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One-Pot Synthesis of Optically Active Allyl Esters via Lipase−Vanadium Combo Catalysis

Shuji Akai,*,† Ryosuke Hanada,† Noboru Fujiwara,† Yasuyuki Kita,‡,§ and Masahiro Egi†

School of Pharmaceutical Sciences, University of Shizuoka, 52-1, Yada, Suruga-ku, Shizuoka, Shizuoka 422-8526, Japan, and Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamadaoka, Suita, Osaka 565-0871, Japan

akai@u-shizuoka-ken.ac.jp

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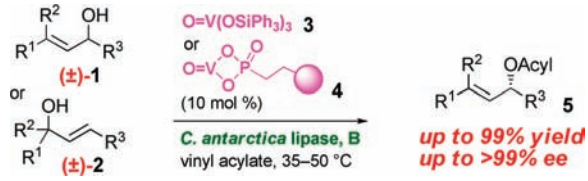
ABSTRACT



The combination of vanadium-oxo compounds (3 or 4) with a lipase produced the regio- and enantioconvergent transformation of racemic allyl alcohols (1 or 2) into optically active allyl esters. In this system, the vanadium compounds catalyzed the continuous racemization of the alcohols along with the transposition of the hydroxyl group, while the lipase effected the chemo- and enantioselective esterification to achieve the dynamic kinetic resolution.

Optically active secondary allyl alcohols and their derivatives are one of the most vital classes of compounds in modern organic synthesis because of their ubiquity and wide applications in the synthesis of optically active molecules including natural products, pharmaceutical and agrochemical products, and functional materials.[1] Therefore, various synthetic methods have been developed over the past decades. The popular ones include the kinetic resolution of racemic allyl alcohols,[1c,2] asymmetric reduction of vinyl ketones by optically active catalysts[1a,b,3] or enzymes,[4] and the enantioselective addition of alkenyl metal reagents to aldehydes.[5] Nevertheless, the development of different approaches that enable an environmentally benign production is still in need.

On the other hand, the 1,3-transposition of allyl alcohols has been studied over several decades mainly using metal-oxo catalysts.[6] It basically produces an equilibrium between the substrates and their regioisomers, and the product distribution depends on the relative thermodynamic stabilities of the two isomers.[7−9] The chiral integrity of optically active allyl alcohols is not always maintained.[8,9a,b] Because of these

† University of Shizuoka.
‡ Osaka University.
§ Current address: School of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Noji Higashi, Kusatsu, Shiga 525-8577, Japan.

(1) For a review, see: (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. For some recent examples, see: (b) Fujioka, H.; Matsuda, S.; Horai, M.; Fujii, E.; Morishita, M.; Nishiguchi, N.; Hata, K.; Kita, Y. *Chem.—Eur. J.* **2007**, *13*, 5238. (c) Sawama, Y.; Sawama, Y.; Krause, N. *Org. Biomol. Chem.* **2008**, *6*, 3573.

(2) For a review, see: (a) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. For an example, see (b) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351.

(3) For a review, see: Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(4) For an example, see: Krausser, M.; Hummel, W.; Gröger, H. *Eur. J. Org. Chem.* **2007**, 5175.

(5) For examples, see: (a) Cozzi, P. G.; Kotrusz, P. *J. Am. Chem. Soc.* **2006**, *128*, 4940. (b) Sokeirik, Y. S.; Mori, H.; Omote, M.; Sato, K.; Tarui, A.; Kumadaki, I.; Ando, A. *Org. Lett.* **2007**, *9*, 1927.

(6) For reviews, see: (a) Chabardes, P.; Kuntz, E.; Varagnat, J. *Tetrahedron* **1977**, *33*, 1775. (b) Bellemin-Laponnaz, S.; Le Ny, J.-P.; Dedieu, A. *Chem.—Eur. J.* **1999**, *5*, 57.

(7) For a review, see: Bellemin-Laponnaz, S.; Le Ny, J.-P. *Compt. Rend. Chim.* **2002**, *5*, 217.

(8) Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844.

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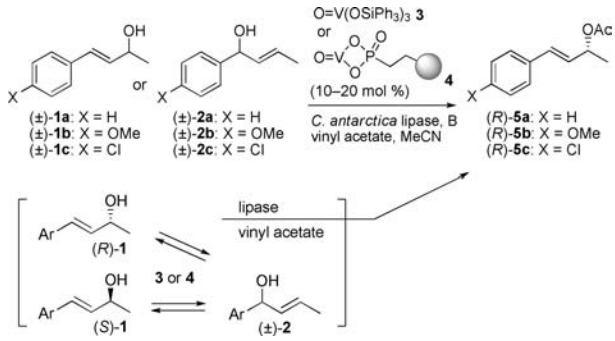
uncertain natures, the 1,3-transposition reaction has received less attention from a synthetic point of view.[10,11] We report herein an asymmetric synthesis of optically active allyl esters **5** from racemic allyl alcohols (**1** or **2**) by the combination of the vanadium (**3** or **4**)-catalyzed 1,3-transposition reaction and the lipase-catalyzed kinetic resolution (schemes in the Abstract and Table 1). In this system, the vanadium-catalyzed

Table 1. Conversion of (±)-**1a**−**c** and (±)-**2a**−**c** into (*R*)-**5** by the Lipase−Vanadium (**3**, **4**) Combo Catalysis



entry	substrate (**1** or **2**)	V catalyst	conditions	product **5**
1	(±)-**1a**	**3**[a]	50 °C, 3 d	(*R*)-**5a** 95% ee, 70%
2	(±)-**1a**	**4**	35 °C, 1 d	(*R*)-**5a** 92% ee, 80%
3	(±)-**1b**	**3**	35 °C, 1 d	(*R*)-**5b** >99% ee, 97%
4	(±)-**1b**	**4**	35 °C, 1 d	(*R*)-**5b** 99% ee, 27%
5	(±)-**1c**	**4**	50 °C, 1 d	(*R*)-**5c** 92% ee, 71%
6	(±)-**2a**	**4**	35 °C, 1 d	(*R*)-**5a** 94% ee, 77%
7	(±)-**2b**	**3**	35 °C, 1 d	(*R*)-**5b** 96% ee, 99%
8	(±)-**2c**	**4**	50 °C, 1 d	(*R*)-**5c** 94% ee, 74%

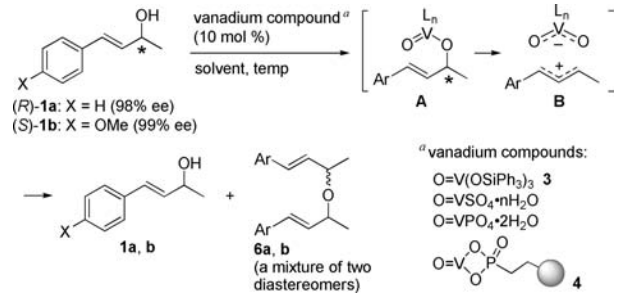
[a] 20 mol % of **3** was used.

1,3-transposition of **1** or **2** generates a dynamic equilibrium between them with continuous racemization, while the lipase effects the chemo- and enantioselective esterification to give optically active **5**.

One of the most difficult obstacles to achieve this idea was the incompatibility of artificial metallic compounds and natural enzymes in a single reaction pot. Although several transition metal-oxo compounds that include V,[8,11] W,[12] Mo,[13,14] and Re[9,10,15−17] have been developed to effectively catalyze the 1,3-transposition of the allyl alcohols below ambient temperature, many are hardly compatible with the lipases. On the contrary, we initially reported that O═V(OSiPh$_3$)$_3$ (**3**) and the lipases were tolerant in acetone at 35 °C for a few days and their combined use accomplished the dynamic kinetic resolution (DKR) of (±)-**1** ($R^1 = R^2$) to give (*R*)-**5**;[18] however, this method was not effective for the unsymmetrically substituted (±)-**1** ($R^1 \neq R^2$) (see the following examples of **1a**). Therefore, our first challenge was the discovery of a more powerful racemization protocol for **1** ($R^1 \neq R^2$) while maintaining the compatibility with the lipases. It is worth noting that no one has positively promoted the racemization of optically active allyl alcohols during the transposition, although the prevention of the racemization has been investigated.[9a,b]

The racemization was studied using (*R*)-**1a** (98% ee) as the test substrate (Scheme 1). Under our previous conditions [use

Scheme 1. Vanadium-Catalyzed Racemization of Optically Active **1a**,**b**



of **3** (10 mol %) in acetone at 35 °C],[18] the racemization was very slow to give (*R*)-**1a** (86% ee) after 72 h. We then screened the solvents, the reaction temperature, and the vanadium compounds: (1) Raising the temperature to 50 °C in acetone or changing the solvent to MeCN at 35 °C significantly enhanced the racemization to give the racemic **1a** after 8 h. (2) Commercially available O═VSO$_4$•*n*H$_2$O (10 mol %) was very reactive and produced the complete racemization within 1 h in MeCN at 35 °C; however, a mixture of diastereomeric ethers **6** was also obtained in approximately 50% yield. A further study disclosed its fatal incompatibility with lipases.[19] (3) While the use of O═VPO$_4$•2H$_2$O (10 mol %) in MeCN at 35 °C was less effective in producing a 2:1 mixture of (*R*)-**1a** (86% ee) and **6** after 13 h, a polymer-bound vanadyl phosphate **4**[20] (10 mol

(9) For recent trials to control the regio- and stereoselectivities of the 1,3-transposition of allyl alcohols, see: (a) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842. (b) Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813. (c) Herrmann, A. T.; Saito, T.; Stivala, C. E.; Tom, J.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 5962.

(10) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262.

(11) For the use of allenic alcohols, see: Trost, B. M.; Jonasson, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2063.

(12) Hosogai, T.; Fujita, Y.; Ninagawa, Y.; Nishida, T. *Chem. Lett.* **1982**, 357.

(13) (a) Belgacem, J.; Kress, J.; Osborn, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 1501. (b) Belgacem, J.; Kress, J.; Osborn, J. A. *J. Mol. Catal.* **1994**, *86*, 267.

(14) Fronczek, F. R.; Luck, R. L.; Wang, G. *Inorg. Chem. Commun.* **2002**, *5*, 384.

(15) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059.

(16) (a) Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J. P.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 976. (b) Bellemin-Laponnaz, S.; Le Ny, J. P.; Osborn, J. A. *Tetrahedron Lett.* **2000**, *41*, 1549.

(17) (a) Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics* **1998**, *17*, 1835. (b) Wang, G.; Jimtaisong, A.; Luck, R. L. *Organometallics* **2004**, *23*, 4522.

(18) Akai, S.; Tanimoto, K.; Kanao, Y.; Egi, M.; Yamamoto, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 2592.

(19) Jacobs also reported the incompatibility of O═VSO$_4$•*n*H$_2$O with *C. antarctica* lipase, B; see: Wuyts, S.; Wahlen, J.; Jacobs, P. A.; De Vos, D. E. *Green Chem.* **2007**, *9*, 1104.

(20) The polymer reagent **4** is commercially available from STREM as PhosphonicS POVO and has been used only for the oxidation of allyl alcohols; see: Jurado-Gonzalez, M.; Sullivan, A. C.; Wilson, J. R. H. *Tetrahedron Lett.* **2004**, *45*, 4465.

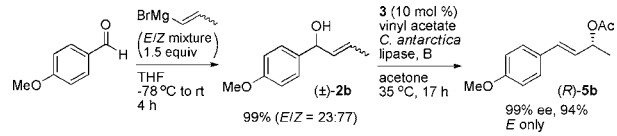
%) in MeCN at 35 °C produced the racemic **1a** (89% yield) and **6** (11% yield) after only 2 h. This implied some beneficial nature of the polymer reagent on the compatibility with lipases.[21]

The racemization of the *p*-methoxy derivative (*S*)-**1b** (99% ee) was much faster than that of **1a**. It was completed by **3** (10 mol %) in MeCN within 2 h at 35 °C to give (±)-**1b**; however, its yield was 28%, and **6b** was formed in 72% yield (Scheme 1). These results indicated that the racemization took place via a cationic intermediate **B** similar to the cases using the rhenium-oxo compounds.[9,15] This is also consistent with the fact that the use of the more polar solvent, MeCN, accelerated the process. However, the formation of dimeric ethers **6** has emerged as another serious problem.

We next examined the DKR of (±)-**1a**−**c** by the combined use of a lipase with **3** or **4**. First, (±)-**1b** was treated with the commercially available immobilized *C. antarctica* lipase, B, and **3** (10 mol %) in MeCN at 35 °C for 1 day to provide the corresponding (*R*)-**5b** (>99% ee) in 97% isolated yield (Table 1, entry 3). This result demonstrated that the presence of a lipase sufficiently depressed the formation of the dimer **6b**. The selection of a racemization catalyst suitable for each substrate was found to be essential for the efficient DKR. Thus, for the racemization resistant (±)-**1a**, the use of **4** (10 mol %) gave slightly better results [(*R*)-**5a**: 92% ee, 80% yield at 35 °C in 1 day] (entry 2) than that of 20 mol % of **3** [(*R*)-**5a**: 95% ee, 70% yield at 50 °C in 3 days] (entry 1). In a like manner, (±)-**1c** was converted into (*R*)-**5c** (92% ee, 71% yield) using **4** (10 mol %) (entry 5). Because the developed method generates an equilibrium between **1** and **2**, a similar treatment of (±)-**2a**−**c** also provided the same products (*R*)-**5a**−**c** in comparable optical and chemical yields (entries 6−8).

The following is another practical advantage of this method: the reaction of anisaldehyde with the commercially available 1-propenylmagnesium bromide (a mixture of *E*- and *Z*-isomers) quantitatively afforded a mixture of (*E*)- and (*Z*)-**2b** (*E*/*Z* = 23:77), which was then converted into (*R*)-**5b** (99% ee, 94% yield) with exclusive *E*-selectivity. Thus, the overall process enabled the two-step preparation of the optically and geometrically pure **5b** starting from commercial raw materials in a 94% overall yield (Scheme 2).

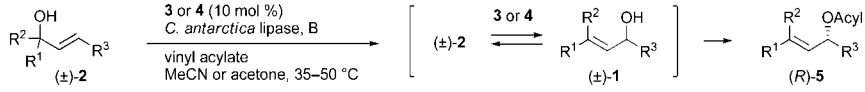
Scheme 2. Two-Step Synthesis of (*R*)-**5b** from Anisaldehyde



The combo-catalysis was applied to a variety of allyl alcohols (±)-**2d**−**n** to give (*R*)-**5d**−**n** (Table 2). For the substrates with electron-rich aromatic rings, such as **2e**,**g**−**i**, the use of **3** yielded the corresponding (*R*)-**5e**,**g**−**i** in good-to-excellent optical and chemical yields (entries 2 and 4−6). For the nonconjugated aliphatic alcohols (**2j** and **2k**), **4** was more suitable to provide **5j** (96% ee) and **5k** (95% ee) in 68−71% yields (entries 7 and 8). Starting from the tertiary cyclic alcohols **2l**−**n**, the secondary alcohols (*R*)-**5l**−**n** were obtained in good yields (entries 9−11). The acylates of **2** were not obtained at all in these reactions.

(*R*)-3-Undecyl-2-cyclohexen-1-ol **7**, derived from (*R*)-**5m**, served as a key synthetic intermediate of (+)-tanikolide.[1b] It had been synthesized from 3-ethoxy-2-cyclohexen-1-one via the CBS asymmetric reduction of 2-iodo-3-undecyl-2-cyclohexen-1-one in 31% overall yield in five steps, while this method provided (*R*)-**7** (96% ee) from the simpler and

Table 2. Asymmetric Synthesis of (*R*)-**5** from (±)-**2** by the Lipase−Vanadium Combo Catalysis



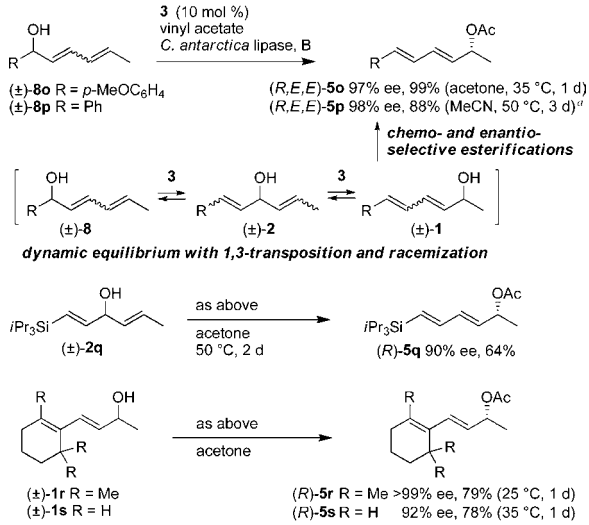
entry	substrate **2**				conditions	product (*R*)-**5**	
		R^1	R^2	R^3			
1	(±)-**2d**	*p*-MeC_6H_4	H	Me	**3**,[a] MeCN, 50 °C, 3 d	(*R*)-**5d**	98% ee, 87%
2	(±)-**2e**	*p*-$MeOC_6H_4$	H	Et	**3**,[a] MeCN, 35 °C, 3 d	(*R*)-**5e**	98% ee, 96%
3	(±)-**2f**	Ph	Me	Me	**3**,[a] MeCN, 35 °C, 3 d	(*R*)-**5f**	98% ee, 89% (*E*:*Z* = 3:1)
4	(±)-**2g**	2-furyl	H	Me	**3**, acetone, 35 °C, 2 d	(*R*)-**5g**	99% ee, 93%
5	(±)-**2h**	2-thienyl	H	Me	**3**, acetone, 35 °C, 1 d	(*R*)-**5h**	97% ee, 99%
6	(±)-**2i**	2-thienyl	H	Et	**3**, MeCN, 35 °C, 4 d	(*R*)-**5i**	98% ee, 80%
7	(±)-**2j**	$Ph(CH_2)_2$	H	Me	**4**, MeCN, 50 °C, 3 d	(*R*)-**5j**	96% ee, 71%
8	(±)-**2k**	c-C_6H_{11}	H	Me	**4**, MeCN, 50 °C, 1 d	(*R*)-**5k**	95% ee, 68%
9	(±)-**2l**	R^1 = *n*-Bu			**3**, heptane, 35 °C, 1 d[b]	(*R*)-**5l**	(R^1 = *n*-Bu, R^4 = *n*-Pr) 96% ee, 76%
10	(±)-**2m**	R^1 = *n*-$C_{11}H_{23}$			**4**, acetone, 25 °C, 1 d[b]	(*R*)-**5m**	(R^1 = *n*-$C_{11}H_{23}$, R^4 = *n*-Pr) 96% ee, 65%
11	(±)-**2n**	R^1 = Ph			**3**, MeCN, 35 °C, 1 d	(*R*)-**5n**	(R^1 = Ph, R^4 = Me) 97% ee, 78%

[a] 20 mol % of **3** was used. [b] Vinyl butyrate was used instead of vinyl acetate.

less expensive 2-cyclohexen-1-one in a 46% overall yield[22] and features the high step-, atom-, and redox-economies.[23]

An additional outstanding aspect of the developed method was demonstrated by the reactions of the dienols [(±)-**8o**,**p**], each of which is a mixture of several stereoisomers, to produce the single products [(*R*,*E*,*E*)-**5o**,**p**]. In these cases, **3** generated a dynamic equilibrium including different regio- and stereoisomers [(±)-**8**, (±)-**2**, and (±)-**1**], while the lipase catalyzed the chemo-, stereo-, and enantioselective esterification of (*R*,*E*,*E*)-**1**. The alcohol **2q** having a hydroxyl group between two olefins produced (*R*)-**5q**. The cyclic dienols [(±)-**1r**,**s**] were converted into their optically active acetates [(*R*)-**5r**,**s**] with excellent optical purities (Scheme 3).

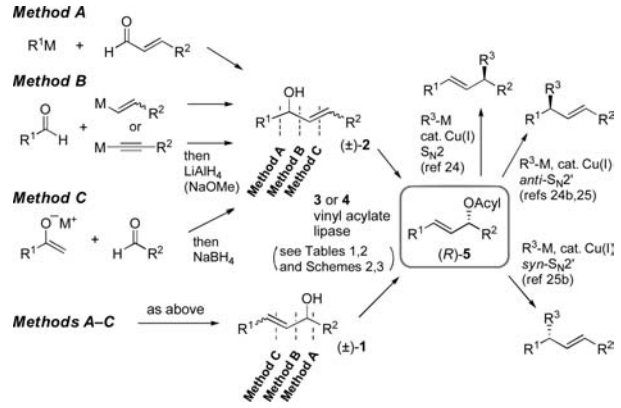
Scheme 3. Asymmetric Synthesis of Dienyl Acetates (*R*)-**5o**−**s**[a]



[a] Use of **3** (20 mol %).

The racemic allyl alcohols (**1** and **2**) were prepared by the common reactions of carbonyl compounds and carbanions, which are classified into three groups based on the carbon−carbon bond to make (methods A−C) (for details, see the Supporting Information). In some cases, the preparation of **2** is more convenient and effective than that of **1** due to the availability and cost of the precursors, efficiency and safety of the reactions, etc. The fact that both **1** and **2** serve as equivalent substrates of the developed method increases flexibility in choosing the most effective synthetic route to (*R*)-**5**. Because the stereo- and regioselective transformations of the allyl esters to various valuable compounds have been developed,[24,25] the overall process provides a few-step synthesis of optically active olefins (Scheme 4).

Scheme 4. Asymmetric Synthesis of the Optically Active Allyl Esters (*R*)-**5** and Some Examples of Their Further Transformation



In conclusion, the combined use of the vanadium-oxo compounds (**3** and **4**) and the lipase produced the regio- and enantioconvergent transformation of racemic allyl alcohols (**1**, **2** or **8**) into optically active allyl esters. This method features a multistep one-pot reaction[26] involving the 1,3-transposition of the hydroxyl group, the continuous racemization of the optically active allyl alcohols, and the enantio-, chemo-, and diastereoselective esterification. Its value also lies in the fact that such a transformation has never been achieved using each catalyst separately. Moreover, this method is different from the well-known dynamic kinetic resolution using a combination of Ru complexes and lipases[27] and offers the following synthetic advantages: (1) all possible regioisomers are available as equivalent substrates to give the same allyl esters in a single step; (2) the best synthetic route to the substrates can be selected among various candidates; and (3) the overall process offers a new methodology for the asymmetric synthesis of the optically active allyl esters from easily obtainable prochiral raw materials in only a few steps. The application of other kinds of hydrolases having different enantio- and chemoselectivities to this combo catalysis is under investigation in our laboratory to expand the availability range of the optically active allyl esters.

Acknowledgment. This work was supported by KAKENHI (No. 21390005) and the Asahi Glass Foundation. Roche Diagnostics K. K., Japan, is thanked for the generous gift of the lipase.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For the detailed time−course of these racemization reactions, see the Supporting Information.

(22) For the detailed comparison of the two methods, see the Supporting Information.

(23) For an example, see: Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(24) (a) Calaza, M. I.; Yang, X.; Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 529. (b) Norinder, J.; Bogár, K.; Kanupp, L.; Bäckvall, J.-E. *Org. Lett.* **2007**, *9*, 5095.

(25) (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111. (b) Breit, B.; Demel, P.; Studte, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3786.

(26) For reviews of the multistep one-pot reactions using cooperative catalysis, see: (a) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745.

(27) For recent reviews, see: (a) Martín-Matute, B.; Bäckvall, J.-E. *Asym. Org. Synth. Enz.* **2008**, 89. (b) Karvembu, R.; Prabhakaran, R.; Tamizh, M.; Natarajan, K. *Compt. Rend. Chim.* **2009**, *12*, 951. (c) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999. (d) Turner, N. J. *Curr. Opin. Chem. Biol.* **2010**, *14*, 115.