ORGANIC LETTERS

2009
Vol. 11, No. 22
5342−5345

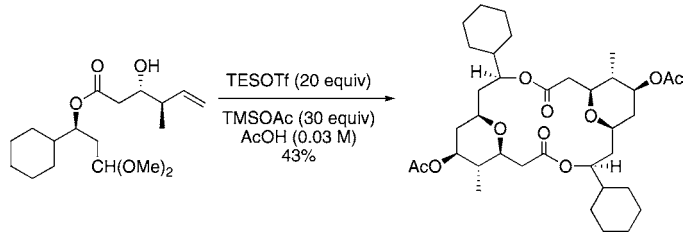
Symmetric Macrocycles by a Prins Dimerization and Macrocyclization Strategy

Michael R. Gesinski, Kwanruthai Tadpetch, and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025
srychnov@uci.edu

Received September 23, 2009

ABSTRACT



A tandem dimerization/macrocyclization reaction utilizing the Prins cyclization has been developed. This reaction develops molecular complexity through the formation of highly substituted dimeric tetrahydropyran macrocycles. Mild conditions utilizing rhenium(VII) catalysts were explored for aromatic substrates, while harsher Lewis acidic conditions were used for aliphatic substrates. Both aldehydes and acetals are shown to be viable substrates for this reaction.

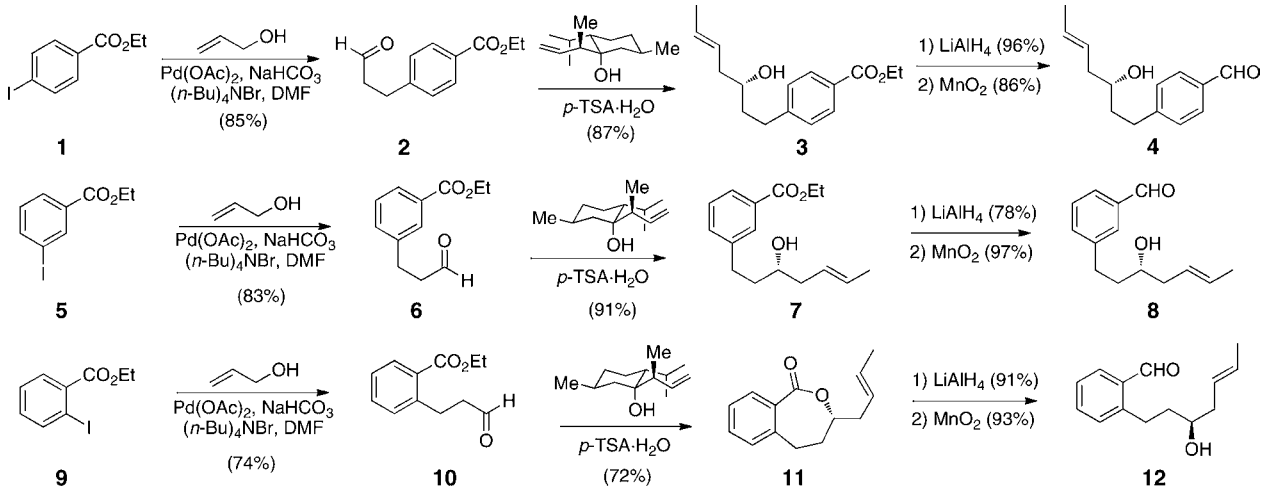
Oxacyclic macrodimers are an important class of natural products offering a wide array of structural complexity and bioactivity.[1] These macrolides have become popular targets for synthetic chemists.[2] The most direct way to construct these molecules is through the union of two monomeric species in a tandem dimerization and macrocyclization reaction. The most common version of this strategy utilizes two esterification reactions between an activated acid and an alcohol, first an initial dimerization followed by a macrolactonization.[3] While often successful, this approach does not greatly enhance the complexity of the intermediate through the formation of carbon−carbon bonds. Alternative bond-forming reactions, such as Suzuki coupling and olefin metathesis, have been used with occasional success in dimerization and macrocyclization strategies.[4,5] Herein we describe a new dimerization and macrocyclization strategy based on the Prins cyclization reaction.

The Prins cyclization is a powerful reaction that forms *cis*-2,6-disubstituted tetrahydropyrans (THPs) through the addition of an olefin to an oxocarbenium ion generated from the condensation of an aldehyde with a homoallylic alcohol.[6] Recently, intramolecular Prins cyclizations have been utilized as key macrocyclization steps in the synthesis of several THP containing natural products (Figure 1A).[7] We report the

(1) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041–2114.
(2) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348–4378.
(3) (a) Wakamatsu, T.; Yamada, S.; Ban, Y. *Heterocycles* **1986**, *24*, 309–312. (b) Furstner, A.; Mlynarski, J.; Albert, M. *J. Am. Chem. Soc.* **2002**, *124*, 10274–10275. (c) Panek, J. S.; Porco, J. A., Jr.; Lobkovsky, E.; Beeler, A. B.; Su, Q. *Org. Lett.* **2003**, *5*, 2149–2152. (d) Barth, R.; Mulzer, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5791–5794.
(4) (a) Cheung, L. L.; Marumoto, S.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101–3104. (b) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6527–6532.
(5) (a) HWE olefinations: Hoye, T. R.; Humpal, P. E.; Moon, B. *J. Am. Chem. Soc.* **2000**, *122*, 4982–4983. (b) Olefin metathesis: Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925–5937. (c) Condensations: Hoye, T. R.; Ye, Z.; Yao, L. J.; North, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 12074–12081.
(6) (a) Recent reviews on the Prins cyclization: Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925–957. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (c) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661–672. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157.
(7) (a) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804–805. (b) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, 3242–3244. (c) Wender, P. A.; DeChristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658–6659. (d) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181.

10.1021/ol9022062 CCC: $40.75
Published on Web 10/29/2009

Scheme 1. Synthesis of the Aldehyde Monomers



extension of this methodology to the formation of oxacyclic macrodimers through sequential Prins dimerization and macrocyclization reactions (Figure 1B). This synthetic strategy has been applied to a model for the marine macrodiolide clavosolide A.

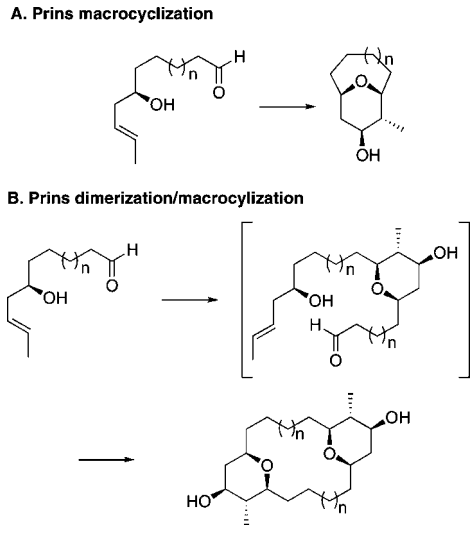


Figure 1. Comparison of Prins macrocyclization reactions.

The [*n*,*n*]-cyclophanes were chosen as targets for the initial study of this reaction since the aromatic ring of these substrates provides rigidity that precludes the undesired macrocyclization reaction, and the starting materials were accessible from simple precursors. The Prins cyclization substrates **4**, **8**, and **12** were synthesized from the corresponding commercially available *para*-, *meta*-, or *ortho*-substituted ethyl iodobenzoate, respectively (Scheme 1). Palladium-mediated coupling of allyl alcohol and ethyl 4-iodobenzoate (**1**) yielded known aldehyde **2** in 85% yield.[8] Nokami's menthone derived allyl-transfer reagent was utilized to yield optically pure *E*-homoallylic alcohol **3**.[9] The ethyl ester was reduced with $LiAlH_4$ to provide the benzylic alcohol, which was selectively oxidized with MnO_2 to afford aldehyde **4** in 61% overall yield. The *meta*- and *ortho*-substituted substrates (**8** and **12**, respectively) were synthesized in a similar manner.

With appropriate starting materials in hand, the dimerization/macrocyclization reaction of aldehyde **4** was explored (Table 1). Previously, $O_3ReOSiPh_3$ has been shown to effectively catalyze Prins reactions of aromatic aldehydes.[10] When aldehyde **4** was exposed to $O_3ReOSiPh_3$ at room temperature for 22 h, 33% of cyclophane **13** was isolated (entry 1). The remainder of the mass was attributed to rhenium(VII)-mediated polymerization. To diminish this byproduct, the reaction was run at lower concentration, which increased the yield of the dimer (entry 2). Gratifyingly, decreasing the catalyst loading to 25% had little effect on the yield (entry 3), but decreasing the loading further resulted in diminished yields (entry 4). Other rhenium(VII) catalysts proved less effective than $O_3ReOSiPh_3$ (entries 5 and 6). Heating the reaction in CH_2Cl_2 decreased the reaction time but had minimal effect on the overall yield (entries 7 and 8). Finally, alternative Prins promoters were investigated. Both TESOTf[11] and trifluoroacetic acid[12] produced acylated variations of cyclophane **13** (entries 9 and 10) but ultimately proved inferior to the rhenium(VII) conditions.

Having developed optimized conditions for the dimerization/macrocyclization reaction of the *para*-substituted aldehyde, the

(8) (a) Taylor, E. C.; Gillespie, P.; Patel, M. *J. Org. Chem.* **1992**, *57*, 3218–3225. (b) Watson, S. E.; Taylor, E. C.; Patel, H. *Synth. Commun.* **1998**, *28*, 1897–1905.

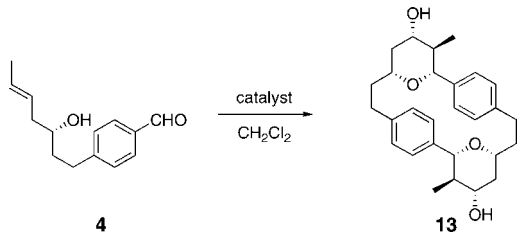
(9) (a) Nokami, J.; Nomiyama, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273–1276. (b) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, H.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168–9169.

(10) Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4839–4842.

(11) Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Tetrahedron* **2007**, *63*, 5797–5805.

(12) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429–2432.

Table 1. Screening Prins Dimerization/Macrocyclization Conditions



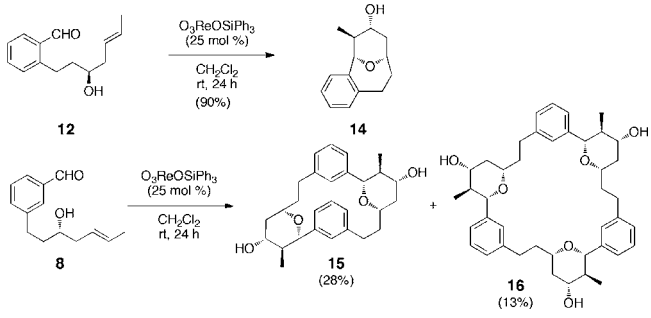
4 13

entry	catalyst	conc	time	temp	yield
1	$O_3ReOSiPh_3$ (40 mol %)	0.10 M	22 h	23 °C	33%
2	$O_3ReOSiPh_3$ (50 mol %)	0.050 M	24 h	23 °C	53%
3	**$O_3ReOSiPh_3$ (25 mol %)**	**0.050 M**	**24 h**	**23 °C**	**51%**
4	$O_3ReOSiPh_3$ (5 mol %)	0.050 M	24 h	23 °C	26%
5	aq O_3ReOH (50 mol %)	0.050 M	24 h	23 °C	29%
6	Re_2O_7 (50 mol %)	0.045 M	25 h	23 °C	38%
7	$O_3ReOSiPh_3$ (25 mol %)	0.050 M	5 h	40 °C	51%
8	$O_3ReOSiPh_3$ (5 mol %)	0.050 M	5 h	40 °C	42%
9	TESOTf[a] (20 equiv)	0.030 M	3 h	23 °C	27%[b]
10	TFA (20 equiv)	0.30 M	3 h	23 °C	11%[b]

[a] Run in AcOH with 30 equiv of TMSOAc. [b] Yield after hydrolysis of the crude acyl trapped product by MeOH/K_2CO_3.

ortho- and *meta*-substituted aldehydes were employed to further expand the scope of the reaction (Scheme 2). The *ortho*-

Scheme 2. Optimized Prins Macrocylization/Dimerization Reactions



substituted aldehyde **12** afforded cyclized monomer **14** via an intramolecular Prins reaction in 90% yield. Prins macrocyclizations can be very effective, when not precluded by the geometry of the substrate.[7] In contrast, when aldehyde **8** was exposed to the Prins conditions, dimeric cyclophane **15** was obtained in 28% yield. Surprisingly, the trimeric macrocycle **16** was also isolated in 13% yield. The remainder of the mass was associated with a small amount of starting material and a complex mixture of other products. The Prins reaction led to significant yields of dimer in two of the three cases examined, and in each case a single enantiomer and diastereomer of the product was obtained.

The C_2-symmetric macrodiolide (−)-clavosolide A (Figure 2) was isolated from the marine sponge *Myriastra clavosa*

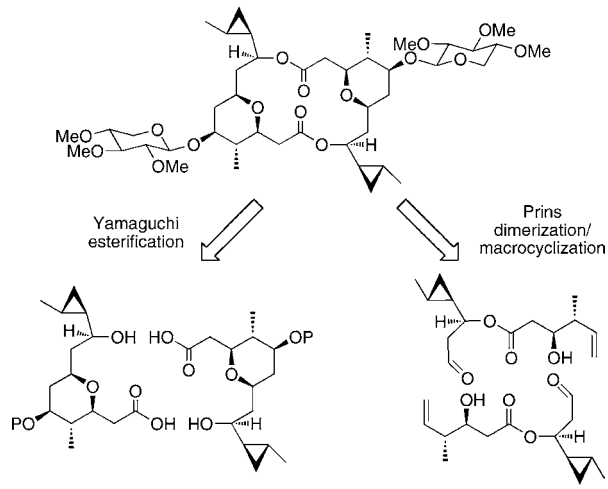


Figure 2. Two alternative strategies for the dimerization and cyclization of (−)-clavosolide A.

gathered off the coast of the Philippines.[13] The unique architecture of this THP-containing macrodimer inspired several total syntheses[14] and a structural revision.[15] All reported approaches utilized Yamaguchi's macrolactonization conditions to form the dimer from a complex, THP-containing monomer.[16] The interesting architecture of clavosolide A appeared to be well suited to a Prins dimerization and macrocyclization strategy.

Due to concern over the lability of the cyclopropylcarbinyl moiety of clavosolide A,[17] a model system was designed that replaced the problematic cyclopropyl side chain with a cyclohexane ring. The cyclohexyl monomer was synthesized from two simple fragments, **20** and **24** (Schemes 3 and 4). Enzymatic resolution of known β-lactone **17** with Lipase PS Amano in the presence of benzyl alcohol afforded the resolved (*S*)-lactone (**18**) and β-hydroxy ester **19**.[18] Both substrates were then reduced with $LiAlH_4$, and the resultant enantiomeric diols were monoprotected as TBS-ethers **20** and **21**.

The synthesis of the acid fragment **24** began with DDQ-mediated deprotection of the *p*-methoxybenzyl ether of known silyl ether **22** to provide an inseparable mixture of alcohol **23** and *p*-anisaldehyde.[19] The *p*-anisaldehyde was then removed by reduction and chromatography. Surprisingly, oxidation to

(13) (a) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, *65*, 1303–1306. (b) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386–388.

(14) (a) Carrick, J. D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 769–772. (b) Chakraborty, T. K.; Reddy, V. R.; Chattopadhyay, A. K. *Tetrahedron Lett.* **2006**, *47*, 7435–7438. (c) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319–3322. (d) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315–3318. (e) Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* **2006**, *8*, 661–664.

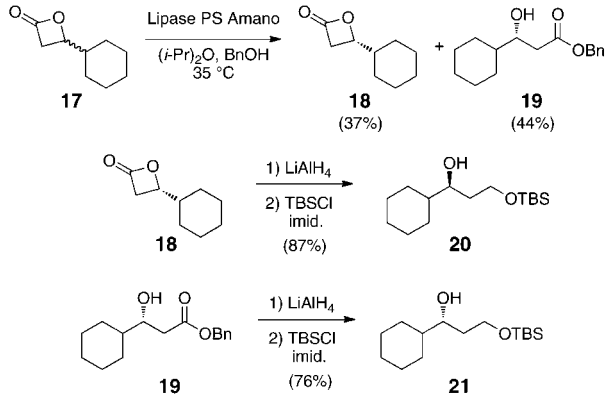
(15) (a) Chakraborty, T. K.; Reddy, V. R. *Tetrahedron Lett.* **2006**, *47*, 2099–2102. (b) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097–5099.

(16) Yamaguchi, M. A.; Katsuki, T.; Sacki, H.; Hirata, K.; Inanaga, J. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

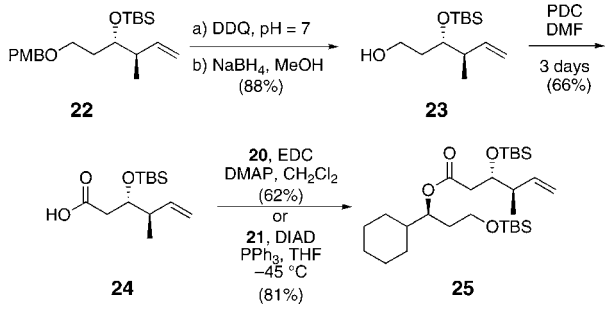
(17) Poulter, D. C.; Winstein, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 3650–3652.

(18) (a) Nelson, S. G.; Spencer, K. L. *J. Org. Chem.* **2000**, *65*, 1227–1230. (b) Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, 6535–6539.

Scheme 3. Synthesis of the Cyclohexyl Alcohols **20** and **21**

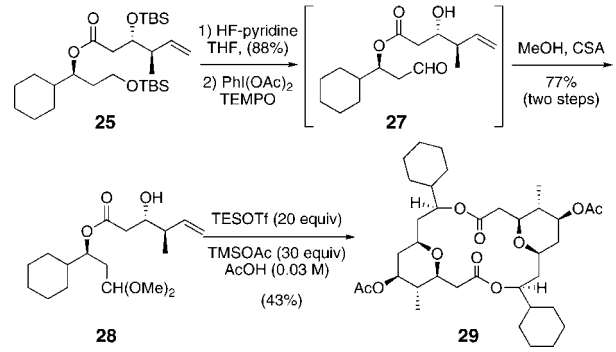


Scheme 4. Synthesis of the Ester Monomer **25**



With the completion of the monomer framework, a few simple manipulations were needed to test the key Prins dimerization/macrocyclization reaction (Scheme 5). Removal of the two silyl groups proved to be surprisingly difficult. Under standard deprotection conditions, only the primary silyl group was cleaved. Unfortunately, unmasking the primary alcohol under more forcing basic or acidic conditions led to a deleterious acyl migration. Ultimately, a large excess of HF·pyridine in THF

Scheme 5. Prins Dimerization and Macrocyclization



was needed to avoid this side reaction, and the diol **26** (not shown) was formed in 88% yield. Finally, TEMPO-catalyzed selective oxidation successfully produced the requisite aldehyde **27**. Aldehyde **27** was labile and decomposed upon silica gel chromatography. Attempts to perform a Prins dimerization and macrocyclization reaction on the crude aldehyde under various conditions led to decomposition of the starting material, presumably through acid-promoted elimination of the β-acyl aldehyde.

To circumvent this decomposition, aldehyde **27** was protected as dimethyl acetal **28**. This substrate proved much more manageable and was easily purified by column chromatography. It has been shown that Lewis acid-promoted Prins cyclizations of acetals are particularly effective with TESOTf in acetic acid.[11,22] Gratifyingly, when acetal **28** was subjected to these conditions, dimeric macrolide **29** was produced in 43% yield. Using acetal **28** avoids the decomposition of the sensitive aldehyde **27**.

The first example of a Prins dimerization and macrocyclization reaction has been developed. This powerful methodology affords macrocyclic dimers while simultaneously enhancing molecular complexity. Several complex [*n*,*n*]-paraphanes were prepared in only five steps from commercially available material. A model for the synthesis of clavosolide A was successfully demonstrated, and studies will continue to apply this strategy to natural product synthesis.

Acknowledgment. This work was supported by the National Institute of General Medicine (GM-43854) and by a generous gift from the Schering-Plough Research Institute. K.T. was supported by a fellowship from the Royal Thai Government, and M.R.G. was supported by a Lilly Graduate Research Fellowship.

Supporting Information Available: Characterization data and experimental procedures for all compounds described are included. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9022062

(19) Eggen, M.; Mossman, C. J.; Buck, S. B.; Nair, S. K.; Bhat, L.; Ali, S. M.; Reiff, E. A.; Boge, T. C.; Georg, G. I. *J. Org. Chem.* **2000**, *65*, 7792–7799.

(20) Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M. *Org. Synth.* **2005**, *81*, 195–203.

(21) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402.

(22) (a) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930–5938. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71–74.