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

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ABSTRACT

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 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

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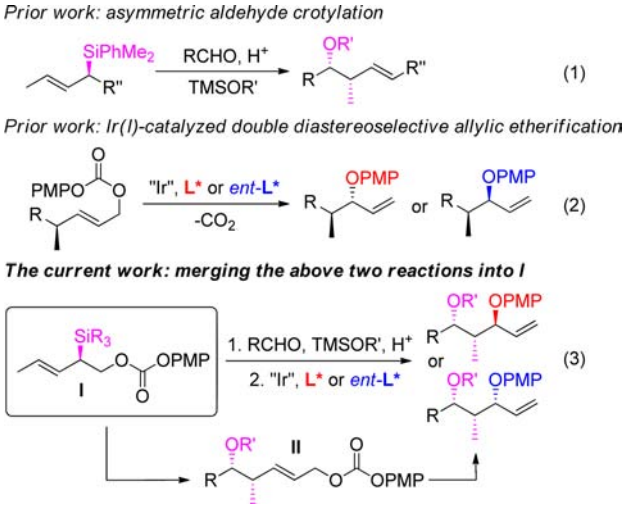
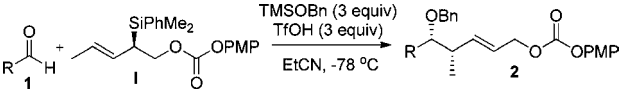
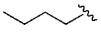
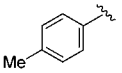
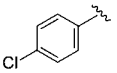
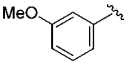
in the presence of TMSOR′ can give rise to *E*-homoallylic ethers with high enantio- and diastereoselectivities (eq 1).[1a,5] However, the resulting homoallylic ethers have been used primarily for simple functional group interconversions and have rarely been employed in catalytic asymmetric reactions 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



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

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		(b)	93	7:1	96
3		(c)	88	>25:1	97
4		(d)	82	>25:1	98
5		(e)	91	>25:1	94
6		(f)	93	>25:1	97
7		(g)	92	>25:1	96
8		(h)	94	>25:1	96
9		(i)	94	>25:1	97
10		(j)	96	>25:1	95
11		(k)	88	>25:1	95

[a] Isolated yields. [b] Determined by the ^{1}H 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 alcohols[5] with $ClCO_2PMP$ in the presence of pyridine in methylene

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(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.

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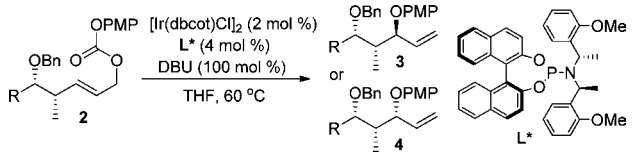
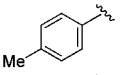
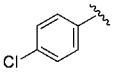
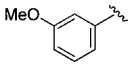
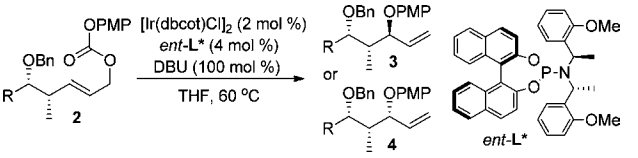
Table 2. Ir(I)-Catalyzed Decarboxylative Double Diastereoselective Allylic Etherification of PMP Allyl Carbonates **2** in the Presence of Phosphoramidite Ligand **L***[a]

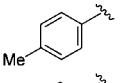
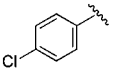
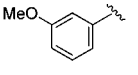


entry	R-	product	yield [%][b]	3:4 dr[c]
1		(*1S, 2R, 3S*)-**3b**	81	10:1
2		(*1S, 2R, 3S*)-**3c**	75	14:1
3		(*1S, 2R, 3S*)-**3d**	82	>25:1
4		(*1S, 2R, 3S*)-**3e**	81	>25:1
5		(*1R, 2S, 3S*)-**3f**	77	20:1
6		(*1R, 2S, 3S*)-**3g**	74	>25:1
7		(*1R, 2S, 3S*)-**3h**	83	21:1
8		(*1R, 2S, 3S*)-**3i**	36[d]	>25:1
9		(*1R, 2S, 3S*)-**3j**	74	>25:1
10		(*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.

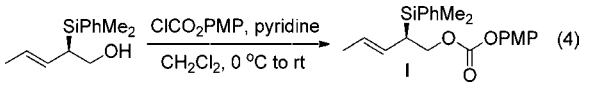
Table 3. Ir(I)-Catalyzed Decarboxylative Double Diastereoselective Allylic Etherification of PMP Allyl Carbonates **2** in the Presence of Phosphoramidite Ligand *ent*-**L***[a]



entry	R-	product	yield [%][b]	3:4 dr[c]
1		(*1S, 2R, 3R*)-**4b**	84	1:>25
2		(*1S, 2R, 3R*)-**4c**	79	1:>25
3		(*1S, 2R, 3R*)-**4d**	86	1:>25
4		(*1S, 2R, 3R*)-**4e**	84	1:>25
5		(*1R, 2S, 3R*)-**4f**	82	1:16
6		(*1R, 2S, 3R*)-**4g**	83	1:>25
7		(*1R, 2S, 3R*)-**4h**	86	1:13
8		(*1R, 2S, 3R*)-**4i**	41[d]	1:10
9		(*1R, 2S, 3R*)-**4j**	83	1:13
10		(*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.

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, $TiCl_4$, and $BF_3 \cdot OEt_2$), solvents (EtCN, MeCN, CH_2Cl_2, 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 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 (≥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

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aldehydes, as well as its position, had very little influence on the diastereoselectivity and reaction yield. In all cases studied, excellent enantionselectivities (≥94%) were obtained, indicating that the reactions proceeded with near-perfect 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 (reagent-controlled 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.

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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.

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The authors declare no competing financial interest.