Kinetic Resolution

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Palladium-Catalyzed Chemo- and Enantioselective C–O Bond Cleavage of α-Acyloxy Ketones by Hydrogenolysis

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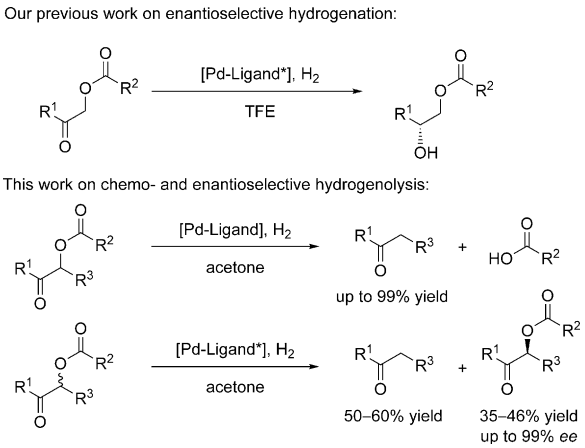
Abstract: *A chemoselective C–O bond cleavage of the ester alkyl side-chain of α-acyloxy ketones was realized for the first time by a highly efficient palladium-catalyzed hydrogenolysis (S/C = 6000, the highest catalytic efficiency by far). Furthermore, a kinetic resolution of α-acyloxy ketones was first developed by enantioselective hydrogenolysis with good yields and up to 99 % ee.*

The α-acyloxy ketones, which can be readily obtained by a classic benzoin condensation or a cross-benzoin reaction,[1] are of great interest and commonly found as useful synthetic intermediates.[2] Generally, further derivation tends to occur selectively at the keto carbonyl group or at the C–O bond in the ester carbonyl side-chain.[3] While the selective C–O bond cleavage of an ester alkyl side-chain is considered to be disfavored and has only garnered little attention, the corresponding products of simple ketone products have a wider use.[4] Previously, to realize the selective cleavage of an inactive C–O bond, either a large excess of reducing agents or photolysis was needed, and always suffered from low efficiency and high cost.[5] In addition, no reports on enantioselective C–O bond cleavage of ester alkyl side-chains have been published thus far, despite chiral α-acyloxy ketones being important structural elements in many optically active substances.[2c,d] Therefore, to further extend the utilization of α-acyloxy ketones, a more efficient and convenient methodology for chemo- and enantioselective C–O bond cleavage is desired.

Recently, our group has developed an efficient palladium-catalyzed asymmetric hydrogenation of C=O bonds of α-acyloxy-1-arylethanones (Scheme 1).[6] During studies on these reactions, a small amount of a C–O bond-cleavage product was observed. This unexpected discovery inspired the current research utilizing palladium-catalyzed hydrogenolysis for the chemo- and enantioselective C–O bond cleavage of ester alkyl side-chains.[7]

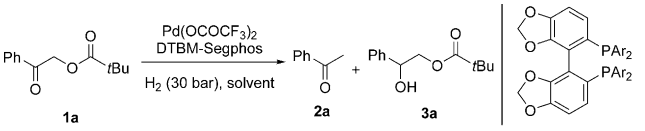
Initially, we carried out the hydrogenolysis of 2-oxo-2-phenylethyl pivalate (**1a**) using a catalytic system of Pd-



Scheme 1. Cleavage of C–O bonds by hydrogenolysis. TFE = 2,2,2-trifluoroethanol.

$(OCOCF_3)_2$ (1.0 mol %) and racemic DTBM-Segphos (1.1 mol %), under 30 bar H_2 pressure at room temperature in different solvents (Table 1). Only the hydrogenated product **3a** was obtained in TFE and DCM with full conversion (entries 1 and 2), and almost no reaction occurred

Table 1: Optimization of the reaction conditions.[a]



Entry	Solvent	Conv. [%][b] 2a	3a
1	TFE	0	>95
2	DCM	0	>95
3	DCE	0	trace
4	$CHCl_3$	0	0
5	MeOH	17	83
6	EtOH	13	87
7	*i*PrOH	trace	27
8	toluene	trace	trace
9	acetone	>95	trace
10[c]	acetone	>95	trace
11[d]	acetone	>95	trace

[a] Reaction conditions: **1a** (0.1 mmol), $Pd(OCOCF_3)_2$ (1.0 mol %), DTBM-Segphos (1.1 mol %), solvent (1.0 mL), RT, 24 h. [b] Determined by ^1H NMR analysis. [c] S/C = 1000, 0.33 g **1a**, 6.0 mL acetone, RT, H_2 (60 bar), 24 h. [d] S/C = 6000, 2.0 g **1a**, 15.0 mL acetone, H_2 (60 bar), 60 °C, 30 h. DCE = 1,2-dichloroethane, DCM = dichloromethane.

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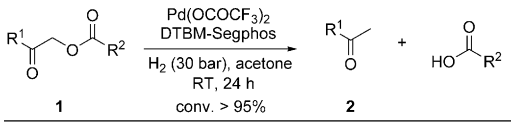
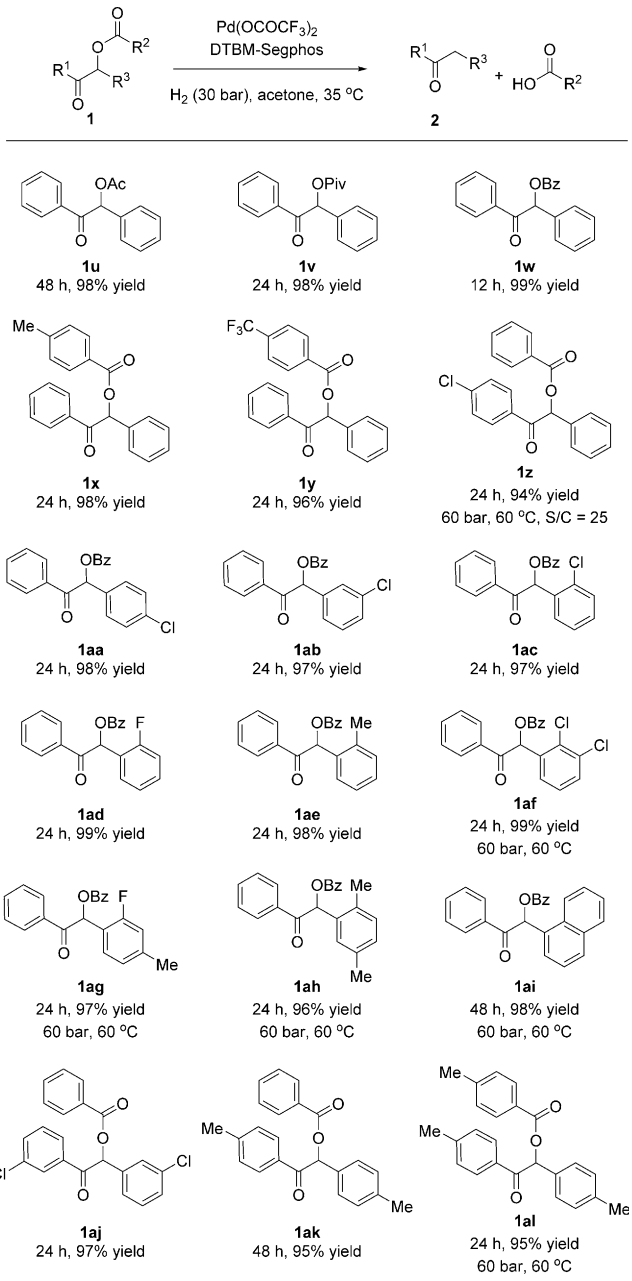
in DCE and $CHCl_3$ (entries 3 and 4). Alcohols such as MeOH, EtOH, and *i*PrOH gave the desired product **2a** in low yield with a large amount of **3a** (entries 5–7). The less polar solvents, for example, toluene, only provided low activity (entry 8). To our surprise, the most promising result was obtained using acetone, a solvent not commonly used in hydrogenation reactions (entry 9). Moreover, different ligands and palladium precursors were also tested in acetone. However no good alternatives to the DTBM-Segphos/Pd-$(OCOCF_3)_2$ catalyst system were discovered (for details, see Table S1 in the Supporting Information). To examine the efficiency of our current catalytic system, the hydrogenolysis of **1a** was tested with a relatively low catalyst loading (entries 10 and 11). To our delight, when the S/C ratio was increased to 6000, the reaction proceeded smoothly with quantitative conversion, albeit requiring a higher reaction temperature and H_2 pressure. The example represents, by far, the highest catalytic efficiency for the palladium-catalyzed homogeneous hydrogenation.[6]

The substrate scope of the catalytic system was explored using the optimized reaction conditions (Schemes 2 and 3). All the tested α-acyloxy ketone substrates were converted into their corresponding products in excellent conversions (Scheme 2). The position of the substituents on the phenyl



1a: R^1=Ph, R^2=*t*Bu
1b: R^1=2-$MeOC_6H_4$, R^2=*t*Bu
1c: R^1=3-$MeOC_6H_4$, R^2=*t*Bu
1d: R^1=4-$MeOC_6H_4$, R^2=*t*Bu
1e: R^1=4-MeC_6H_4, R^2=*t*Bu
1f: R^1=4-HOC_6H_4, R^2=*t*Bu
1g: R^1=4-PhC_6H_4, R^2=*t*Bu
1h: R^1=2-Naphthyl, R^2=*t*Bu
1i: R^1=2-Thienyl, R^2=*t*Bu
1j[a]: R^1=4-FC_6H_4, R^2=*t*Bu
1k: R^1=3,4-$(MeO)_2C_6H_3$, R^2=*t*Bu
1l: R^1=3,4-$OCH_2OC_6H_3$, R^2=*t*Bu
1m: R^1=*t*Bu, R^2=*t*Bu
1n: R^1=*t*Bu, R^2=Ph
1o[a]: R^1=Ph, R^2=Me
1p: R^1=Ph, R^2=Ph
1q: R^1=Ph, R^2=2-$ClOC_6H_4$
1r: R^1=Ph, R^2=2-$MeOC_6H_4$
1s: R^1=Ph, R^2=3-$MeOC_6H_4$
1t: R^1=Ph, R^2=4-$MeOC_6H_4$

Scheme 2. Chemoselective hydrogenolysis of α-acyloxy ketones. [a] 60 bar, 60°C.



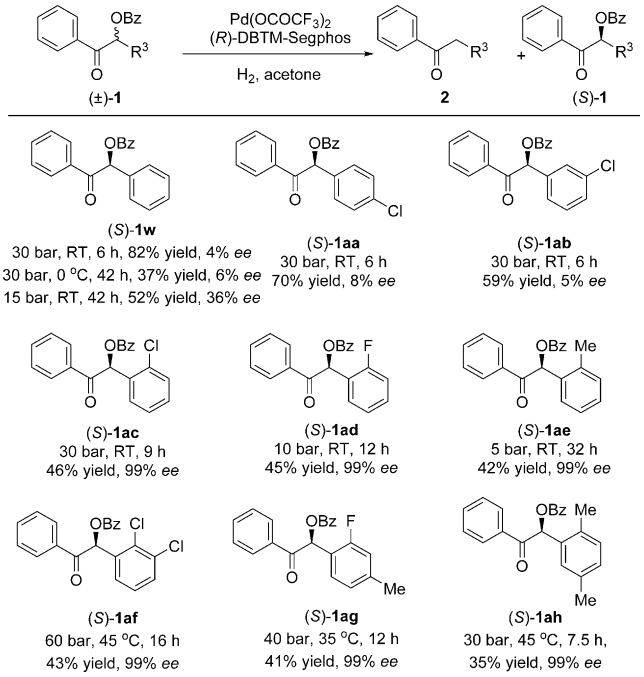
Scheme 3. Chemoselective hydrogenolysis of acyloins. Bz = benzoyl.

ring (R^1) did not alter the reaction efficiency as shown with methoxy substrates (**1b–d**). Similarly, different R^1 groups had no influence on the overall yields (**1e–i, 1k–n**). For complete transformation of **1j**, 60 bar H_2 pressure and 60°C were needed because of its low reaction activity. In addition, different R^2 groups were also evaluated with the catalyst system. This method was efficient for the chemoselective hydrogenolysis of methyl-substituted substrates (**1o**) under 60 bar H_2 pressure at 60°C. Other substrates with different R^2 groups, including Ph, 2-ClC_6H_4 and 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, and 4-$MeOC_6H_4$, were successfully reacted under standard reaction conditions (**1p–t**).

To further extend the substrate scope, the α-acyloxy-α-substituted-1-arylethanones (acyloins) were subjected to the hydrogenolysis reaction (Scheme 3). Under a catalytic system of $Pd(OCOCF_3)_2$ and racemic DTBM-Segphos, with 30 bar H_2 pressure at 35°C in acetone, the three substrates bearing different ester groups, such as OAc, OPiv, and OBz, showed distinguished reactivities (**1u–w**). The compound **1w** with an OBz was the most active. When the OBz was decorated with 4-Me or 4-CF_3 (**1x,y**), the reaction went to completion in 24 hours. Changing R^1 to 4-ClC_6H_4 (**1z**) also gave a good result, albeit with a low reaction activity. Substrates bearing a Cl group at the 2-, 3-, or 4-position on the aromatic ring (R^3) also gave excellent yields (**1aa–ac**). Other substrates with different substituents, such as 2-FC_6H_4 and 2-MeC_6H_4 (**1ad** and **1ae**), also underwent complete hydrogenolysis within 24 hours. Substrates with disubstituted aromatic rings at R^3 were investigated in the hydrogenolysis and the correspond-

ing products were obtained with quantitative conversions (**1af**–**ah**), however a higher H_2 pressure and reaction temperature were required. When R^3 was replaced by 1-naphthalene (**1ai**), excellent chemoselectivity was also observed. When R^1 and R^3 were 3-chlorophenyl and 4-methylphenyl, respectively, the substrates were transformed completely after 24 hours (**1aj**,**ak**). Changing R^1, R^2, and R^3 to 4-methylphenyl groups had no effect on the reaction conversion (**1al**).

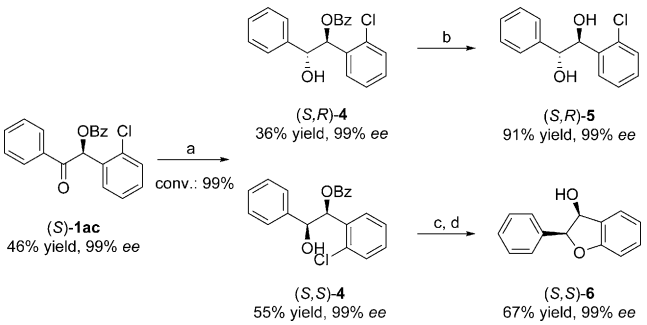
Furthermore, it was very interesting that the acyloins can be kinetically resolved using (*R*)-DTBM-Segphos as a chiral ligand (Scheme 4). A substrate bearing OBz [(±)-**1w**] was reacted under 30 bar hydrogen pressure for 6 hours to recover **1w** with 82% yield and 4% *ee*. By lowering the reaction



Scheme 4. Kinetic resolution of acyloins by enantioselective hydrogenolysis.

temperature to 0 °C, enantioselectivity increased slightly to 6% *ee* (37% yield). Reducing the H_2 pressure to 15 bar increased the enantioselectivity to 36% *ee* (52% yield). Substrates with a Cl group at the 4- and 3-positions on the benzene ring also displayed less than promising results under 30 bar H_2 pressure (**1aa** and **1ab**), while a substrate bearing Cl at the 2-position on the benzene ring of R^3 showed excellent performance (99% *ee* for (*S*)-**1ac** in 46% yield). Similarly excellent enantioselectivities were achieved for the substrates bearing 2-F and 2-Me at the benzene ring when a suitable H_2 pressure was used [(*S*)-**1ad** and (*S*)-**1ae**]. Substrates in which R^3 possessed two functional groups in different positions on the benzene ring were also explored in the enantioselective hydrogenolysis. The recovered substrates were obtained with excellent enantioselectivities and good yields [(*S*)-**1af**, (*S*)-**1ag**, and (*S*)-**1ah**]. To the best of our knowledge, this is the first report on kinetic resolution by catalytic enantioselective hydrogenolysis.

The chiral compounds **1** have the potential for use in simple transformations for the synthesis of unsymmetrical chiral 1,2-diol structural motifs commonly found in various biologically active compounds and chiral ligands.[8] By using the same catalytic system of hydrogenolysis but replacing acetone with TFE, (*S*)-**1ac** was hydrogenated smoothly to give the corresponding products (*S,R*)-**4** (36% yield) and (*S,S*)-**4** (55% yield) without loss in the *ee* value (Scheme 5). The corresponding unsymmetrical chiral 1,2-diol (*S,R*)-**5** was obtained by removal of the ester in 91% yield and 99% *ee*.[9] Meanwhile, according to a reported literature,[10] (*S,S*)-**4** could be cyclized directly using $Pd(OAc)_2$/X-Phos and hydrolyzed to give the dihydrobenzofuran derivative (*S,S*)-**6** in 67% yield and 99% *ee*.[11]



Scheme 5. Product derivatization. Reagents and conditions: a) (*S*)-**1ac** (0.4 mmol), $Pd(OCOCF_3)_2$ (1.0 mol%), (*R*)-DBTM-Segphos (1.1 mol%), TFE (4.0 mL), H_2 (30 bar), RT, 24 h. b) (*S,R*)-**4** (0.1 mmol), MeOH (2.0 mL), THF (2.0 mL), 10% K_2CO_3 aq. (2.0 mL), RT, 8 h. c) (*S,S*)-**4** (0.1 mmol), 7.0 mol% $Pd(OAc)_2$, 7.0 mol% X-Phos, Cs_2CO_3 (1.2 equiv), 1,4-dioxane (3.0 mL), 90 °C, 12 h. d) MeOH (1.0 mL), THF (1.0 mL), 10% Cs_2CO_3 aq. (1.0 mL), RT, 18 h. THF = tetrahydrofuran, X-Phos = dicyclohexyl[2′,4′,6′-tris(prop-2-yl)biphenyl-2-yl]phosphane.

In conclusion, under mild reaction conditions, a chemoselective C–O bond cleavage of an ester alkyl side-chain of α-acyloxy ketones by palladium-catalyzed hydrogenolysis has been reported for the first time. A variety of substrates were investigated with almost quantitative conversions. And reducing the catalyst loading to 1/6000 still provided a quantitative yield of the product, and represents, by far, the lowest catalyst loading for homogeneous palladium-catalyzed hydrogenation. Furthermore, an enantioselective C–O bond cleavage of ester alkyl side-chain was also reported for the first time and further applied to the kinetic resolution of some acyloins with up to 99% *ee*. The corresponding chiral products could serve as important intermediates for the preparation of some useful optically active substances.

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