment of bromobenzene also resulted in the recovery of the starting materials.

In conclusion, we have demonstrated that the addition of pyridine derivatives is effective to attain higher yields and higher regioselectivities in the halohydrin-ester synthesis from acyl halides and epoxides. In addition, we also established a three-component coupling reaction with alkyl halides, carbon monoxide, and epoxides by using $[PPN]^+[Rh(CO)_4]^-$ as a catalyst to produce halohydrin esters. The reaction can be applied to a variety of epoxides and activated alkyl halides. When using terminal epoxides, exclusively high regioselectivity was accomplished.

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