Organic LETTERS

Letter

pubs.acs.org/OrgLett

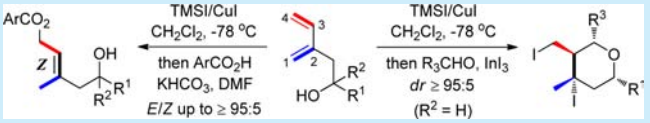
1,4-Hydroiodination of Dienyl Alcohols with TMSI To Form Homoallylic Alcohols Containing a Multisubstituted *Z*-Alkene and Application to Prins Cyclization

Yongjin Xu,[†] Zhiping Yin,[†] Xinglong Lin,[†] Zubao Gan,[†] Yanyang He,[†] Lu Gao,*[,†] and Zhenlei Song*[,†,‡]

[†] Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, and [‡] State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, P. R. China

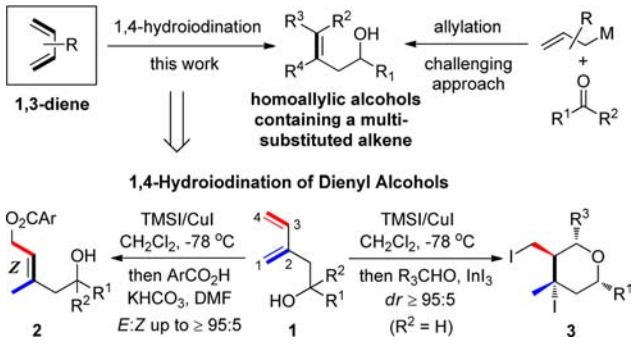
Supporting Information

ABSTRACT: A regioselective 1,4-hydroiodination of dienyl alcohols has been developed using trimethylsilyl iodide as Lewis acid and iodide source. A range of homoallylic alcohols containing a multisubstituted *Z*-alkene was synthesized with good to excellent configurational control. The approach was applied in sequential hydroiodination/Prins cyclization to afford multisubstituted tetrahydropyrans diastereoselectively.



Homoallylic alcohols[1] are valuable synthons that have found widespread use in organic synthesis. One of the most efficient methods to synthesize these species relies on allylation of aldehydes and ketones with various allylic organometallic reagents (Scheme 1).[2] While these approaches are powerful, they are poorly suited for constructing homoallylic alcohols containing a geometrically defined multisubstituted alkene. This may be due to the limited availability of the requisite allylic organometallic reagents or to difficulty controlling regio- and stereoselectivity during the allylation.

Scheme 1. 1,4-Hydroiodination of Dienyl Alcohols with TMSI (1 to 2) and Sequential Hydroiodination/Prins Cyclization (1 to 3)



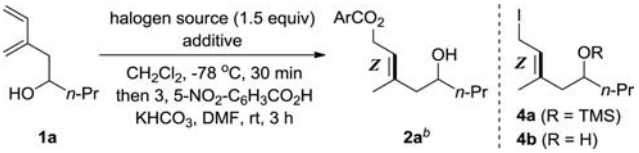
We envisioned that 1,4-disubstitution of 1,3-dienes by a double-bond shift may be a practical way to achieve this goal. Previous investigations of disubstitution of 1,3-dienes have focused on transition metal-catalyzed element−element addition,[3] in which 2 equiv of the same element (Si, B, NR_2, OR, etc.) are incorporated into dienes. In contrast, disubstitutions of unsymmetric 1,3-dienes with two distinct functional groups[4] have been studied in a limited scope due to the difficulties of regio- and stereocontrol. For example, using highly reactive electrophiles to initiate 1,4-disubstitution frequently results in poor or moderate regio- and stereoselectivity.[5] Here, we describe our discovery that trimethylsilyl iodide[6] can serve as both Lewis acid and iodide source to promote a regioselective 1,4-hydroiodination[7] of dienyl alcohols **1**, giving homoallylic alcohols **2** containing a multisubstituted *Z*-alkene[8] with good to excellent configurational control (Scheme 1). We have applied this approach in sequential hydroiodination/Prins cyclization[9] to afford multisubstituted tetrahydropyrans **3** diastereoselectively.

The model scaffold dienyl alcohol **1a** was prepared using a Sn-promoted Barbier reaction[10] of 2-bromoallyl bromide with *n*-PrCHO, which was followed by Kumada cross-coupling[11] with vinylmagnesium bromide (72% yield over two steps). Hydroiodination of **1a** was initially examined using 1.5 equiv of TMSI in CH_2Cl_2 at −78 °C. The in situ formed **4a** underwent rapid desilylation during workup to give **4b** with a *Z*/*E* ratio of 85:15. No other regioisomers due to 1,2-, 3,4-, or 4,1-hydroiodination were observed. The labile allyl iodide motif gave **4b** low stability. Therefore, a mild allylic substitution of crude **4b** with 3,5-$NO_2C_6H_3CO_2H$ was developed to give **2a** as a stable solid in 78% overall yield (Table 1, entry 1). A wide range of additives was screened to improve *Z*-selectivity (entries 2−9). Most gave *Z*/*E* ratios that were similar to, or lower than, the one obtained in the absence of additive. However, catalyzing the reaction with 0.2 equiv of CuI gave **2a** with the highest ratio of 91:9 (entry 10). While decreasing CuI loading to 0.05 equiv lowered the *Z*/*E* ratio (entry 11), using 1.0 equiv of CuI did not improve the *Z*-selectivity (entry 12). TMSI proved to be the optimal iodide source, as using aq HI instead of TMSI decreased the *Z*/*E* ratio to 80:20 with only 15% conversion (entry 13), and using I_2 or KI completely inhibited the reaction (entries 14 and 15). The low conversion in entry 13 also implies that the 1,4-hydroiodination should not be promoted simply by HI species. The halogen source also influenced configurational control and hydrohalogenation efficiency: TMSBr-promoted hydrobromination

Received: February 15, 2015
Published: March 31, 2015

DOI: 10.1021/acs.orglett.5b00485
Org. Lett. 2015, 17, 1846−1849

Table 1. Screening of Reaction Conditions[a]



entry	X source	additive (equiv)	**2a**[c] (%)	Z/E[d]
1	TMSI		78	85:15
2	TMSI	$BF_3{\cdot}OEt_2$ (0.2)	70	80:20
3	TMSI	TMSOTf (0.2)	75	80:20
4	TMSI	$EtAlCl_2$(0.2)	72	80:20
5	TMSI	$PtCl_2$(0.2)	71	85:15
6	TMSI	InI_3(0.2)	69	67:33
7	TMSI	ZnI_2(0.2)	70	80:20
8	TMSI	AgOTf (0.2)	74	87:13
9	TMSI	$SnCl_2$ (0.2)	72	89:11
10	**TMSI**	**CuI (0.2)**	**76**	**91:9**
11	TMSI	CuI (0.05)	74	87:13
12	TMSI	CuI (1.0)	76	89:11
13	aq HI	CuI (0.2)	10[e]	80:20
14	I_2	CuI (0.2)	N.R.	
15	KI	CuI (0.2)	N.R.	
16	TMSBr	CuI (0.2)	60	77:23
17	TMSCl	CuI (0.2)	N.R.	

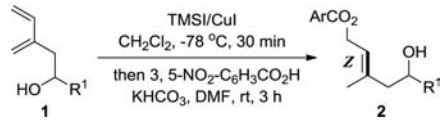
[a]Reaction conditions: 0.2 mmol of **1a**, 0.3 mmol of halogen source in 2.0 mL of CH_2Cl_2 at −78 °C, 30 min, then 0.4 mmol of 3,5-NO_2−$C_6H_3CO_2H$ and 0.44 mmol of $KHCO_3$ in 8.0 mL of DMF, rt, 3.0 h. [b]The *Z*-configuration of **2a** was determined on the basis of NOE experiments. [c]Isolated yields after purification by silica gel column chromatography. [d]Ratios were determined by ^1H NMR spectroscopy of crude **4b**. [e]65% yield based on 15% conversion.

of **1a** with moderate *Z*-selectivity (entry 16), while no hydrochlorination took place with TMSCl (entry 17).

The scope of this approach was tested using various dienyl secondary alcohols **1a**−**m**. Generally good Z/E ratios were obtained from hydroiodination of **1a**−**g** containing an unbranched or branched alkyl group (Table 2, entries 1−7). For terminal bromide-substituted **1f**, cyclization to tetrahydrofuran occurred during allylic substitution with 3,5-$NO_2C_6H_3CO_2H$, giving **2f** in 66% yield with a Z/E ratio of 94:6 (entry 6). Phenyl-substituted dienyl alcohol **1h** and its analogues **1i** and **1j** carrying an electron-withdrawing group on the phenyl ring underwent smooth hydroiodination (entries 8−10). However, **1k** with an electron-donating methoxy group on the phenyl ring appeared to be an inert substrate (entry 11). The reaction of **1l** containing an allylic alcohol motif provided a complex mixture (entry 12). In contrast, the reaction of **1m** containing a propargyl alcohol motif led to the desired hydroiodination product **2m** in 70% yield with a Z/E ratio of 93:7 (entry 13).

Hydroiodination of dienyl tertiary alcohols **1n**−**q** showed distinctly higher *Z*-selectivity than hydroiodination using dienyl secondary alcohols, though the yields were lower in some cases (Table 3). It is possible that dehydroxylation under acidic conditions to form a tertiary carbocation, which is more stable than the secondary carbocation, complicated the reaction and lowered the yield. Interestingly, hydroiodination of dienyl alcohol **5** with a methyl group substituted at the 3-position showed reversal of configurational selectivity, giving **6** with an E/Z ratio of 88:12 (Scheme 2). The overall yield in this reaction was 33%, much lower than in the reaction using **1**.

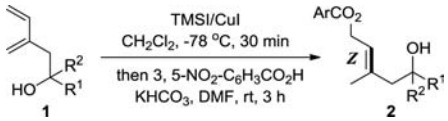
Table 2. Scope of Dienyl Secondary Alcohols[a]



entry	substrate	product	**2** (%)[b]	Z/E[c]
1	**1a**: R_{Alkyl} = *n*-Pr		**2a**: 76	91:9
2	**1b**: R_{Alkyl} = $(CH_2)_3OBn$		**2b**: 63	88:12
3	**1c**: R_{Alkyl} = *i*-Pr		**2c**: 74	90:10
4	**1d**: R_{Alkyl} = Cy		**2d**: 81	88:12
5	**1e**: R_{Alkyl} = *t*-Bu		**2e**: 79	90:10
6	**1f**		**2f**: 66	94:6
7	**1g**		**2g**: 76	90:10
8	**1h**: R_{Aryl} = Ph		**2h**: 68	90:10
9	**1i**: R_{Aryl} = 3-Cl-Ph		**2i**: 71	93:7
10	**1j**: R_{Aryl} = 4-CF_3-Ph		**2j**: 78	93:7
11	**1k**: R_{Aryl} = 4-OMe-Ph		**2k**: N.R.	—
12	**1l**: R =		**2l**: complex	—
13	**1m**: R = TBS		**2m**: 70	93:7

[a]Reaction conditions: 0.4 mmol of **1**, 0.6 mmol of TMSI, 0.08 mmol of CuI in 4.0 mL of CH_2Cl_2 at −78 °C, 30 min, then 0.8 mmol of 3,5-NO_2−$C_6H_3CO_2H$ and 0.88 mmol of $KHCO_3$ in 16.0 mL of DMF, rt, 3.0 h. [b]Isolated yields after purification by silica gel column chromatography. [c]Ratios were determined by ^1H NMR spectroscopy of crude hydroiodination product.

Table 3. Scope of Dienyl Tertiary Alcohols[a]

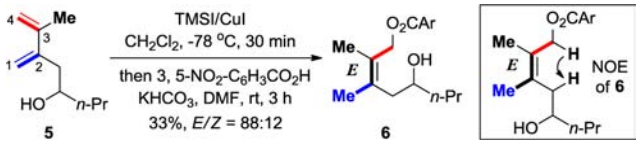


entry	substrate	product	**2** (%)[b]	Z/E[c]
1	**1n**		**2n**: 62	≥95:5
2	**1o**		**2o**: 52	95:5
3	**1p**		**2p**: 55	95:5
4	**1q**		**2q**: 84	≥95:5

[a]Reaction conditions: 0.4 mmol of **1**, 0.6 mmol of TMSI, 0.08 mmol of CuI in 4.0 mL of CH_2Cl_2 at −78 °C, 30 min, then 0.8 mmol of 3,5-NO_2−$C_6H_3CO_2H$ and 0.88 mmol of $KHCO_3$ in 16.0 mL of DMF, rt, 3.0 h. [b]Isolated yields after purification by silica gel column chromatography. [c]Ratios were determined by ^1H NMR spectroscopy of crude hydroiodination product.

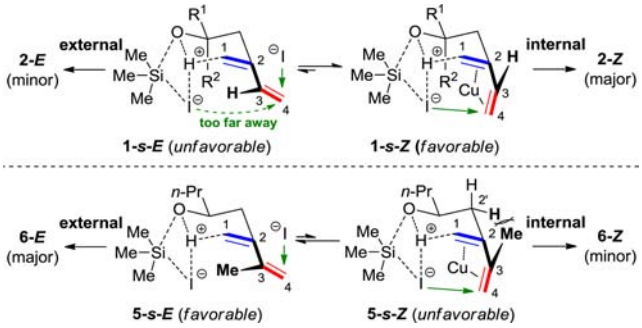
DOI: 10.1021/acs.orglett.5b00485
Org. Lett. 2015, 17, 1846−1849

Scheme 2. 1,4-Hydroiodination of Dienyl Alcohol 5 To Form 6



A model analysis to rationalize the configurational control during 1,4-hydroiodination is outlined in Scheme 3. We propose

Scheme 3. Model Analysis To Explain Differences in Configurational Control

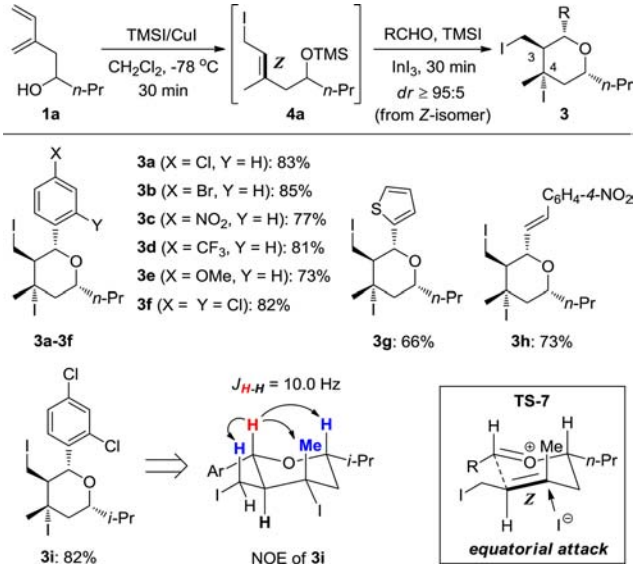


that hydroiodination begins with coordination of the Lewis acidic Si center to oxygen to form an associated ion pair.[12] This Lewis acid-enhanced Brønsted acidity[13] subsequently facilitates intramolecular protonation at the 1-position of the diene.[14] This may explain the distinct reactivity shown in entries 8−11 of Table 2, since the weaker inductive effect of the electron-donating aryl group in **1k** should render the proton less acidic than the equivalent proton in **1i** and **1j**, preventing the protonation required to trigger the entire process.

In the iodination step, the transition state **1-s-*Z*** appears to be favorable because the iodo anion can internally attack the 4-position in a pathway involving a least motion pathway[15] (Scheme 3). Coordination of copper to the diene may also favor such an s-*Z* conformation. The higher *Z*-selectivity observed for dienyl tertiary alcohols may be attributed to the Thorpe−Ingold effect,[16] which should bring the ion pair closer to the 4-position and favor internal iodide transfer. In the **1-s-*E*** transition state, in contrast, the associated iodo anion lies far from the 4-position. As a result, iodination can proceed only via an unfavorable external 4-attack to give **2-*E*** as the minor isomer. In the reaction of **5** containing a 3-Me group, the transition state **5-s-*Z*** is less favorable than transition state **5-s-*E*** because of the increased $A^{1,2}$ strain[17] between the Me and the methylene group at the 2′-position. Thus, transition state **5-s-*E*** should undergo reaction to give **6-*E*** as the major isomer. Since this pathway is external, the iodination efficiency should be low.

To demonstrate its synthetic usefulness, we applied this approach to a sequential hydroiodination/Prins cyclization (Scheme 4). After hydroiodination of **1a** to generate TMS-protected *Z*-homoallylic alcohol **4a**, another 2.0 equiv of TMSI and 0.45 equiv of InI_3[18] were added at −78 °C to promote a Prins cyclization/iodination with aldehydes.[19] Multisubstituted tetrahydropyran **3** was obtained from the *Z*-isomer in good yield with ≥95:5 dr.[20] Product stereochemistry was determined on the basis of NOE experiments on **3i**. We assume that Prins cyclization proceeds via the Alder's chairlike transition state **TS-7**,[21] in which the *Z*-alkene accounts for the *trans*-stereo-

Scheme 4. Sequential Hydroiodination/Prins Cyclization of 1a To Construct Tetrahydropyrans 3



control at the 3-position and equatorial iodide addition accounts for the *cis*-stereocontrol at the 4-position.[22]

In summary, we have shown that trimethylsilyl iodide serves as Lewis acid and iodide source to promote a regioselective 1,4-hydroiodination of dienyl alcohols. We have demonstrated that the approach is useful for synthesizing homoallylic alcohols containing a multisubstituted *Z*-alkene with good to excellent configurational control. Detailed model analysis is presented that rationalizes the observed regio- and stereoselectivity. The approach has been applied in sequential hydroiodination/Prins cyclization to give multisubstituted tetrahydropyrans diastereoselectively. Further applications of this method are under development.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: lugao@scu.edu.cn.
*E-mail: zhenleisong@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the NSFC (21172150, 21321061, 21290180), the NCET (12SCU-NCET-12-03), and the Sichuan University 985 project.

■ REFERENCES

(1) For a review on homoallylic alcohols, see: Perkins, M. V. *Sci. Synth.* **2008**, *36*, 667.

(2) For selected reviews on allylation of aldehydes and ketones, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (c) Denmark, S. E.; Fu, J. *Chem.*

DOI: 10.1021/acs.orglett.5b00485
Org. Lett. 2015, 17, 1846−1849

Rev. **2003**, *103*, 2763. (d) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367.

(3) For selected reviews on transition-metal-catalyzed element−element addition of 1,3-diene, see: (a) Baeckvall, J. E. *Acc. Chem. Res.* **1983**, *16*, 335. (b) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. For selected advances, see: (c) Tsuji, Y.; Obora, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9368. (d) Ishikawa, M.; Okazaki, S.; Naka, A.; Tachibana, A.; Kawauchi, S.; Yamabe, T. *Organometallics* **1995**, *14*, 114. (e) Obora, Y.; Tsuji, Y.; Kawamura, T. *J. Am. Chem. Soc.* **1995**, *117*, 9814. (f) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689. (g) Yu, C.-M.; Youn, J.; Yoon, S.-K.; Hong, Y.-T. *Org. Lett.* **2005**, *7*, 4507. (h) Coscia, R. W.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 2496. (i) Zhao, B.; Peng, X.; Zhu, Y.; Ramirez, T. A.; Cornwall, R. G.; Shi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20890. (j) Jeffrey, C. S.; Anumandla, D.; Carson, C. R. *Org. Lett.* **2012**, *14*, 5764. (k) Lishchynskyi, A.; Muñiz, K. *Chem.—Eur. J.* **2012**, *18*, 2212. (l) Cornwall, R. G.; Zhao, B.; Shi, Y. *Org. Lett.* **2013**, *15*, 796.

(4) For selected advances, see: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911. (c) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (d) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543. (e) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386. (f) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (g) Ikeda, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120. (h) Hirashita, T.; Kambe, S.; Tsuji, H.; Araki, S. *Chem. Commun.* **2006**, 2595. (i) Cho, H. Y.; Yu, Z. Y.; Morken, J. P. *Org. Lett.* **2011**, *13*, 5261. (j) Leung, J. C.; Geary, L. M.; Chen, T. Y.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 15700. (k) Xing, D.; Yang, D. *Org. Lett.* **2013**, *15*, 4370. (l) Bao, H. L.; Bayeh, L.; Tambar, U. K. *Chem. Sci.* **2014**, *5*, 4863.

(5) For selected examples, see: (a) Babler, J. H.; Buttner, W. J. *Tetrahedron Lett.* **1976**, *17*, 239. (b) Heasley, G. E.; Smith, D. A.; Smith, J. N. *J. Org. Chem.* **1980**, *45*, 5206. (c) Nguyen Van, T.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7969.

(6) For selected reviews on trimethylsilyl iodide, see: (a) Groutas, W. C.; Felker, D. *Synthesis* **1980**, *11*, 861. (b) Schmidt, A. H. *Aldrichimica Acta* **1981**, *14*, 31. (c) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225. (d) Voronkov, M. G.; Dubinskaya, E. I. *J. Organomet. Chem.* **1991**, *410*, 13. (e) Jung, M. E.; Martinelli, M. J.; Olah, G. A.; Prakash, G. K. S.; Hu, J. B. Reagents for Silicon-Mediated Organic Synthesis. In *Handbook of Reagents for Organic Synthesis: Reagents for Silicon-Mediated Organic Synthesis*; Fuchs, P. L., Ed.; John Wiley and Sons: New York, 2011; pp 325−336.

(7) For selected examples of hydroiodination, see: (a) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. (b) Brown, H. C.; Somayaji, V.; Narasimhan, S. *J. Org. Chem.* **1984**, *49*, 4822. (c) Reddy, Ch. K.; Periasamy, M. *Tetrahedron Lett.* **1990**, *31*, 1919. (d) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675. (e) Kropp, P. J.; Crawford, S. D. *J. Org. Chem.* **1994**, *59*, 3102. (f) Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem.* **1995**, *60*, 290. (g) Campos, P. J.; García, B.; Rodríguez, M. A. *Tetrahedron Lett.* **2002**, *43*, 6111. (h) Shimizu, M.; Toyoda, T.; Baba, T. *Synlett* **2005**, 2516. (i) Bartoli, G.; Cipolletti, R.; Di Antonio, G.; Giovannini, R.; Lanari, S.; Marcolini, M.; Marcantoni, E. *Org. Biomol. Chem.* **2010**, *8*, 3509. (j) Kawaguchi, S-i.; Ogawa, A. *Org. Lett.* **2010**, *12*, 1893. (k) Ez-Zoubir, M.; Brown, J. A.; Ratovelomanana-Vidal, V.; Michelet, V. *J. Organomet. Chem.* **2011**, *696*, 433.

(8) The product, in which the CH_2O_2CAr group falls on the same side as the methyl group, is assigned to have a *Z* configuration. For a latest study on the synthesis of *Z*-alkenes, see: (a) Zhuo, L. G.; Yao, Z. K.; Yu, Z. X. *Org. Lett.* **2013**, *15*, 4634. For a recent review of the synthesis of *Z*-alkenes, see: (b) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2012**, *113*, 1313.

(9) For selected reviews on Prins cyclization, see: (a) Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316. (b) Han, X.; Peh, G. R.; Floreancig, P. E. *Eur. J. Org. Chem.* **2013**, *7*, 1193. (c) Greco, S. J.; Fiorot, R. G.; Lacerda, V.; dos Santos, R. B. *Aldrichimica Acta* **2013**, *46*, 59.

(10) Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172.

(11) Carreno, M. C.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **1998**, *63*, 8320.

(12) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46.

(13) For selected reviews, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (c) Zhou, J. *Chem.—Asian J.* **2010**, *5*, 422. (d) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. (e) Loh, C. C. J.; Enders, D. *Chem.—Eur. J.* **2012**, *18*, 10212. (f) Parra, A.; Reboredo, S.; Martin Castro, A. M.; Alemán, J. *Org. Biomol. Chem.* **2012**, *10*, 5001. (g) Lv, J.; Luo, S. *Chem. Commun.* **2013**, *49*, 847.

(14) The reaction of TBS-protected **1a** only led to 40% conversion at −78 °C for 1 h. No further iodination continued at this temperature with longer reaction time. This result partially supports that the hydroxyl group is crucial to initiate protonation at the 1-position of the diene.

(15) Zhang, Y. D.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720.

(16) For a review on Thorpe−Ingold effect, see: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

(17) For reviews on allylic strain, see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(18) Yu and co-workers have shown that the real catalytic species of InX_3 is InX_2^+. For the related elegant studies, see: (a) Zhuo, L. G.; Zhang, J. J.; Yu, Z. X. *J. Org. Chem.* **2012**, *77*, 8527. (b) Zhuo, L. G.; Shi, Y. C.; Yu, Z. X. *Asian J. Org. Chem.* **2014**, *3*, 842. (c) Zhuo, L. G.; Zhang, J. J.; Yu, Z. X. *J. Org. Chem.* **2014**, *79*, 3809.

(19) (a) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491. (b) Sabitha, G.; Reddy, K. B.; Bhikshapathi, M.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 2807. (c) Dobbs, A. P.; Pivnevi, L.; Penny, M. J.; Martinović, S.; Iley, J. N.; Stephensond, P. T. *Chem. Commun.* **2006**, *29*, 3134. (d) Liu, F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063. (e) Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939. (f) Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett.* **2009**, *11*, 1741. (g) Li, H.; Loh, T. P. *Org. Lett.* **2010**, *12*, 2679. (h) Saikia, A. K.; Bondalapati, S.; Indukuri, K.; Gogoi, P. *Chem. Lett.* **2011**, *40*, 1176. (i) Li, B.; Lai, Y. C.; Zhao, Y. J.; Wong, Y. H.; Shen, Z. L.; Loh, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10619. (j) Clarisse, D.; Pelotier, B.; Piva, O.; Fache, F. *Chem. Commun.* **2012**, *48*, 157.

(20) $InCl_3$ or $InBr_3$ instead of InI_3 also led to the formation of iodo-THP **3f** in 80% and 73% yield, respectively. Neither chloro- nor bromo-THP was detected. These results imply that TMSI should be the iodide source, which is responsible for the attack at the 4-position of THP.

(21) (a) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960. (b) Jasti, R.; Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2175.

(22) Rychnovsky observed that TMSBr- or TMSI-promoted Prins cyclization of α-acetoxy ethers gave axial-substituted tetrahydropyran predominantly. (a) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904. (b) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939.

DOI: 10.1021/acs.orglett.5b00485
Org. Lett. 2015, 17, 1846−1849