LETTERS 2013 Vol. 15, No. 19 5142–5145

ORGANIC

Enantioenriched Bifunctional Crotylsilanes for the Asymmetric Synthesis of Orthogonally Protected 2-Methyl-1,3-diols

Dongeun Kim, Jae Seung Lee, Lucia Lozano, Suk Bin Kong, and Hyunsoo Han*

Department of Chemistry, University of Texas at San Antonio, San Antonio, Texas 78249, United States

Hyunsoo.han@utsa.edu

Received September 10, 2013



Enantiomerically pure α -substituted crotylsilane reagents I and *ent*-I undergo asymmetric aldehyde crotylation followed by Ir(I)-catalyzed diastereoselective allylic etherification to give a variety of orthogonally protected 2-methyl-1,3-diols at the synthetically useful level of yields and stereoselectivity. The reagents are air-stable and bifunctional so that they can be used in these reactions sequentially without recourse to functional group adjustments.

Enantioenriched α -substituted allyl/crotylsilanes have played an important role in organic synthesis.¹ Many

(2) (a) Panek, J. S.; Yang, M. J. Am. Chem. Soc. 1991, 113, 9868–9870. (b) Micalizio, G. C.; Roush, W. R. Org. Lett. 2000, 2, 461–464. (c) Peng, Z.-H.; Woerpel, K. A. Org. Lett. 2001, 3, 675–678. (d) Huang, H.; Panek, J. S. J. Am. Chem. Soc. 2000, 122, 9836–9837. (e) Su, Q.; Panek, J. S. J. Am. Chem. Soc. 2004, 126, 2425–2430. (f) Su, Q.; Panek, J. S. J. Am. Chem. Soc. 2004, 126, 2425–2430. (f) Su, Q.; Panek, J. S. Angew. Chem., Int. Ed. 2005, 44, 1223–1225. (g) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K. Angew. Chem., Int. Ed. 2010, 49, 4264–4268. (h) Wu, J.; Zhu, K.-C.; Yuan, P.-W.; Panek, J. S. Org. Lett. 2012, 14, 3624–3627. (i) Wu, J.; Becerril, J.; Lian, Y.; Davies, H. M. L.; Porco, J. A., Jr.; Panek, J. S. Angew. Chem., Int. Ed. 2011, 50, 5938–5942. (j) Franz, A.K.; Dreyfuss, P. D.; Schreiber, S. L. J. Am. Chem. Soc. 2007, 129, 1020–1021. (k) Lipomi, D. J.; Panek, J. S. Org. Lett. 2005, 7, 4701–4704.

synthetically useful structures can be accessed through the use of these reagents.² Furthermore, numerous total syntheses of biologically and therapeutically important compounds have been accomplished by employing these reagents in the key step.³ As such, developing new such reagents and/or novel synthetic strategies based on these reagents has been a focus of recent studies.⁴

Numerous studies, mainly from Panek's group, have established that acid-mediated asymmetric crotylation of aldehydes and acetals by chiral α -substituted crotylsilanes

^{(1) (}a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. (c) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173–3199. (d) Bates, R. H.; Chen, M.; Roush, W. R. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 778–792. (e) Shimizu, M.; Hiyama, T. *Handbook of Functionalized Organometallics* **2005**, *1*, 173–202.

^{(3) (}a) Wu, J.; Panek, J. S. J. Org. Chem. 2011, 76, 9900–9918. (b) Wu, J.; Panek, J. S. Angew. Chem., Int. Ed. 2010, 49, 6165–6168. (c) Robinson, A.; Aggarwal, V. K. Angew. Chem., Int. Ed. 2010, 49, 6673–6675. (d) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. Angew. Chem., Int. Ed. 2007, 46, 9211–9214. (e) Va, P.; Roush, W. R. J. Am. Chem. Soc. 2006, 128, 15960–15961. (f) Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. J. Am. Chem. Soc. 2005, 127, 15026–15027. (g) Tinsley, J. M.; Roush, W. R. J. Am. Chem. Soc. 2004, 126, 2425–2430.

^{(4) (}a) Nagao, K.; Yokobori, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. J. Am. Chem. Soc. 2012, 134, 8982–8987. (b) Hodgson, D. M.; Salik, S. Org. Lett. 2012, 14, 4402–4405. (c) Chen, M.; Roush, W. R. Org. Lett. 2011, 13, 1992–1995. (d) Aggarwal, V. K.; Binanzer, M.; de Ceglie, M. C.; Gallanti, M.; Glasspoole, B. W.; Kendrick, S. J. F.; Sonawane, R. P.; Vázquez-Romero, A.; Webster, M. P. Org. Lett. 2011, 13, 1490–1493. (e) Selander, N.; Paasch, J. R.; Szabó, K. J. J. Am. Chem. Soc. 2010, 132, 9153–9156. (g) Fukuda, K.; Miyashita, M.; Tanino, K. Tetrahedron Lett. 2010, 51, 4523–4525. (h) Li, D.; Tanaka, T.; Ohmiya, H.; Sawamura, M. Org. Lett. 2010, 12, 3h44–3347. (i) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. J. Am. Chem. Soc. 2007, 129, 12650–12651. (j) Lira, R.; Roush, W. R. Org. Lett. 2007, 9, 4315–4318. (k) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2010, 49, 8513–8515 (racemic version).

in the presence of TMSOR' can give rise to *E*-homoallylic ethers with high enantio- and diastereoselectivities (eq 1).^{1a,5} However, the resulting homoallylic ethers have been used primarily for simple functional group interconversions and have rarely been employed in catalytic asymmetric reactions where a new bond is stereoselectively introduced by using a pair of enantiomeric catalysts/ligands. This may be in large part due to the fact that almost all prior chiral α -substituted crotylsilanes, to our knowledge, produce homoallylic ethers, which are not appropriately appended with functional groups for subsequent catalytic asymmetric reactions.⁶ In this regard, new chiral α -substituted crotylsilanes that can undergo an asymmetric crotylation immediately followed by a catalytic asymmetric reaction without recourse to functional group adjustments would be highly desirable. We considered this need in relation with our recent reports that described Ir(I)-catalyzed

Prior work: asymmetric aldehyde crotylation

$$\xrightarrow{\text{SiPhMe}_2} \text{RCHO, H}^+ \xrightarrow{\text{OR}'} \text{R}^+ \qquad (1)$$

Prior work: Ir(I)-catalyzed double diastereoselective allylic etherification



The current work: merging the above two reactions into I



diastereoselective allylic etherification of *p*-methoxyphenyl (PMP) allyl carbonates (eq 2)^{7,8} and wondered whether it would be possible to merge Panek's asymmetric aldehyde crotylation with our Ir(I)-catalyzed diastereoselective allylic etherification to devise a new chiral bifunctional crotylsilane I (eq 3). Herein we report that the crotylsilane I and its enantiomer *ent*-I indeed undergo the above two reactions sequentially to deliver orthogonally protected 2-methyl-1,3-diols in a highly stereoselective and efficient fashion, which are common structural motifs in many natural products.⁹ We believe that the

(5) Wu, J.; Chen, Y.; Panek, J. S. Org. Lett. 2010, 12, 2112–2115.
(6) (a) Wu, J.; Zhu, K.-C.; Yuan, P.-W.; Panek, J. S. Org. Lett. 2012,

(7) (a) Kim, D.; Reddy, S.; Singh, O. V.; Lee, J. S.; Kong, S. B.; Han, H. Org. Lett. **2013**, 15, 512–515. (b) Kim, D.; Lee, J. S.; Kong, S. B.; Han, H. Angew. Chem., Int. Ed. **2013**, 52, 4203–4206.
 Table 1. Asymmetric Crotylation of Aldehydes by the Crotylsilanes I and *ent*-I

entry	R-		yield [%] ^a	syn:anti ^b	ee [%] ^c
1	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	(a)	92	4:1	97
2	- The	(b)	93	7:1	96
3	Y Yr	(c)	88	>25:1	97
4	- r	(d)	82	>25:1	98
5	- The	(e)	91	>25:1	94
6	- Nr	(f)	93	>25:1	97
7	Me	(g)	92	>25:1	96
8	Me	(h)	94	>25:1	96
9	CI	(i)	94	>25:1	97
10	CI	(j)	96	>25:1	95
11	MeO Ju	(k)	88	>25:1	95

^{*a*} Isolated yields. ^{*b*} Determined by the ¹H NMR spectrum of reaction mixtures. ^{*c*} Determined by chiral HPLC.

developed synthetic strategy utilizing I and *ent*-I are compared very favorably with other state-of-art methods for the asymmetric synthesis of 2-methyl-1,3-diol derivatives.⁹

The enantioenriched crotylsilanes I and *ent*-I were prepared by acylating the corresponding known alcohols⁵ with ClCO₂PMP in the presence of pyridine in methylene

^{(6) (}a) Wu, J.; Zhu, K.-C.; Yuan, P.-W.; Panek, J. S. *Org. Lett.* **2012**, *14*, 3624–3627. (b) Panek, J. S.; Yang, M.; Solomon, J. S. *J. Org. Chem.* **1993**, *58*, 1003–1010. In these papers, crotylation products were used in Pd(II)-catalyzed intramolecular allylic acetate transposition and Pd(0)-catalyzed intramolecular allylic substitution reactions. Since these reactions are intramolecular reactions and their stereochemistry is controlled by substrate stereochemistry or solvents used, they are not true catalytic asymmetric reactions, where a new bond is stereoselectively introduced by a pair of enantiomeric catalysts/ligands.

⁽⁸⁾ For reviews on Ir(I)-catalyzed allylation: (a) Hartwig, J. F.; Pouy, M. J. *Top. Organomet. Chem.* **2011**, *34*, 169–208. (b) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691.

⁽⁹⁾ For recent approaches, see: (a) Gao, X.; Han, H.; Krische, M. J. J. Am. Chem. Soc. 2011, 133, 12795–12800. (b) Ichibakase, T.; Nakajima, M. Org. Lett. 2011, 13, 1579–1581. (c) Rohr, K.; Herre, R.; Mahrwald, R. J. Org. Chem. 2009, 74, 3744–3749. (d) Mlynarski, J.; Rakiel, B.; Stodulski, M.; Suszczyńska, A.; Frelek, J. Chem.—Eur. J. 2006, 12, 8158–8167. (e) Gnanadesikan, V.; Horiuchi, Y.; Oshima, T.; Shibasaki, M. J. Am. Chem. Soc. 2004, 126, 7782–7783. (f) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. Angew. Chem., Int. Ed. 2001, 40, 601–603. (g) Evans, D. A.; Hoveyda, A. H. J. Am. Chem. Soc. 1990, 112, 6447–6449. (h) Dorgan, P. D.; Durrani, J.; Cases-Thomas, M. J.; Hulme, A. N. J. Org. Chem. 2010, 75, 7475–7478. (i) Esteve, J.; Matas, S.; Pellicena, M.; Velasco, J.; Romea, P.; Urpí, F.; Font-Bardia, M. Eur. J. Org. Chem. 2010, 3146–3151. (j) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Yamaguchi, E.; Krische, M. J. J. Am. Chem. Soc. 2009, 131, 2514–2520. (m) Gao, X.; Townsend, I. A.; Krische, M. J. J. Org. Chem. 2011, 76, 2350–2354.

Table 2. Ir(I)-Catalyzed Decarboxylative Double Diastereoselective Allylic Etherification of PMP Allyl Carbonates **2** in the Presence of Phosphoramidite Ligand L^{*a}

OPMP OBn 0 0	[Ir(dbcot)CI] ₂ (2 mol %) L* (4 mol %) DBU (100 mol %)	OBn OPMP R or	COP-N
R	THF, 60 °C	QBn QPMP	
= 2		R 4	

entry	R-	product	yield [%] ^b	3:4 dr ^c
1	ru	(1S, 2R, 3S)- 3b	81	10:1
2	- Yrr	(1S, 2R, 3S)- 3c	75	14:1
3	- r	(1S, 2R, 3S)- 3d	82	>25:1
4	- the	(1S, 2R, 3S)- 3e	81	>25:1
5	- The	(1R, 2S, 3S)- 3f	77	20:1
6	Me	(1R, 2S, 3S)- 3g	74	>25:1
7	Me	(<i>1R, 2S,</i> 3S)- 3h	83	21:1
8	CI	(1R, 2S, 3S)- 3 i	36 ^d	>25:1
9	CI	(1R, 2S, 3S)- 3j	74	>25:1
10	MeO The	(1R, 2S, 3S)- 3k	75	11:1

^{*a*} PMP allyl carbonate (0.2 mmol), $[Ir(dbcot)Cl]_2$ (0.004 mmol), L* (0.008 mmol), DBU (0.2 mmol) in THF (3 mL) at 60 °C. ^{*b*} Isolated yields. ^{*c*} Determined by the ¹H NMR spectrum of reaction mixtures. ^{*d*} Linear product/branched product = 1:1.

chloride (eq 4). The crotylsilanes I and *ent*-I are air-stable and can be stored without any precautions.



Acid-mediated asymmetric crotylation of benzaldehyde by I in the presence of TMSOBn was used to determine the optimal conditions. After various acids (TfOH, TMSOTf, TMSI, TiCl₄, and BF₃·OEt₂), solvents (EtCN, MeCN, CH₂Cl₂, and toluene), and temperatures (-78, -50, -20, and 0 °C) were screened, as well as the amounts of TMSOBn, the reaction conditions involving TfOH (3 equiv) and TMSOBn (3 equiv) in EtCN at -78 °C were determined to be optimal to give the corresponding homoallylic ether in 95% yield in 5 h. The conditions using 1.5 equiv of TfOH could be used, but the reaction became very sluggish, taking > 24 h to complete. When less than 3 equiv of TMSOBn were used, the corresponding tetrahydrofuran **Table 3.** Ir(I)-Catalyzed Decarboxylative Double Diastereoselective Allylic Etherification of PMP Allyl Carbonates **2** in the Presence of Phosphoramidite Ligand *ent*- L^{*a}



entry	R-	product	yield [%] ^b	3:4 dr ^c
1	- Jon	(1S, 2R, 3R)- 4b	84	1:>25
2	- The	(1S, 2R, 3R)- 4c	79	1:>25
3	- The	(1S, 2R, 3R)- 4d	86	1:>25
4	- re	(1S, 2R, 3R) -4e	84	1:>25
5	"The	(1R, 2S, 3R) -4f	82	1:16
6	Me	(1R, 2S, 3R) -4g	83	1:>25
7	Me	(<i>1R, 2S, 3R</i>) -4h	86	1:13
8	CI	(1R, 2S, 3R)- 4i	41 ^d	1:10
9	CI	(1R, 2S, 3R)- 4j	83	1:13
10	MeO Y	(1R, 2S, 3R)- 4k	80	1:13

^{*a*} PMP allyl carbonate (0.2 mmol), $[Ir(dbcot)Cl]_2$ (0.004 mmol), *ent*-L* (0.008 mmol), DBU (0.2 mmol) in THF (3 mL) at 60 °C. ^{*b*} Isolated yields. ^{*c*} Determined by the ¹H NMR spectrum of reaction mixtures. ^{*d*} Linear product/branched product = 1:1.

byproduct started to form.^{5,10} The crotylsilane I tended to decompose to give PMPOH at higher temperatures than -20 °C. All attempts to generate the corresponding homoallylic alcohol were unsuccessful.

The optimal conditions were applied to a group of aldehydes, and the results are presented in Table 1. Unbranched linear aliphatic aldehydes (entries 1 and 2) resulted in high yields, but exhibited modest *syn/anti* selectivities (4–7:1). On the other hand, branched (entries 3 and 4) and cyclic (entry 5) aliphatic aldehydes worked well to give the corresponding homoallylic ethers in good yields and with excellent *syn/anti* selectivities (>25:1). Uniformly high yields (\geq 88%) and excellent *syn/anti* selectivities (>25:1) were obtained with all aromatic aldehydes tested (entries 6–11). The electron-donating and -withdrawing ability of a substituent on the benzene ring of aromatic

⁽¹⁰⁾ Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. Org. Lett. **2005**, 7, 2405–2408.

aldehydes, as well as its position, had very little influence on the diastereoselectivity and reaction yield. In all cases studied, excellent enantionselectivities ($\geq 94\%$) were obtained, indicating that the reactions proceeded with nearperfect chirality transfer. The relative and absolute stereochemistry of **2** were assigned by hydrolyzing **2f** to the known allylic alcohol (see the Supporting Information) and analogy to the literature.⁵

Table 2 depicts Ir(I)-catalyzed decarboxylative double diastereoselective allylic etherification of **2** in the presence of phosphoramidite ligand L*, which gives rise to orthogonally protected 2-methyl-1,3-diols.¹¹ The catalytic conditions involving [Ir(dbcot)Cl]₂ (2 mol %), L* (4 mol %), and DBU (100 mol %) in THF that we recently reported for Ir(I)-catalyzed enantioselective decarboxylative allylic etherification were used at 60 °C.⁷ Gratifyingly, high yields and diastereoselectivities were obtained with almost all aliphatic and aromatic substrates studied. Only the *o*-chlorophenyl substrate (entry 8) exhibited a modest yield (36%) due to the formation of the corresponding linear allylation product, but still showed excellent > 25:1 diastereoselectivity.

Ir(I)-catalyzed decarboxylative double diastereoselective allylic etherification of 2 was also conducted with phosphoramidite ligand *ent*-L* under otherwise identical conditions, and the results are shown in Table 3. Again, high yields and diastereoselectivities were observed in all cases except for the *o*-chlorophenyl substrate (entry 8), which suffered from modest yield. Compared with *o*-tolyl and *p*-chlorophenyl substrates that gave a good branched to linear ratio and reaction yield, these results are surprising and the reason is not clear. The use of *ent*-L* reversed the diastereofacial preference to favor the other diastereomers **4**. The stereochemistry of the allylic etherification was assigned by converting **3c** and **4c** to the respective known compound (see the Supporting Information) and by analogy to the literature.^{8,12} Taken together with those in Table 2, these stereochemical outcomes clearly indicate that double diastereoselectivity in the Ir(I)-catalyzed decarboxylative allylic etherification of **2** is primarily governed by ligand/catalyst stereochemistry (reagentcontrolled stereochemistry).¹¹

In summary, we report new bifunctional chiral crotylsilanes I and *ent*-L*, which are air-stable and can undergo highly enantio-/diasteoselective aldehyde crotylation followed by Ir(I)-catalyzed double diastereoselective decarboxylative allylic etherification. To the best of our knowledge, these reagents represent the first example of chiral α -substituted crotylsilanes that can undergo asymmetric aldehyde crotylation followed by a catalytic asymmetric reaction without recourse to functional group adjustments. Considering the prevalence of 2-methyl-1,3-diol motifs in natural products and biologically interesting compounds, the method should find broad applications in organic synthesis.

Acknowledgment. Research reported in this publication was supported by the National Science Foundation (CHE 0911134).

Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

⁽¹¹⁾ Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. Angew. Chem., Int. Ed. 1985, 24, 1–30.

⁽¹²⁾ Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. Chem. Commun. 2004, 896-897.

The authors declare no competing financial interest.