

Article

Completely OH-Selective FeCl3-Catalyzed Prins Cyclization: Highly Stereoselective Synthesis of 4-OH-Tetrahydropyrans

Ke Zheng, Xiaohua Liu, Song Qin, Mingsheng Xie, Lili Lin, Changwei Hu, and Xiaoming Feng

J. Am. Chem. Soc., Just Accepted Manuscript • Publication Date (Web): 02 Oct 2012

Downloaded from http://pubs.acs.org on October 8, 2012

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036 Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

9

10 11 12

13 14

15

16

17

18

19

20

21

22

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58 59 60

Completely OH-Selective FeCl₃-Catalyzed Prins Cyclization: Highly Stereoselective Synthesis of 4-OH-Tetrahydropyrans

Ke Zheng, Xiaohua Liu, Song Qin, Mingsheng Xie, Lili Lin, Changwei Hu and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China.

Supporting Information Placeholder

ABSTRACT: The completely OH-selective Prins cyclization has been realized from the enantioselective ene reaction product. A variety of 4-hydroxyl-tetrahydropyrans were exclusively generated via $FeCl_3$ catalyzed Prins reaction. Excellent stereoselectivities (up to >99:1 dr and >99.5:0.5 er) were obtained for a remarkably broad substrates under mild reaction conditions. The control experiments, including NOE effects and ¹⁸O-labeling studies, as well as DFT calculations were conducted to provide fundamental insights into the mechanism of the reaction. A different [2+2] cycloaddition process was suggested to rationalize the observed OH-selectivity.

INTRODUCTION

Substituted tetrahydropyrans represent a common structural motif featured in a large number of natural products and biologically active compounds.¹ In particular, chiral 4hydroxyl substituted tetrahydropyran derivatives play an important role in therapeutic area. In virtue of the varied and significant biological activities²⁻⁴ observed for such a class of compounds, the development of catalytic asymmetric synthesis of 4-hydroxyl tetrahydropyrans is highly valuable. Therefore, a number of reactions have been developed to approach to this target.⁵ Among existing approaches, the Prins cyclization, a coupling of a homoallylic alcohol with a carbonyl compound in the presence of an acid catalyst, stood out as one of the most attractive.6-11 However, the enantioselective access to substituted tetrahydropyrans via the Prins cyclization was restricted to two of the problems common to the typical Prins cyclization protocols: side-chain exchange and partial racemization by reversible 2-oxonia Cope rearrangement and solvolvsis effect, which has been demonstrated as a competitive process in Prins cyclization by Rychnovsky and Willis (Scheme 1).8 On the other hand, in previous works, the halogenated Lewis acid-promoted (such as MX_n and TMSX) Prins cyclizations usually gave the halosubstituted tetrahydropyrans as products, which formed as the result of intermediate-trapping by halogen ion (most commonly from the original acid MX_n and TMSX). And hydroxyl-substituted products were only obtained as the byproducts.⁹ Although hydroxyl-added products could be achieved as the main products in the presence of TFA or $M(OTf)_n$ (a Lewis acid with a non-nucleophilic anion), more generally, strongly acidic conditions and stoichiometric amounts of catalyst were required,



affording a mixture of products in some case.¹⁰ Thus, the development of catalytic methods that selectively produce optically active 4-hydroxyl-tetrahydropyrans would be particularly valuable.

The design of practically simple and efficient organic transformations is one of the main challenges of current organic synthesis. The formation of multiple bonds through sequential reactions constitutes one approach to achieving this goal.¹² Considering the fact that homoallylic alcohols achieved by ene reaction are pivotal substrates for the Prins cyclization, we envisioned that a stepwise catalytic asymmetric ene reaction, followed by an intermolecular Prins cyclization would produce optically active substituted tetrahydropyrans (Scheme 2). Herein, we report our investigations on stereoselective synthesis of 4-hydroxyl tetrahydropyrans by sequential ene/Prins cyclization reactions. Chiral Ni(II)–N,N'-dioxide complex^{13,14} and FeCl₃ were used for the two processes, respectively. None of 2-oxonia-Cope

Scheme 2. Lewis acid catalyzed ene-Prins cyclizations

Scheme 1. OH-Selective FeCl₃-catalyzed Prins cyclization





rearrangement was observed in the reaction. This new approach permitted an easy and straight route to a range of optically active 4-hydroxyl-tetrahydropyrans with excellent outcomes (up to 92% yield, >99:1 dr, >99:1 er) under mild conditions. We also detailed mechanistic studies such as control experiments, NOE effects, and Oxygen-18 labeling studies, as well as computational calculation.

RESULTS AND DISCUSSION

Reaction Optimization.

 Table 1. Examination of Lewis acid in the Prins cyclization^a



entry	Lewis acid	catalyst loading	t (h)	yield of 5n/7n (%) ^b	er of 5n
1	TFA	300 mol %	24	36/42	98:2
2	In(OTf) ₃	20 mol %	24	52/32	99:1
3	Sc(OTf) ₃	20 mol %	24	46/35	99:1
4	AlCl ₃	20 mol %	48	-	-
5	$SnCl_4$	20 mol %	48	-	-
6	InCl ₃	20 mol %	48	-	-
7	InBr ₃	20 mol %	48	-	-
8	FeCl ₃	20 mol %	24	72/12	99:1
9	FeBr ₃	20 mol %	24	63/22	98.5:1.5
10	anhydrous HCl	-	6	-	-

^{*a*} Unless otherwise noted, the crude product **4a** (0.2 mmol) obtained from asymmetric catalytic carbonyl-ene reaction was added to a test tube with 2-naphthaldehyde **3n** (0.24 mmol), acid catalyst in CH₂Cl₂ (1.0 mL) at 10 °C. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC.

 Table 2. Examination of additives in the Prins cyclization^a



entry	additive	x (mol %)	t (h)	yield of 5n/7n (%) ^b	er of 5n ^c
1	TMSCl	20	6	<5/68	-
2	TESCI	20	6	18/62	99:1
3	TBSCl	20	12	92/<5	99:1
4	Ph ₃ SiCl	20	24	84/10	99:1
5	TBSOTf	20	0.5	12/65	-
6	TMSOTf	20	0.5	<5/72	-
7	TBSCl	10	12	90/<5	99:1
8	TBSC1	50	12	92/<5	99:1
9	TBSCl	120	12	89/<5	99:1
10	NEt ₃	20	48	-	-
11	H_2O	120	32	89/<5	99:1
12	H_2O	500	64	82/<5	99:1
13 ^d	TBSCl	20	48	-	-

^{*a*} Unless otherwise noted, the crude product **4a** (0.2 mmol) of carbonyl-ene reaction was added to a test tube with 2-naphthaldehyde **3n** (0.24 mmol), FeCl₃ (20 mol %) and additive (x mol %) in CH₂Cl₂ (1.0 mL) at 10 °C. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC. ^{*d*} The reaction was performed without FeCl₃. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

Initially, the chiral homoallylic alcohol 4a (99:1 er), generated from chiral N,N'-dioxide L-Ni(II) complex catalyzed ene reaction, was used for the Prins reaction with 2naphthaldehyde **3n**. Various acidic catalysts, generally used in Prins cyclization,⁹⁻¹⁰ were examined. To our surprise, 4hydroxy tetrahydropyran 5n was exclusively obtained no matter what kind of Lewis acid was used. As shown in Table 1, with 3.0 equivalences of TFA, the Prins cyclization proceeded at 10 °C to afford 4-hydroxyl-tetrahydropyran 5n in 36% yield with 98:2 er, and a 42% yield of dihydro-2H-pyran derivatives $7n^{15}$ (Table 1, entry 1). In the presence of 20 mol % catalyst of Sc(OTf)₃ or In(OTf)₃ (the Lewis acid with a non-nucleophilic anion), the reactivity was slightly improved, and the product 5n was obtained in 52% yield and 46% yield, respectively (Table 1, entries 2-3). Interestingly, when halogenated Lewis acids, which generally afforded 4-halosubstituted products in previously related work, were tested in the reaction, 4-hydroxy tetrahydropyran **5n** rather than 4-halo tetrahydropyran 6n was generated.⁹ In the presence of 20 mol % of FeCl₃, the unexpected hydroxyl-added product 5n was generated in 72% yield and 99:1 er within 24 hours (Table 1, entry 8). Moreover, no competitive 2-oxonia Cope rearrangement and side-chain exchange occurred. Contrastingly, other

Table 3. Optimization of other reaction conditions^a

3

4

5

6



entry	Conc. ^b	x (mol %)	t (h)	yield of 5n/7n (%) ^c	er of 5n
1	0.05 M	20	32	89/<5	99:1
2	0.1 M	20	24	90/<5	99:1
3	0.2 M	20	12	92/<5	99:1
4	0.5 M	20	10	90/<5	99:1
5	0.2 M	10	24	89/<5	99:1
6	0.2 M	50	4	<5/73	-
7	0.2 M	100	1	<5/80	-
8 ^e	0.2 M	20	48	87/<5	99:1
9^{f}	0.2 M	20	24	92/<5	99:1
10 ^g	0.2 M	20	4	<5/75	-

^{*a*} Unless otherwise noted, the crude product **4a** (0.2 mmol) of carbonyl-ene reaction was added to a test tube with 2-naphthaldehyde **3n** (0.24 mmol), FeCl₃ (x mol %) and additive (20 mol %) in CH₂Cl₂ at 10 °C. ^{*b*} With respect to **4a**. ^{*c*} Isolated yield. ^{*d*} Determined by chiral HPLC. ^{*e*} The reaction was performed at -20 °C. ^{*f*} The reaction was performed at 0 °C. ^{*g*} The reaction was performed at 35 °C.

Lewis acids such as AlCl₃, SnCl₄, InCl₃, and InBr₃ afforded no products, reflecting the importance and particular characteristic of metal iron (Table 1, entries 4–7 vs 8). Changing the counterion of the iron(III) salt provided no improvement in the reaction efficiency (Table 1, entry 9). The anhydrous HCl was also used in the reaction, but no desired product **5n** was obtained, and the reaction only gave some impurity with the same R_f value, which were difficult to separate via flash chromatography (Table 1, entry 10).

These results promoted us to carry out an exhaustive study to find the optimal conditions for the formation of optically active 4-hydroxy tetrahydropyran derivative **5n**. Silicon Lewis acids is an useful mediator in carbon-carbon bond forming reactions.¹⁶ Inspired by previous works,⁹ some acidic compounds such as the TMSCl, TESCl, TMSOTf as additives were examined to further improved the selectivity and activity of reaction.¹⁷ As shown in Table 2, it was found that the additives had a significant effect on the outcome of the ratio between **5n** and elimination product **7n**. Excitingly, TBSC1 was found as the most effective additive, affording the product 5n/7n in 92% and <5% yield, respectively (Table 2, entries 1-6). The enantiomeric excess of the product **5n** was maintained. However, when TMSCl or TESCl was used, the amount of byproduct 7n exceeded that of 5n (Table 2, entries 1–2). TBSOTf and TMSOTf shorten the reaction time, but

accelerated the generation of the byproduct **7n** (Table 2, entries 5–6). Moreover, varying the amount of TBSCl (0.1–1.2 equiv) had no obvious effect upon the outcomes (Table 2, entries 7–9). The use of base additive NEt₃ inhibited the occurrence of Prins cyclization (Table 2, entry 10). The reaction time prolonged with an increase of the amount of H₂O, but the elimination product somewhat decreased (Table 2, entries 11–12 vs Table 1, entry 8).¹⁸ Additionally, in the absence of FeCl₃, no reaction was observed using TBSCl alone (Table 2, entry 13).

With FeCl₃ and TBSCl identified as the optimized catalyst system for the Prins cyclization, effects related to reaction concentration, temperature and catalyst loading were next examined. As shown in Table 3, a slight enhancement in reactivity was observed when the concentration was increased (Table 3, entries 1–4). It is worth pointing out that decreasing the catalyst loading to 10 mol % resulted in a slightly reduced yield of **5n** (Table 3, entry 5). While, when large quantities of FeCl₃ were present, the elimination product **7n** was obtained as the major product (Table 3, entries 6–7). Additionally, decreasing the reaction temperature to 0 °C or -20 °C led to no improvements (Table 3, entries 8–9). High temperature was favorable for the formation of the product **7n**, and only trace of product **5n** was obtained at 35 °C (Table 3, entry 10).

Substrate Scope. With the optimal reaction conditions established, the substrate scope was extended. As summarized in Table 4, the reaction displayed a broad scope for aldehydes, and excellent levels of chemo- and stereoselectivity were achieved. Aromatic aldehydes with either electron donating or withdrawing substituents at the ortho-, meta-, or para- positions all performed well, furnishing the corresponding products with 68-90% yields, 80:20->95:5 dr, and 98:2->99:1 er (Table 4, entries 2–12). In general, the reaction rate of the Prins cyclization was higher with electron-rich aldehydes. For example, methylbenzaldehydes and methoxylbenzaldehydes underwent the reaction within 4-6 hours (Table 4, entries 2-7), whereas chloro-, fluoro-, and trifluoromethyl-substituted benzaldehydes required 12-36 hours (Table 4, entries 8-12). It was noteworthy that the naphthaldehydes 3m, 3n, and the heteroaromatic aldehydes 30, 3p also well tolerated, giving the corresponding products in high yields with excellent stereoselectivities (Table 4, entries 13-16). Some representative aliphatic aldehydes were also evaluated. Excitingly, linear aldehydes, such as n-propanal, n-butanal, n-hexanal, 3phenylpropanal, cinnamaldehyde, and (E)-but-2-enal gave the corresponding products with high yields within 3-8 hours (Table 4, entries 17–18, 21, and 24–26). Comparatively, steric bulkier aldehydes gave moderate yields with somewhat longer reaction time (Table 4, entries 19-20 and 22-23). It suggested that for the cyclization of aliphatic aldehydes, smaller steric hindrance significantly benefited the reactivity.

Additionally, a series of alkenes were proven suitable for this reaction as highlighted in Table 5. For the first step, the asymmetric ene reaction of various alkenes (2b–2i)

Table 4. Substrate scope of aldehydes in the synthesis of 4-hydroxyl tetrahydropyrans^a

0 H ^{⊥⊥} CO ₂ 1a	Et + Ph	EtO ₂ C R OH Fec Ph CH; 4a	³ CHO 3 Cl ₃ /TBSCI mol %) 2 ^c l ₂ , 10 °C	Ph_OH R ³ CO ₂ Et 5a-5z	$ \begin{array}{c} $, , , , , , , , , , , , , , , , , , ,
entry	3 , R ³	x (mol %)	t (h) ^b	yield (%) ^c	dr ^d	er ^{e,g}
1	3a , C ₆ H ₅	20	12	5 a, 74	90:10	99:1
2	3b , 2-CH ₃ C ₆ H ₄	10	6	5b , 85	85:15	99:1
3	3c , 3-CH ₃ C ₆ H ₄	10	6	5c , 83	90:10	98.5:1.5
4	3d , 4-CH ₃ C ₆ H ₄	10	6	5d , 88	80:20	99:1
5	3e , 2-CH ₃ OC ₆ H ₄	10	4	5 e, 72	90:10	99:1
6	3f , 3-CH ₃ OC ₆ H ₄	10	4	5f , 82	85:15	99:1
7	3g , 4-CH ₃ OC ₆ H ₄	10	4	5g , 90	80:20	98:2
8	3h , 4-FC ₆ H ₄	20	24	5h , 82	80:20	99:1
9	3i , 4-ClC ₆ H ₄	20	24	5i , 81	80:20	99:1
10	3j , 3-BrC ₆ H ₄	20	24	5 j, 70	>95:5	99.5:0.5
11 ^f	3k , 4-BrC ₆ H ₄	20	12	5k , 90	>95:5	99.5:0.5
12	31 , 4-CF ₃ C ₆ H ₄	20	36	51 , 68	>95:5	99:1
13	3m , 1-naphthyl	20	16	5m , 87	85:15	97.5:2.5
14	3n , 2-naphthyl	20	12	5n , 92	>95:5	99:1
15	30 , 2-furyl	20	12	50 , 58	80:20	99:1
16	3p , 2-thienyl	20	12	5p , 80	90:10	99:1
17	3q , Et	10	6	5q , 88	99:1	99:1
18	3r , <i>n</i> -Pr	20	8	5r , 85	99:1	99.5:0.5
19	3s , <i>i</i> -Pr	20	12	5s , 84	99:1	98:2
20	3t , <i>t</i> -Bu	20	24	5t , 75	>99:1	97.5:2.5
21	3u, <i>n</i> -pentyl	20	8	5u , 88	>99:1	99:1
22	3v , <i>c</i> -hexyl	20	24	5v , 73	99:1	99.5:0.5
23	3w, 3w,	20	24	5w , 68	99:1	98.5:1.5
24	3x, Ph	20	6	5x , 80	>95:5	99:1
25	3y, Ph	10	3	5y , 92	90:10	99:1
26	3z, /~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	20	8	5z , 76	99:1	98.5:1.5

^{*a*} Unless otherwise noted, the reaction was carried out with ethyl glyoxylate **1a** (0.2 mmol), 2-phenylpropene **2a** (2.0 equiv) and 10 mol % of Ni(II)–L in CH₂Cl₂ (1.0 mL) at 35 °C for 48 hours. After flash column chromatography, the crude product **4a** was added to a test tube with aldehyde **3** (0.24 mmol), FeCl₃ and TBSCl in CH₂Cl₂ (1.0 mL) at 10 °C. ^{*b*} The reaction time of the Prins cyclization. ^c Isolated yield on the basis of **1a**. ^{*d*} Determined by ¹H NMR spectroscopy of the crude product and chiral HPLC analysis. ^e Determined by chiral HPLC analysis. ^f The absolute configuration of the product **5k** was determined to be (2*S*, 4*S*, 6*R*) by X-ray diffraction analysis. ^{19 g} For most products the stereochemistry of the minor diastereomer were the same to the major diastereomer.²⁰

Table 5. Substrate scope of alkenes in the synthesis of 4-hydroxyl tetrahydropyrans^a



	2	3	Proc	Product 4		Product 5		
entry	2		yield (%) ^b	er ^d	yield (%) ^b	dr (%) ^c	er ^{d,e}	
1	2b , $R^2 = 2 - CH_3C_6H_4$	$R^3 = 4 - BrC_6H_4$	77	99.5:0.5	5aa , 50	99:1	98.5:1.5	
2	2c , $R^2 = 4$ -CH ₃ C ₆ H ₄	$R^3 = 4 - BrC_6H_4$	95	99:1	5ab , 58	99:1	99:1	
3	2d , $R^2 = 4 - FC_6H_4$	$R^3 = 4 - BrC_6H_4$	94	98.5:0.5	5ac , 58	90:10	98:2	
4	2e , $R^2 = 4 - ClC_6H_4$	$R^3 = 4 - BrC_6H_4$	82	99:1	5ad , 62	80:20	99:1	
5	2f , $R^2 = 4$ -BrC ₆ H ₄	$R^3 = 4 - BrC_6H_4$	90	99:1	5ae , 52	99:1	99:1	
6	$2c, R^2 = 4-CH_3C_6H_4$	$R^3 = Et$	95	99:1	5af , 63	99:1	99:1	
7	2d , $R^2 = 4 - FC_6H_4$	$R^3 = Et$	94	98.5:0.5	5ag , 76	99:1	98.5:1.5	
8	$2e, R^2 = 4-ClC_6H_4$	$R^3 = Et$	82	99:1	5ah , 72	99:1	99:1	
9	2f , $R^2 = 4 - BrC_6H_4$	$R^3 = Et$	90	98.5:0.5	5 ai, 75	99:1	98.5:1.5	
10	$2g, R^2 = 4-CH_3OC_6H_4$	$R^3 = Et$	95	99:1	-	-	-	
11	2h,	$R^3 = Et$	96	99.5:0.5	-	-	-	
12	21.	$R^3 = Et$	92	99.5:0.5	-	-	-	

^{*a*} The procedure was similar to that in Table 4. ^{*b*} Isolated yield on the basis of **1a**. ^{*c*} Determined by ¹H NMR spectroscopy of the crude product and chiral HPLC analysis. ^{*d*} Determined by chiral HPLC analysis. ^{*e*} The stereochemistry of the minor diastereomer is unknown.

Table 6. Substrate scope of glyoxal derivatives in the synthesis of 4-hydroxyl tetrahydropyrans^a



	D l	D ³	Prod	Product 4		Product 5		
entry	R ¹	R	yield (%) ^b	er ^d	yield (%) ^b	dr (%) ^c	er ^{d,e}	
1	Ph	4-BrC ₆ H ₄	98	>99.5:0.5	5 aj, 65	99:1	>99.5:0.5	
2	$4-CH_3C_6H_4$	$4-BrC_6H_4$	97	>99.5:0.5	5ak , 42	99:1	>99.5:0.5	
3	$4-ClC_6H_4$	$4-BrC_6H_4$	88	>99.5:0.5	5al , 48	99:1	99.5:0.5	
4	Ph	2-naphthyl	98	>99.5:0.5	5am , 56	99:1	98.5:1.5	
5	Ph	Et	98	>99.5:0.5	5an , 76	99:1	98.5:1.5	
6	$4-CH_3C_6H_4$	Et	97	>99.5:0.5	5ao , 52	99:1	>99.5:0.5	
7	4-CH ₃ OC ₆ H ₄	Et	99	99.5:0.5	5 ap, 50	99:1	98.5:1.5	
8	$4-FC_6H_4$	Et	92	>99.5:0.5	5aq , 58	>95:5	98.5:1.5	
9	$4-ClC_6H_4$	Et	88	>99.5:0.5	5ar , 56	99:1	99:1	
10	$4-BrC_6H_4$	Et	95	99.5:0.5	5as, 62	>95:5	98.5:1.5	
11	2-naphthyl	Et	93	99.5:0.5	5at , 58	99:1	97.5:2.5	

^{*a*} The procedure was similar to that in Table 4. ^{*b*} Isolated yield on the basis of 1. ^{*c*} Determined by ¹H NMR spectroscopy of the crude product and chiral HPLC analysis. ^{*d*} Determined by chiral HPLC analysis. ^{*e*} The stereochemistry of the minor diastereomer is unknown.

with ethyl glyoxylate could afford the corresponding homoallylic alcohols **4** in high yields with excellent enantioselectivities (in the range of 98.5:0.5–99.5:0.5 er). As expected, for the following Prins cyclization, both aromatic

aldehyde and aliphatic aldehyde reacted well with the intermediate 4, affording the corresponding 4-hydroxyl tetrahydropyrans with moderate to high yields, and excellent stereoselectivities (50-76% vields, 80:20-99:1 dr, 98:2-99:1 er; Table 5, entries 1-9). The electronic nature of the aromatic alkenes had little effect on the yields and stereoselectivities except 4-MeO-substituted one (Table 5, entry 10). Both the electron-donating substituted alkenes and the electronwithdrawing substituted alkenes gave the desired products with moderate yields and excellent stereoselectivities (Table 5, entries 1-5). n-Propanal gave slightly higher yield compared with the aromatic aldehyde (Table 5, entries 6-9 vs entries 1-5). It is worth pointing out that although the ene reaction could give the intermediates 4 with excellent outcomes, no cyclization products were detected if the alkene 2g with a methoxy group on the aromatic ring or benzocyclic alkenes 2h and 2i was used as the starting materials (Table 5, entries 10-12).

 Following the studies of asymmetric ene/Prins cyclization with various alkenes, we next examined the scope of the glyoxal derivatives. Unfortunately, the reaction proceeded sluggishly with aromatic aldehydes, and the desired 4hydroxyl tetrahydropyrans **5aj–5am** were obtained in moderate yields (Table 6, entries 1–4). We considered that the steric hindrance effect between the aryl group of glyoxal derivative **1** and the aryl group of the aldehyde **3** increased in the Prins cyclization

Scheme 3. Substrate scope of ene/Prins cyclization in the synthesis of multi-substituted tetrahydropyrans



conditions: FeCl_3/TBSCI (1:1, 20 mol %), CH_2Cl_2, 10 $^{\rm o}{\rm C}$

process, and thus lowered the yield. Accordingly, *n*-propanal was used to minimize this adverse effect. To our delight, the corresponding product **5an** was performed with 76% yield and excellent enantiomeric excess (99:1 dr, 98.5:1.5 er; Table 6, entry 5). Next, the substrate scope of glyoxal derivatives was briefly examined. As shown in Table 6, the electronic nature

of the glyoxal derivatives had little effect on the reaction activity and stereoselectivity (Table 6, entries 6–10). The condensed-ring glyoxal also performed well, giving the corresponding product in moderate yield with excellent er ratio (Table 6, entry 11).

To further investigate potential utility of the reaction, we chose different homoallylic alcohols as the substrates under the standard Prins reaction conditions. The cyclization of alkyl-substituted olefin was investigated. After optimizing the conditions, the cinnamaldehyde **3y** was used to react with alkyl-substituted olefin **4u** and **4v**, and the corresponding products with aliphatic group at the C4 of the THP were obtained with 35-38% yields within 48 hours (Scheme 3, eq. 1–2). Besides, the elimination products accompanied in the reaction.²¹ In addition, when the multisubstituted olefin **8–10** were treated with 2-naphthaldehyde **3n** or *n*-propanal **3q** under the standard reaction conditions, the corresponding tetrahydropyrans **11–13** with methyl substitutents at 3- or 5-positions were obtained in 63-72% yields (Scheme 3, eq. 3–5).

Scheme 4. Asymmetric ene/Prins cyclization on a gram scale



For the purpose of examining the potential utility of this methodology, a model reaction was carried out on a gram scale. As shown in Scheme 4, the reaction took place smoothly in the presence of 10 mol % of Ni(II)–L and 10 mol % of FeCl₃/TBSCl, affording a slightly better yield of the product **5q** (90%) without any loss of the enantiomeric excess.

Stereochemical Assignment. It is worth pointing out that in most cases high diastereoselective products were obtained, even single diastereomer for most substrates. The stereochemistry of substituted tetrahydropyrans **5q**, **5m**, **5r** and **5u** was confirmed by NOE studies,²⁰ which clearly revealed that three bulky substituents at C-2, C-4 and C-6 on the tetrahydropyranyl ring occupied equatorial positions. In each case, an excellent degree of selectivity was observed for the newly formed stereogenic centers at the 4-, and 6-positions of the tetrahydropyran ring. These results were consistent with Alder's computational calculation and the previous works.^{8,22} Furthermore, the absolute configuration of the product **5k** was determined as (*2S*, *4S*, *6R*) by X-ray



Figure 1. The X-ray crystallographic structure of the product **5k**. The thermal ellipsoids' level is 30% for the above crystal structure.



Figure 2. The selected CD (circular dichroism) spectra of a part of the products.

crystallographic analysis (Figure 1).¹⁹ The CD (circular dichroism) spectra of products were measured in ethanol. These of 4-hydroxyl tetrahydropyrans exhibited a similar (+) Cotton effect in their CD spectra (as shown in Figure 2).

Mechanism Study. The unique chemoselectivity (completely OH-selective) in the FeCl₃-catalyzed Prins cyclization of aldehydes encouraged us to investigate the reaction mechanism. Firstly, in order to verify whether the elimination products 7 arose solely through eliminating water from compounds 5 or they formed via eliminating hydrogen ion directly from the carbocation intermediate. A careful monitoring of the reaction under the standard conditions was investigated. The reaction profile in Figure 3 clearly showed the formation of the product 7q during the reaction course. The amount of elimination products 7q increased sharply after six hours along with the diminution of the product 5q. It indicated that the product 7 formed more likely through eliminating water from the precursor 5. In order to find out the linchpin subject of the elimination process, the catalyst components of Prins reaction were introduced to the isolated product 5q (Scheme 5). In the presence of 1.2 equivalences of TBSCl at 35 °C, 5q could not transform into 7q after 24 hours (Scheme 5, eq. 1). However, the addition of 1.2 equivalences of FeCl₃ led to a full conversion of 5q into 7q within 1 hour (Scheme 5,



Figure 3. Reaction profile of $FeCl_3$ -catalyzed Prins cyclization, picturing the formation and elimination of the product 5q.

Scheme 5. Elimination reactions from the product 5q



eq. 2). The elimination reaction were effectively suppressed (65% yield of 7q in 1 h) when 20 mol % of TBSCl was added in the reaction (eq. 3 vs. eq. 2). Expectedly, 5q was slowly transformed into 7q under the standard reaction conditions (eq. 4). These results indicated that FeCl₃ mediated both the formation and elimination of the product 5q, and the formation of the product 5q was prior to the elimination.²³

We next tried to rationalize the phenomenon of excellent stereoselectivity of the highly substituted tetrahydropyran products.⁸ Relative rates of Prins cyclization versus competing oxonia-Cope rearrangement had a dramatic effect upon the stereoselectivity. Stabilizing the tetrahydropyranyl cation intermediate raised the transition state energy for ring-opening and effectively eliminates oxonia-Cope rearrangement.^{8d} Alder's model had shown that



Figure 4. Stabilization of tetrahydropyranyl cation.

Scheme 6. Control Experiments



oxocarbenium ion 14 is 13.4 kJ/mol stable than tetrahydropyranyl cation 15. The activation barrier for the ring opening of cation 15 to oxocarbenium ion 14 is only 1.9 kJ/mol.²² Thus, the oxonia-Cope rearrangements were rapid for monosubstituted olefins.

To provide insight into the tetrahydropyranyl cation stability in this case, DFT (B3LYP/6-31G*) calculations were performed (Figure 4). In contrast, tetrahydropyran cation **21** was stabilized due to the delocalization of the phenyl group at 4-position, which is 85.0 kJ/mol lower in energy than oxocarbenium ion **19**. In addition, the oxocarbenium ion resulting from the hypothetical rearrangement was also destablized. The results were similar to Rychnovsky's report, in which the tetrahydropyranyl cation with a methyl group at 4-position **18** is 40.9 kJ/mol lower in energy than oxocarbenium ion **17**.^{8d} Therefore, cyclization was irreversible, and the 2-oxonia Cope rearrangement was disfavored than the nucleophilic capture. As a result, oxonia Cope rearrangement mediated racemization was ruled out.

With an initial survey of reaction stereoselectivity, our attention turned to the chemoselectivity of the reaction that 4-hydroxyl-tetrahydropyran 5 rather than 4-chloro-substituted one was observed in the FeCl₃-catalyzed Prins cyclization. The monosubstituted olefin 22 was used as the substrate to react with 2-naphthaldehyde 3n under the FeCl₃/TBSCl conditions, but no cyclization

Scheme 7. Oxygen-18 labeling studies of the FeCl₃mediated Prins cyclizations and ¹³C NMR spectra of the corresponding product

a) The Prins cyclization with ¹⁸O-labeled aldehyde



c) The Prins cyclization with ¹⁸O-labeled 3a and naphthaldehyde 3n







58

59 60 product was observed with the starting materials being recovered quantitatively after 48 hours (Scheme 6, eq. 1). The results indicated that the substituent at the C4 position played an important role for the formation of the 4-hydroxyl tetrahydropyran. Whereas, for the initial substrate 4a, no trace of chloro-added product was detected even the amount of TBSCl was increased to five equivalences. Interestingly, the 4hydroxyl-tetrahydropyran 5n was obtained in 82% yield within 1 hour (Scheme 6, eq. 2). These results indicated that the nucleophile concentration (Cl⁻ or OH⁻) did not affect the selectivity of the reaction. TBSCl might assist the FeCl₃mediated Prins reaction.

To further verify the generation of the reactive hydroxyl nucleophile, as well as the OH-trapped product **5** via solely a direct intramolecular or an intermolecular process, the isotopic labeling experiments were performed. As shown in Scheme 7, the ¹⁸O-labeled aldehyde **3a** was used under the standard cyclization conditions, and the product was analyzed by ¹³C NMR spectroscopy and ESI-MS. It was found that ¹⁸O-labeled product **5a** was formed with ca. 72% ¹⁸O-labeled solely at 4-position. The corresponding ¹³C NMR spectrum illustrated

apparently a small upfield shift (ca. δ 0.02 ppm) of the signal, assigning to C-4 in each case as a result of the α -isotope effect (Scheme 7, a). The result indicated that the oxygen atom of the hydroxy at C4 position of products was transformed from the aldehyde **3a**. In contrast, when the 1.2 equivalences of $H_2^{18}O$ were added under the standard conditions, the 4-hydroxyltetrahydropyran 5a was formed with ca. 29% ¹⁸O-labeled (Scheme 7, b). We also found that the ¹⁸O-labeled product **5n** was observed excepted for the ¹⁸O-labeled product 5a, when olefin 4a was added to the mixture of the ¹⁸O-labeled benzaldehyde **3a** and ¹⁶O-labeled naphthaldehyde **3n** with the catalyst FeCl₃/TBSCl (Scheme 7, c).²⁴ Moreover, the ¹⁸Olabeled product 5a (50% ¹⁸O-labeled) was also observed when the product 5a was treated with the 1.2 equivalences of $H_2^{18}O$ under the standard reaction conditions (Scheme 7, d). These results suggested that the products 5 were more likely to be formed through an intramolecular way. The hydroxyl group at C4 position might exchange with the OH⁻ from the reaction system under the standard reaction conditions via carbonium ion intermediate.



Figure 5. Gibbs free energy diagram and the proposed entire reaction mechanism of the FeCl₃-catalyzed Prins cyclization

To provide further insight into the observed OH-selective process of 4-phenyl tetrahydropyran catalyzed by FeCl₃, DFT (B3LYP(PCM,CH2Cl2)//B3LYP/6-31G**) calculations were performed.²⁰ A different Prins cyclization mechanism was suggested. The results of calculations related to the entire reaction mechanism were illustrated in Figure 5. It shown that the entire catalytic cycle contains three successive stages: (1) stepwise [2+2] cycloaddition reaction via **TS1** and **TS2**; (2) migration of O atom of acetaldehyde to **4a** with the cleavage of C–O bond of the carbonyl group via **TS3**; (3) migration of H of -OH in **4a** via **TS4**, leading to the formation of **5q**. PCM calculation placed the largest barrier in Gibbs free energy to be 112.0 kJ/mol, which corresponds to the step from **IM2** to **TS3** in stage 2. This step is rate-determining in the entire reaction process. Moreover, the calculation predicted that the O atom

of -OH in **5q** comes from acetaldehyde and H from **4a**, respectively. It also showed that the release of FeCl₃, corresponding to **IM4** to FeCl₃+**5q**, must over a significant large energy barrier of ca. 140 kJ/mol, which is comparable to the barrier of RDS. This means that the catalytic cycle would be hindered in the step of recovery of FeCl₃ if no other auxiliary reagent is involved.

However, when TBSCl is considered, DFT calculation predicted that TBSCl might coordinate to the FeCl₃ with the formation of TBSCl-FeCl₃ species form **IM4**, resulting the yield of **5q** with a smaller energy barrier of 70.0 kJ/mol. Therefore, the existence of TBSCl might facilitate the formation of **5q** and exert positive effect on the present FeCl₃ catalytic systems.²³ This theoretical prediction is in agreement with the present experimental observation. In previous works, the general mechanism of Lewis acid catalyzed Prins

cyclization is that the key intermediate is an oxocarbenium ion, which generated from a hemiacetal. Then the oxo-carbenium ion could be captured with a large array of nucleophiles to afford substituted tetrahydropyrans. The nature of such a difference between the two mechanisms is not yet clear at present. It might be due to the variation of catalysts as well as the homoallylic alcohols used in the reactions.

CONCLUSION

In conclusion, we have established a general method for the completely OH-selective sequential ene/Prins cyclization by using Ni(II)–N,N'-dioxide complex and FeCl₃ as the catalysts, respectively. The method enabled an efficient access to optically pure 4-hydroxyl-tetrahydropyran derivatives. The extremely high enantiomeric excess, broad substrate scope, facile procedure, and mild reaction conditions showed the potential of the catalytic system for practical synthesis. This method will be a valuable complement to the existing arsenal of the enantioselective synthesis of 4-hvdroxvl tetrahydropyrans via Prins cyclization. Moreover, mechanistic investigations including control experiments, NOE effects, Oxygen-18 labeling studies, DFT calculations were also investigated to gain insights into the mechanism of the reaction. Additional investigations aimed at expanding the scope of the application are underway.

EXPERIMENTAL SECTION

Typical experimental procedure for the sequential ene/Prins reaction: The mixture of N.N'-dioxide L (12.8 mg, 0.02 mmol) and Ni(BF₄)₂·6H₂O (6.8 mg, 0.02 mmol) in CH₂Cl₂ (1.0 mL) were stirred at 30 °C for 30 min. Then, the ethyl glyoxylate 1a (0.2 mmol) and 2.0 equiv of 2phenylpropene 2a was added at 35 °C and being stirred for 48 hours. After flash column chromatography, the crude product of the carbonyl-ene reaction was added into the test tube with 1.2 equiv of 2-naphthaldehyde **3n** (0.24 mmol), 20 mol % of FeCl₃ and 20 mol % of TBSCl in CH₂Cl₂ (1.0 mL) at 10 °C. After being stirred at 10 °C for 12 hours, the reaction mixture was directly purified by column chromatography on silica gel (ethyl acetate : petroleum ether = 1 : 8) to afford the corresponding product 5n in 92% yield as a colourless liquid. The enantiomeric excess of **5n** was determined by using chiral HPLC analysis.

ASSOCIATED CONTENT

Supporting Information. Experimental details and analytic data (NMR, HPLC and ESI-HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

xmfeng@scu.edu.cn

ACKNOWLEDGMENT

We appreciate the National Natural Science Foundation of China (Nos. 21021001 and 21172151) and National Basic Research Program of China (973 Program: No. 2010CB833300) for financial support and Sichuan University Analytical & Testing Centre for NMR and X-ray diffraction analysis. The paper is dedicated to Professor Michael P. Doyle on the occasion of his 70^{th} birthday.

REFERENCES

- For a general review on the synthesis of tetrahydropyrans, see: (a) Muzart, J. J. Mol. Catal. A: Chem. 2010, 319, 1. (b) Boivin, T. L. B. Tetrahedron 1987, 43, 3309. (c) Clarke, P. A.; Santos, S. Eur. J. Org. Chem. 2006, 2045. (d) Larrosa, I.; Romea, P.; Urpí, F. Tetrahedron 2008, 64, 2683.
- (2) (a) Lin, Y. -Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. J. Am. Chem. Soc. 1981, 103, 6773. (b) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. J. Antibiot. 1998, 51, 1075. (c) Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. J. Nat. Prod. 2001, 64, 491. (d) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. J. Am. Chem. Soc. 2003, 125, 6650. (e) Cossey, K. N.; Funk, R. L. J. Am. Chem. Soc. 2004, 126, 12216. (f) Bahnck, K. B.; Rychnovsky, S. D. Chem. Commun. 2006, 2388. (g) Bahnck, K. B.; Rychnovsky, S. D. J. Am. Chem. Soc. 2008, 130, 13177. (h) Wang, X.; Zheng, J.; Chen, Q.; Zheng, H.; He, Y.; Yang, J.; She, X. J. Org. Chem. 2010, 75, 5392.
- (3) (a) Paterson, I.; Anderson, E. A. Science 2005, 310, 451. (b) Wender, P. A.; Schrier, A. J. J. Am. Chem. Soc. 2011, 133, 9228. For reviews, see: (c) Benson, S.; Collin, M. P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. Angew. Chem., Int. Ed. 2011, 50, 8739. (d) Hale, K. J.; Manaviazar, S. Chem. Asian J. 2010, 5, 704. and references therein.
- (4) (a) Singh, P.; Bhardwaj, A. J. Med. Chem. 2010, 53, 3707. (b) Rao, P. N. P.; Uddin, M. J.; Knaus, E. E. J. Med. Chem. 2004, 47, 3972. (c) Delorme, D.; Ducharme, Y.; Brideau, C.; Chan, C.; Chauret, N.; Desmarais, S.; Dubé, D.; Falgueyret, J.; Fortin, R.; Guay, J.; Hamel, P.; Jones, T.; Lépine, C.; Li, C.; McAuliffe, M.; McFarlane, C. S.; Nicoll-Griffith, D. A.; Riendeau, D.; Yergey, J. A.; Girard, Y. J. Med. Chem. 1996, 39, 3951. and references therein.
- (5) For selected examples, see: (a) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. J. Org. Chem. 2000, 65, 8730. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. J. Am. Chem. Soc. 2001, 123, 10942. (c) Paterson, I.; Chen, D. Y. -K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. Angew. Chem., Int. Ed. 2001, 40, 4055. (d) Hilli, F.; White, J. M.; Rizzacasa, M. A. Org. Lett. 2004, 6, 1289. (e) Smith, A. B., III; Fox, R. J. Org. Lett. 2004, 6, 1477. (f) Ding, F.; Jennings, M. P. Org. Lett. 2005, 7, 2321. (g) Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadère, B. Tetrahedron Lett. 2004, 45, 6603. (h) Pellissier, H. Tetrahedron 2009, 65, 2839. (i) Sabitha, G.; Rao, A. S.; Yadav, J. S. Synthesis 2010, 505. (j) Yadav, J. S.; Ather, H.; Rao, N. V.; Reddy, M. S.; Prasad, A. R. Synlett 2010, 1205. and references therein.
- (6) For a general review of the Prins cyclization reactions, see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505. (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925. (c) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413. (d) Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316. (e) Overman, L. E.; Pennington, L. D. J. Org. Chem. **2003**, *68*, 7143.
- (7) For recently examples of Prins cyclizations (a) Crane, E. A.; Zabawa, T. P.; Farmer, R. L.; Scheidt, K. A. Angew. Chem., Int. Ed. 2011, 50, 9112. (b) Ramachandran, P. V.; Gagare, P. D. Tetrahedron Lett. 2011, 52, 4378. (c) Ghosh, A. K.; Nicponski, D. R. Org. Lett. 2011, 13, 4328. (d) Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Sridhar, B.; Grée, R. J. Org. Chem. 2011, 76, 7677. (e) Reddy, B. V. S.; Ganesh, A. V.; Krishna, A. S.; Kumar, G. G. K. S. N.; Yadav, J. S. Tetrahedron Lett. 2011, 52, 3342. (f) Chio,

F. K.; Warne, J.; Gough, D.; Penny, M.; Green, S.; Coles, S. J.; Hursthouse, M. B.; Jones, P.; Hassall, L.; McGuire, T. M.; Dobbs, A. P. Tetrahedron 2011, 67, 5107. (g) Chen, Z. H.; Tu, Y. Q.; Zhang, S. Y.; Zhang, F. M. Org. Lett. 2011, 13, 724 (h) Karmakar, R.; Mal, D. Tetrahedron Lett. 2011, 52, 6098. (i) Jacolot, M.; Jean, M.; Levoin, N.; Weghe, P. Org. Lett. 2012, 14, 58.

- (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; (8)Willis, C. L. Org. Lett. 2002, 4, 577. (b) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. Chem. Commun. 2005, 3727. (c) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. Org. Lett. 2002, 4, 3919. (d) Jasti, R.; Rychnovsky, S. D. J. Am. Chem. Soc. 2006, 128, 13640.
- (9) For selected examples for synthesis of 4-halo-tetrahydropyrans, see: 4-F: (a) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. Chem. Commun. 2008, 3876. (b) Kishi, Y.; Inagi, S.; Fuchigami, T. Eur. J. Org. Chem. 2009, 103. 4-Cl: (c) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. Org. Lett. 2003, 5, 1979. (d) Biermann, U.; Lützen, A.; Metzger, J. O. Eur. J. Org. Chem. 2006, 2631. (e) Dobbs, A. P.; Pivnevi, L.; Penny, M. J.; Martinović, S.; Iley, J. N.; Stephenson, P. T. Chem. Commun. 2006, 3134. (f) Lee, C. H. A.; Loh, T. P. Tetrahedron Lett. 2006, 47, 1641. (g) Miranda, P. O.; Ramirez, M. A.; Martin, V. S.; Padron, J. I. Org. Lett. 2006, 8, 1633. 4-Br: (h) Vitale, J. P.; Wolckenhauer, S. A.; Do, N. M.; Rychnovsky, S. D. Org. Lett. 2005, 7, 3255. (i) Patterson, B.; Rychnovsky, S. D. Synlett 2004, 543. (j) Jasti, R.; Vitale, J.; Rychnovsky, S. D. J. Am. Chem. Soc. 2004, 126, 9904. (k) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. J. Am. Chem. Soc. 2005, 127, 9939. (1) Liu, F.; Loh, T. P. Org. Lett. 2007, 9, 2063. (m) Li, H.; Loh, T. P. Org. Lett. 2010, 12, 2679. 4-I: (n) Sabitha, G.; Reddy, K. B.; Bhikshapathi, M.; Yadav, J. S. Tetrahedron Lett. 2006, 47, 2807. (o) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Reddy, G. M. Chem. Lett. 2007, 36, 426. And more examples see the review ref. 6b
- (10) For selected examples for synthesis of 4-hydroxyltetrahydropyrans, see: (a) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035. (b) Zhang, W. C.; Viswanathan, G. S.; Li, C. J. *Chem. Commun.* **1999**, 291. (c) Zhang, W. C.; Li, C. J. Tetrahedron 2000, 56, 2403. (d) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Murthy, C. V. S. R. Tetrahedron Lett. 2001, 42, 89. (e) Keh, C. C. K.; Namboodiri, V. V.; Varma, R. S.; Li, C. J. Tetrahedron Lett. 2002, 43, 4993. (f) Hart, D. J.; Bennett, C. E. Org. Lett. 2003, 5, 1499. (g) 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. (h) Yadav V. K.; Kumar, N. V. J. Am. Chem. Soc. 2004, 126, 8652. (i) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Aravind, S. Synthesis 2008, 395. (j) Tadpetch, K.; Rychnovsky, S. D. Org. Lett. 2008, 10, 4839. (k) Reddy, B. V. S.; Venkateswarlu, A.; Kumar, G. G. K. S. N.; Vinu, A. Tetrahedron Lett. 2010, 51, 6511.
- (11) For other selected examples of Prins cyclizations, see: (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. Org. Lett. 2002, 4, 3407. (b) Dalgard, J. E.; Rychnovsky, S. D. J. Am. Chem. Soc. 2004, 126, 15662. (c) Yadav, J. S.; Subba Reddy, B. V.; Reddy, Y. J.; Reddy, N. S. Tetrahedron Lett. 2009, 50, 2877. (d) Matsumoto, K.; Fujie, S.; Ueoka, K.; Suga, S.; Yoshida, J. Angew. Chem., Int. Ed. 2008, 47, 2506. (e) Epstein, O. L.; Rovis, T. J. Am. Chem. Soc. 2006, 128, 16480. (f) Sabitha, G.; Bhikshapathi, M.; Nayak, S.; Yadav, J. S.; Ravi, R.; Kunwar, A. C. Tetrahedron Lett. 2008, 49, 5727. (g) Reddy, U. C.; Rama Raju, B.; Pramod Kumar, E. K.; Saikia, A. K. J. Org. Chem. 2008, 73, 1628. (h) Yadav, J. S.; Subba Reddy, B. V.; Maity, T.; Narayana Kumar, G. G. K. S. Synthesis 2008, 2739. (i) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. J. Org. Chem. 2006, 71, 3176. (j) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. J. Org. Chem. 2009,

74, 2605. (k) Overman, L. E.; Velthuisen, E. J. J. Org. Chem. 2006, 71, 1581. (1) Van Orden, L. J.; Patterson, B. D.; Rychnovsky, S. D. J. Org. Chem. 2007, 72, 5784. (m) Yu, B.; Jiang, T.; Li, J.; Su, Y.; Pan, X.; She, X. Org. Lett. 2009, 11, 3442. (n) Woo, S. K.; Lee, E. J. Am. Chem. Soc. 2010, 132, 4564. (o) Bondalapati, S.; Reddy, U. C.; Kundu, D. S.; Saikia, A. K. J. Fluorine Chem. 2010, 131, 320. (p) Miranda, P. O.; Carballo, R. M.; Mart" n, V. S.; Padr" n J. I. Org. Lett. 2009, 11, 357. and more examples see the review ref. 6b

- (12) For selected reviews, see: (a) Tietze, L. F. Chem. Rev. 1996, 96, 115. (b) Tietze, L. F.; Haunert, F. Stimulating Concepts in Chemistry, Wiley-VCH, Weinheim, 2000, 39. (c) Trost, B. M. Acc. Chem. Res. 2002, 35, 695. (d) Nicolaou, K. C.; Chen, J. S. Chem. Soc. Rev. 2009, 38, 2993.
- (13) Zheng, K.; Shi, J.; Liu, X. H.; Feng, X. M. J. Am. Chem. Soc. 2008, 130, 15770.
- (14) For selected examples of N,N'-dioxide-metal complexes, see: (a) Liu, X. H.; Lin, L. L.; Feng, X. M. Acc. Chem. Res. 2011, 44, 574. (b) Zheng, K.; Yang, Y.; Zhao, J. N.; Yin, C, K.; Lin, L. L.; Liu, X. H.; Feng, X. M. Chem. Eur. J. 2010, 16, 9969. (c) Li, W.; Wang, J.; Hu, X. L.; Shen, K.; Wang, W. T.; Chu, Y. Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. J. Am. Chem. Soc. 2010, 132, 8532. (d) Cai, Y. F.; Liu, X. H.; Jiang, J.; Chen, W. L.; Lin, L. L.; Feng, X. M. J. Am. Chem. Soc. 2011, 133, 5636. (e) Xie, M. S.; Chen, X. H.; Zhu, Y.; Gao, B.; Lin, L. L.; Liu, X. H.; Feng, X. M. Angew. Chem., Int. Ed. 2010, 49, 3799. (f) Zheng, K.; Yin, C. K.; Liu, X. H.; Lin, L. L.; Feng, X. M. Angew. Chem., Int. Ed. 2011, 50, 2573. (g) Li, W.; Liu, X. H.; Hao, X. Y.; Hu, X. L.; Chu, Y. Y.; Cao, W. D.; Qin, S.; Hu, C. W.; Lin, L. L.; Feng, X. M. J. Am. Chem. Soc. 2011, 133, 15268. and references therein.
- (15) The product 7n was always obtained as a mixture (1/1) of two inseparable dihydropyrans, and the combined yield was given.



- (16) Dilman, A. D.; Ioffe, S. L. Chem. Rev. 2003, 103, 733.
- (17) Other additives such as PhCO₂H, PhOH, TMSOH and TMSH were also examined, but no better results were obtained.
- (18) The clarified reaction solution became turbid, generating brown viscous compounds on the tube wall when H2O was added. It might be the hydrolysis of FeCl₃.
- (19) CCDC 855357 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif
- (20) More data see support information.
- (21) The separation of them from the reaction mixture was difficult via flash chromatography as the elimination products have the same R_f value with the cinnamaldehyde **3**y.
- (22) Alder, R. W.; Harvey, J. N.; Oakley, M. T. J. Am. Chem. Soc. 2002, 124, 4960.
- (23) The role of TBSCl in suppressing the eliminated products is uncertain at present. The reactivity of R₃SiCl is different by varying the steric volume of alkyl substituents which might lead to the contrast results by the use of TMSCl and TESCl.
- (24) The separation of pure **5a** or **5n** from the reaction mixture was difficult via flash chromatography due to that they have the same

 R_f value. And the mixture of **5a** and **5n** were analyzed by ESI-MS.

```
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
```

Journal of the American Chemical Society

1 2 3 4 5 6 7 8	$R^{4} \underbrace{OH}_{R^{5}} COR^{1} + eCI_{3} \\ R^{5} \underbrace{COR^{1}}_{R^{5}} + eCI_{3} \\ R^{1} = Aryl, OEt; R^{2} = Aryl, Alky \\ R^{3} = Aryl, Alkyl, etc; R^{4}, R^{5} = H, CH_{3} \\ COR^{1} \underbrace{OH}_{R^{5}} \underbrace{OR}_{R^{3}} \underbrace{OH}_{R^{3}} OH$
9 10 11 12 13 14 15 12	
16 17 18 19 20 21 22 23	
23 24 25 26 27 28 29 30	
31 32 33 34 35 36 37	
38 39 40 41 42 43 44	
45 46 47 48 49 50 51 51	
53 54 55 56 57 58 59	13