

Highly Diastereo- and Enantioselective
Reagents for Aldehyde Crotylation

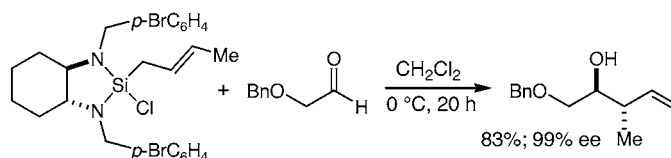
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ABSTRACT

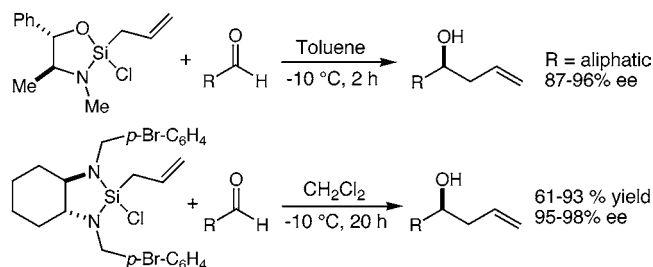


Two new, crystalline solid, storable, and highly enantioselective reagents for aldehyde crotylation have been developed. Both (*cis* and *trans*) crotylsilane reagents are easily prepared in bulk, require trivial reaction conditions, and provide the homoallylic alcohol products with near diastereo- and enantiospecificity in many cases.

For over 20 years, asymmetric aldehyde crotylation reactions have played a prominent role in polyketide natural product synthesis and continue to be widely employed to this day.¹ The most extensively used crotylboranes developed by Brown^{1d} and boronate esters developed by Roush^{1e} are type I reagents² in that they proceed through closed transition states and do not require the use of an external Lewis acid. In contrast, the versatile and highly selective chiral crotylsilanes developed by Panek^{1g,h} are type II reagents that require the use of an external Lewis acid and react through open transition states. Crotylsilanes may be rendered type I reagents as exemplified by the chiral Lewis base-catalyzed addition of crotyltrichlorosilanes to aldehydes developed by Denmark,³ but these reactions are not generally compatible with aliphatic aldehydes. Our recent discovery that ring strain

presents an alternative method for creating reactive type I allylsilane reagents⁴ (Scheme 1) has prompted us to inves-

Scheme 1



(1) (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11. (c) Ramachandran, P. V. *Aldrichim. Acta* **2002**, 35, 23–35. (d) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, 54, 1570–1576. (e) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, 112, 6339–6348. (f) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, 114, 2321–2336. (g) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, 95, 1293–1316. (h) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, 124, 12806–12815. (i) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, 125, 10160–10161.

(2) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, 66, 1655–1660.

(3) (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, 123, 9488–9489. (b) Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, 4, 1951–1953.

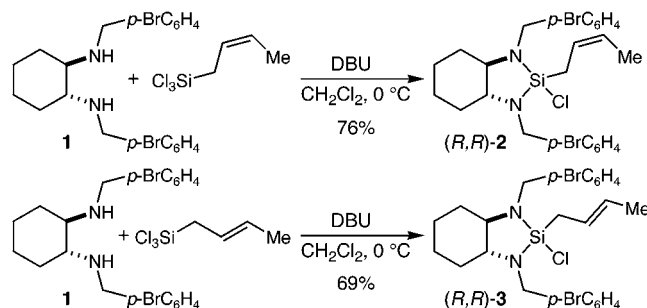
tigate whether the concept could be extended to crotylation. Beyond this question, however, we also targeted easily prepared, storable, crystalline solid reagents that would react with aldehydes with excellent diastereo- and enantioselectivities.

The known *cis*- and *trans*-crotyltrichlorosilanes⁵ were reacted with diamine **1** in the presence of 2 equiv of 1,8-

(4) (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, 124, 7920–7921. (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, 42, 946–948. (c) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, 125, 9596–9597. (d) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, 126, 5686–5687.

diazabicyclo[5.4.0]undec-7-ene (DBU) to give reagents **2** and **3** (Scheme 2). We have been able to develop this procedure

Scheme 2



such that it may be easily carried out on large (e.g., ~30 g) scale, with isolation of the reagents accomplished by simple crystallization. We note that this is a slightly modified, and improved, version of our previously reported method^{4b} for the synthesis of the allyl reagent. For all three reagents, the procedure reported here should be considered the method of choice.

A survey of the performance of reagent **2** was carried out with a variety of aliphatic, aromatic, and α,β -unsaturated aldehydes (Table 1). In every case, the *syn* diastereomer was

Table 1. *Syn*-Selective Aldehyde Crotylation with (*R,R*)-**2**

entry	R	yield (%)	ee ^a (%)
1	PhCH ₂ CH ₂	83	97
2	(CH ₃) ₂ CHCH ₂	70	96
3	Cy	67	97
4	BnOCH ₂	82	96
5	PMBOCH ₂ CH ₂	73	96
6	Ph	67	95
7	<i>p</i> -CF ₃ C ₆ H ₄	61	96
8	(<i>E</i>)-PhCH=CH	67	95

^a Enantiomeric excess determined by chiral GLC or HPLC.

produced with at least good (>15:1), and in most cases excellent (>25:1), diastereoselectivity. The yields were generally good, although it was observed that the yields with aromatic and α,β -unsaturated aldehydes tend to be lower than with aliphatic aldehydes. Pivalaldehyde was not successfully

crotylated by reagent **2**, establishing that the reagent has limited tolerance for steric hindrance. Notwithstanding these caveats, reagent **2** is a highly effective and enantioselective reagent that may be prepared in bulk and employed using trivial experimental conditions.

A survey of the performance of reagent **3** was then carried out with the same set of aliphatic, aromatic, and α,β -unsaturated aldehydes (Table 2). In every case, the *anti*

Table 2. *Anti*-Selective Aldehyde Crotylation with (*R,R*)-**3**

entry	R	yield (%)	ee ^a (%)
1	PhCH ₂ CH ₂	81	98
2	(CH ₃) ₂ CHCH ₂	71	97
3	Cy	68	97
4	BnOCH ₂	83	99
5	PMBOCH ₂ CH ₂	82	99
6	Ph	54	93
7	<i>p</i> -CF ₃ C ₆ H ₄	60	96
8	(<i>E</i>)-PhCH=CH	52	94

^a Enantiomeric excess determined by chiral GLC or HPLC.

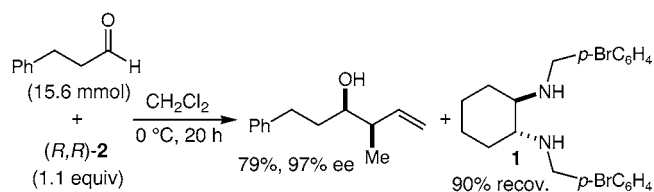
diastereomer was produced with at least good (>15:1), and in most cases excellent (>25:1), diastereoselectivity. As was observed with reagent **2**, the yields were generally good, although the yields with aromatic and α,β -unsaturated aldehydes tend to be somewhat lower than with aliphatic aldehydes. Also as was observed with reagent **2**, reagent **3** was found to be incompetent to crotylate very sterically hindered aldehydes such as pivalaldehyde. These caveats aside, reagent **3** is a highly effective and enantioselective reagent that may be prepared in bulk and employed using trivial experimental conditions.

Reagents **2** and **3** are moisture-sensitive, and care must be taken to exclude moisture if they are stored for any length of time. We have found that they possess unlimited shelf life if stored in an inert atmosphere glovebox. In dry environments, they may be handled in air, but repeated exposure to air does cause some degradation over time.

The choice of *p*-bromobenzyl groups for the diamine substituents was guided not by enantioselectivity (other groups provide similar levels of selectivity) but by the fact that they (uniquely, among the groups screened) confer the much desired property of crystallinity on reagents **2** and **3**. This crystallinity comes at a price, however, in that the bromine atoms result in reagents of high molecular weight (569). This raises reasonable concerns about atom economy, and it was therefore desirable to establish that the diamine controller could be readily recovered in high yield. The reaction of reagent **2** with dihydrocinnamaldehyde (15.6 mmol) was carried out under the standard conditions (Scheme

(5) (a) Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* **1974**, *30*, 2143–2146. (b) Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1–C3. (c) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099–1102. (d) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513–3526.

Scheme 3



3). Following chromatographic purification of the product, the column was simply flushed with EtOAc/hexanes/Et₃N (1:1:0.1) to provide recovered diamine **1** in 90% yield.

We have developed the *cis*- and *trans*-crotylsilane reagents **2** and **3** and demonstrated their use in highly enantioselective *syn*- and *anti*-selective aldehyde crotylation reactions, respectively. The reagents are easily prepared in bulk and are storable crystalline solids, the crotylation reactions are experimentally trivial, and the chiral diamine controller may

be easily recovered in high yield. Current efforts are focused on improving the efficiency and scope of the reaction with sterically hindered aldehydes and on the discovery of lower molecular weight—but still crystalline solid—variants of these reagents.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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