Kinetic Resolution

Deutsche Ausgabe: DOI: 10.1002/ange.201603590
Internationale Ausgabe: DOI: 10.1002/anie.201603590

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

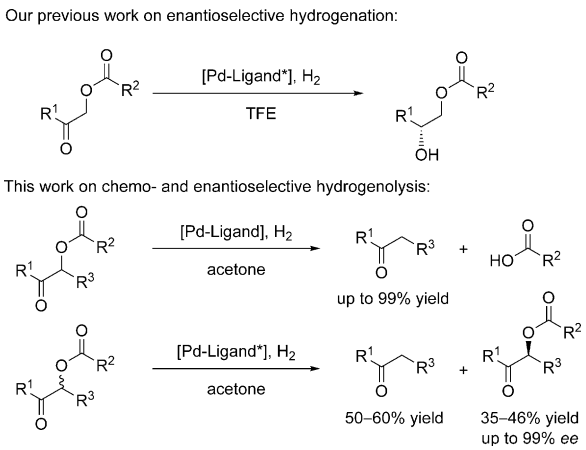
*Jianzhong Chen, Zhenfeng Zhang, Delong Liu, and Wanbin Zhang**

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]

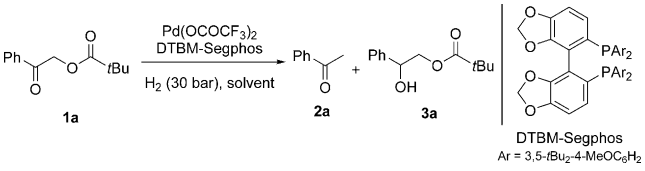
Initially, we carried out the hydrogenolysis of 2-oxo-2-phenylethyl pivalate (**1a**) using a catalytic system of Pd-



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

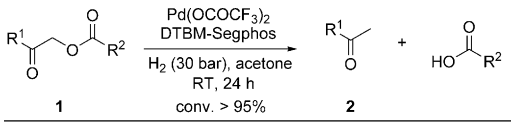
[a] Reaction conditions: **1a** (0.1 mmol), $Pd(OCOCF_3)_2$ (1.0 mol %), DTBM-Segphos (1.1 mol %), solvent (1.0 mL), RT, 24 h. [b] Determined by ^1H NMR analysis. [c] S/C = 1000, 0.33 g **1a**, 6.0 mL acetone, RT, H_2 (60 bar), 24 h. [d] S/C = 6000, 2.0 g **1a**, 15.0 mL acetone, H_2 (60 bar), 60 °C,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

[*] Dr. J. Chen, Prof. W. Zhang
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (P.R. China)
E-mail: wanbin@sjtu.edu.cn
Homepage: http://wanbin.sjtu.edu.cn
Dr. Z. Zhang, Dr. D. Liu, Prof. W. Zhang
School of Pharmacy, Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (P.R. China)

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201603590.

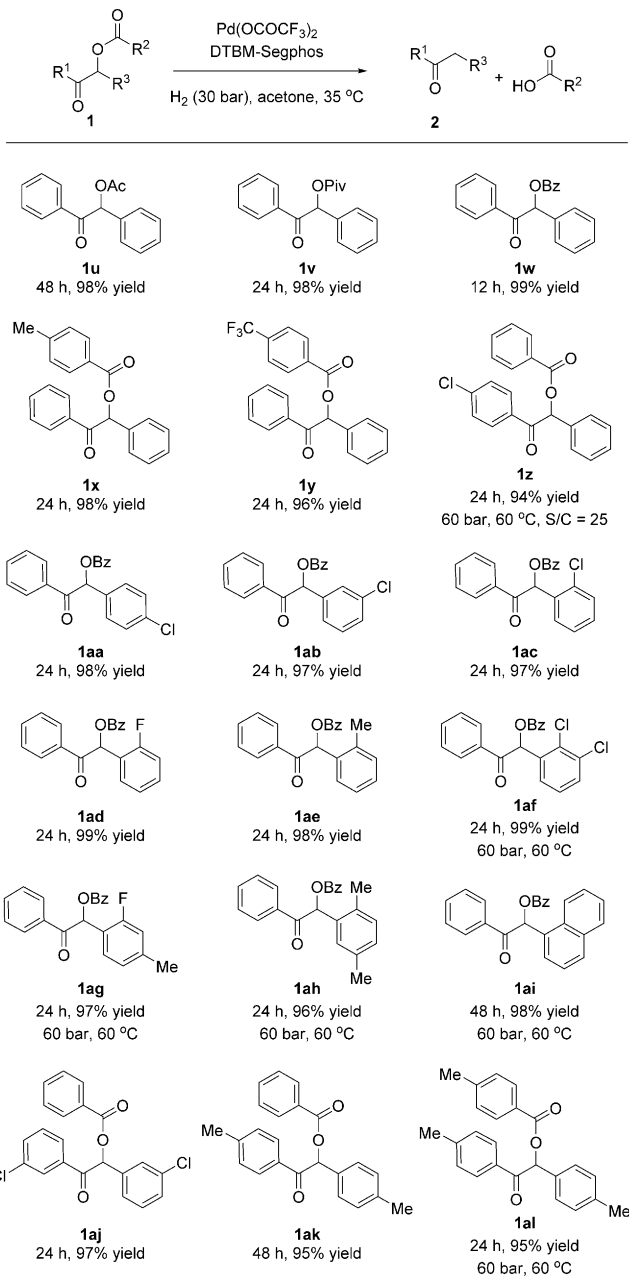
in DCE and $CHCl_3$ (entries 3 and 4). Alcohols such as MeOH, EtOH, and *i*PrOH gave the desired product **2a** in low yield with a large amount of **3a** (entries 5–7). The less polar solvents, for example, toluene, only provided low activity (entry 8). To our surprise, the most promising result was 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.



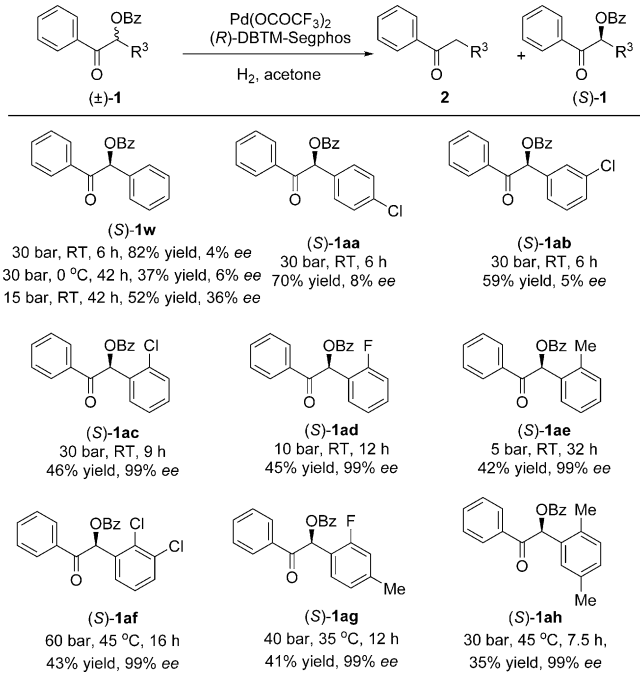
Scheme 3. Chemoselective hydrogenolysis of acyloins. Bz = benzoyl.

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**).

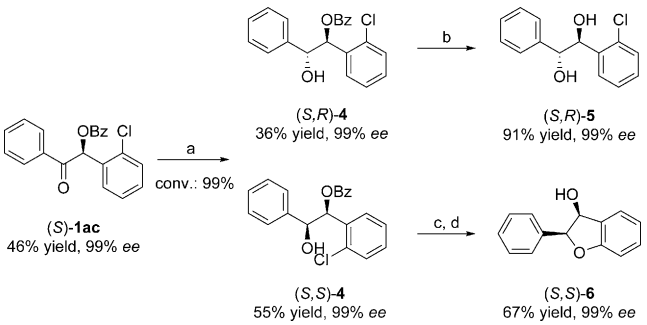
Furthermore, it was very interesting that the acyloins can be kinetically resolved using (*R*)-DTBM-Segphos as a chiral ligand (Scheme 4). A substrate bearing OBz [(±)-**1w**] was reacted under 30 bar hydrogen pressure for 6 hours to recover **1w** with 82% yield and 4% *ee*. By lowering the reaction



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.

Acknowledgments

This work was partially supported by the National Natural Science Foundation of China (No. 21232004, 21372152, 21472123, and 21572131), Science and Technology Commission of Shanghai Municipality (No. 14XD1402300), and the China Postdoctoral Science Foundation (No. 2014M551397).

We also thank the Instrumental Analysis Center of SJTU for characterization.

Keywords: cleavage reactions · hydrogenolysis · ketones · kinetic resolution · palladium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8444 – 8447
Angew. Chem. **2016**, *128*, 8584 – 8587

[1] a) W. Liu, K. Bensdorf, M. Proetto, U. Abram, A. Hagenbach, R. Gust, *J. Med. Chem.* **2011**, *54*, 8605 – 8615; b) O. Bortolini, G. Fantin, V. Ferretti, M. Fogagnolo, P. P. Giovannini, A. Massi, S. Pacifico, D. Ragno, *Adv. Synth. Catal.* **2013**, *355*, 3244 – 3252; c) Y.-J. Kim, N. Y. Kim, C.-H. Cheon, *Org. Lett.* **2014**, *16*, 2514 – 2517.

[2] Selected papers on application of achiral α-acyloxy ketones: a) R. Epple, C. Cow, Y. Xie, M. Azimioara, R. Russo, X. Wang, J. Wityak, D. S. Karanewsky, T. Tuntland, V. T. Nguyentran, *J. Med. Chem.* **2010**, *53*, 77 – 105; b) J. E. Pickett, *Tetrahedron Lett.* **2015**, *56*, 3023 – 3026; selected papers on application of chiral α-acyloxy ketones: c) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3492 – 3494; *Angew. Chem.* **2006**, *118*, 3572 – 3574; d) G. He, F. Wu, W. Huang, R. Zhou, L. Ouyang, B. Han, *Adv. Synth. Catal.* **2014**, *356*, 2311 – 2319.

[3] a) T. Ema, H. Yagazaki, N. Okita, M. Takeda, T. Sakai, *Tetrahedron* **2006**, *62*, 6143 – 6149; b) S. Agrawal, E. Martínez-Castro, R. Marcos, B. Martín-Matute, *Org. Lett.* **2014**, *16*, 2256 – 2259.

[4] a) B. Xu, S.-F. Zhu, X.-D. Zuo, Z.-C. Zhang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 3913 – 3916; *Angew. Chem.* **2014**, *126*, 3994 – 3997; b) Y. Wei, B. Rao, X. Cong, X. Zeng, *J. Am. Chem. Soc.* **2015**, *137*, 9250 – 9253; c) Y. Zhao, A. Aguilar, D. Bernard, S. Wang, *J. Med. Chem.* **2015**, *58*, 1038 – 1052; d) J. Ke, Y. Tang, H. Yi, Y. Li, Y. Cheng, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 6604 – 6607; *Angew. Chem.* **2015**, *127*, 6704 – 6707.

[5] Methods involving reducing agents: a) T. Inokuchi, H. Kawatichi, S. Torii, *Chem. Lett.* **1992**, 1895 – 1896; b) M. Ueki, A. Okamura, J. Yamaguchi, *Tetrahedron Lett.* **1995**, *36*, 7467 – 7470; c) S. P. Y. Cutulic, N. J. Findlay, S.-Z. Zhou, E. J. T. Chrystal, J. A. Murphy, *J. Org. Chem.* **2009**, *74*, 8713 – 8718; methods involving photolysis: d) A. Banerjee, D. E. Falvey, *J. Org. Chem.* **1997**, *62*, 6245 – 6251; e) A. Banerjee, D. E. Falvey, *J. Am. Chem. Soc.* **1998**, *120*, 2965 – 2966; f) R. Ruzicka, M. Zabadal, P. Klán, *Synth. Commun.* **2002**, *32*, 2581 – 2590.

[6] J. Chen, D. Liu, N. Butt, C. Li, D. Fan, Y. Liu, W. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 11632 – 11636; *Angew. Chem.* **2013**, *125*, 11846 – 11850.

[7] A palladium-catalyzed stereoconvergent formal asymmetric hydrogenolysis of alcohol via a vinyl intermediate has been reported recently: C.-B. Yu, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 13365 – 13368; *Angew. Chem.* **2013**, *125*, 13607 – 13610.

[8] a) C. Zhu, Y. Shi, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2008**, *10*, 1243 – 1246; b) L. Wang, X. Wang, J. Cui, W. Ren, N. Meng, J. Wang, X. Qian, *Tetrahedron: Asymmetry* **2010**, *21*, 825 – 830; c) L. Bagnoli, C. Scarponi, M. G. Rossi, L. Testaferri, M. Tiecco, *Chem. Eur. J.* **2011**, *17*, 993 – 999; d) R. S. Reddy, I. N. C. Kirana, A. Sudalai, *Org. Biomol. Chem.* **2012**, *10*, 3655 – 3661.

[9] a) H. Aida, K. Mori, Y. Yamaguchi, S. Mizuta, T. Moriyama, I. Yamamoto, T. Fujimoto, *Org. Lett.* **2012**, *14*, 812 – 815; b) the absolute configuration of product was determined by comparison of the specific rotations with the literature data: Y. Du, D. Feng, J. Wan, X. Ma, *Appl. Catal. A* **2014**, *479*, 49 – 58.

[10] G. C. Tsui, J. Tsoung, P. Dougan, M. Lautens, *Org. Lett.* **2012**, *14*, 5542 – 5545.

[11] a) Z. Shen, V. M. Dong, *Angew. Chem. Int. Ed.* **2009**, *48*, 784 – 786; *Angew. Chem.* **2009**, *121*, 798 – 800; b) T. Horaguchi, C. Tsukada, E. Hasegawa, T. Shimizu, T. Suzuki, K. Tanemura, *J. Heterocycl. Chem.* **1991**, *28*, 1261 – 1272.

Received: April 13, 2016
Revised: May 11, 2016
Published online: June 17, 2016

