Asymmetric Crotylation Reactions on Solid Support: Synthesis of Stereochemically Well-Defined Polypropionate-Like Subunits

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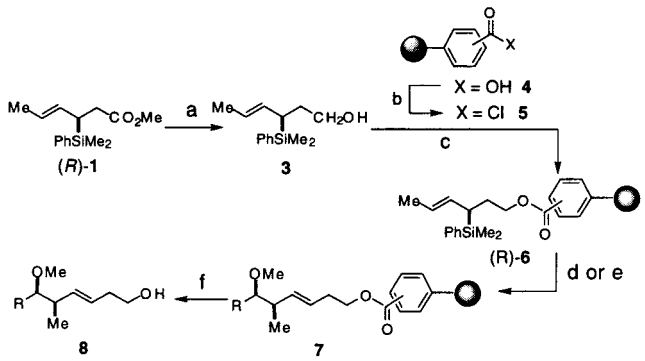
Received August 15, 1997

Polymer-supported synthesis has rapidly emerged as an important strategy in synthetic organic chemistry. This notion is supported by the large body of literature associated with polymer-supported reactions, which are aimed at generating libraries of molecularly diverse compounds for biological evaluation in either a lead discovery or an optimization process.[1] However, methods for stereoselective bond construction on solid support remain highly underdeveloped.[2,3] Our interest in this area is to extend our asymmetric crotylation bond construction methodology[4] to a solid phase format to achieve the synthesis of stereochemically well-defined small molecules. Such bond formation methodology holds enormous potential in constructing stereochemically well-defined biopolymer-like molecules and polypropionate-like subunits on solid support.

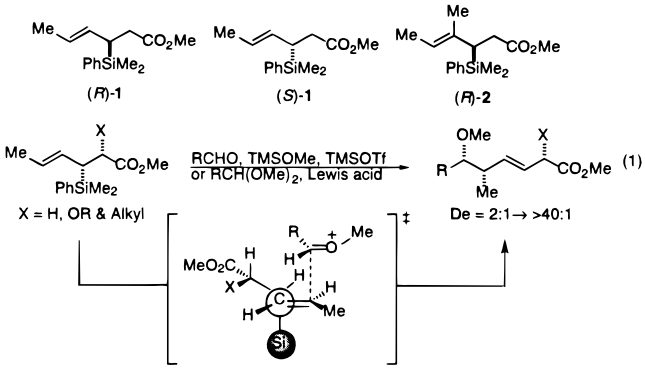
The purpose of this paper is to report the preliminary results of our investigation concerning the development of chiral (*E*)-crotylsilane-based bond construction methodology on solid support. We have already established that chiral crotylsilane reagents **1** and **2** are capable of providing excellent levels of diastereo- and enantioselectivity in condensation reactions with various acetals and aldehydes in solution phase.[4] The reaction of (*E*)-crotylsilanes with achiral/chiral acetals and aldehydes (through *in situ* generated oxocarbenium ions) exhibit *syn*-selectivity in homoallylic ether generation.[5] Mechanistic considerations have lead us to conclude that the silane reagents may be ideally suited for asymmetric synthesis on solid phase. Equation 1 illustrates these reactions with their accompanying transition state, which may be used to explain the facial bias of the silane reagents.

In our first series of experiments, the asymmetric crotylation reaction was performed with polymer-supported chiral silane reagents. The preparation of reagent **6** was initiated with the $LiAlH_4$ reduction of chiral silane reagent (*R*)-**1**[6] to primary alcohol **3**,[7] which was then coupled to the carboxylated polystyrene **4** through the corresponding acid chloride **5** to afford the immobilized chiral (*E*)-crotylsilane reagent (*R*)-**6** with greater than 90% loading yield (Scheme 1).

Scheme 1



(a) $LiAlH_4$, THF, 100%; (b) $(COCl)_2$, benzene, reflux, 12 h; (c) Et_3N, DMAP, CH_2Cl_2, 90~95% (b) and (c); (d) Acetal, TMSOTf, CH_2Cl_2, -78 → -55 °C, 72 h; (e) Aldehyde, TMSOMe, TMSOTf, CH_2Cl_2, -78 → -55 °C, 72 h; (f) K_2CO_3, THF/MeOH (2:1), r.t., 16 h.



In order to evaluate the reactivity and stereoselectivity of the polymer-supported silane reagent in the asymmetric crotylation reaction, a range of aryl and alkyl acetals were surveyed. Silane reagent (*R*)-**6** when combined with excess acetal in the presence of trimethylsilyl triflate (TMSOTf) at low temperature afforded the polymer-supported homoallylic ether **7**. Linker cleavage was achieved by base hydrolysis (K_2CO_3, THF/MeOH) to provide the functionalized homoallylic ether **8**. The important results of this study in the construction of homoallylic ethers are summarized in Table 1 (**8a**−**f**).[8] The crotylation reactions of (*E*)-crotylsilanes with aldehydes via reaction with *in situ* generated oxocarbenium ions[9] were also successfully performed with the immobilized silane reagent **6**. In this three-component reaction, immobilized silane reagent **6** with excess aldehyde and methoxytrimethylsilane (TMSOMe) in CH_2Cl_2 was treated with TMSOTf under similar conditions as those used for the acetal reactions to provide functionalized homoallylic ethers **8g**−**i** with high yield and diastereo/enantioselectivity (Scheme 1). The results of this reaction are summarized in Table 1. The ratio of the *syn*- to *anti*-adduct was measured by ^1H NMR analysis of the crude product **8** after linker cleavage with the diastereoselectivity ranging from 7:1 to 30:1 (*syn*/*anti*).[10] The purity of

(1) For reviews, see: (a) Moos, W. H.; Green, G. D.; Pavia, M. R. *Annu. Rep. Med. Chem.* **1993**, *28*, 315−324. (b) Thompsom, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527−4554. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643−5678. (d) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−1401.

(2) For recent reports concerning aldol reactions on solid support without emphasizing diastereoselection, see: (a) Kobayashi, S.; Hachiya, I.; Yasuda, M. *Tetrahedron Lett.* **1996**, *37*, 5569−5572. (b) Kurth, M. J.; Randall, L. A. A.; Chen, C.; Melander, C.; Miller, R. B. *J. Org. Chem.* **1994**, *59*, 5862−5864. For examples of asymmetric aldol reactions on solid support, see: (c) Reggelin, M.; Brenig, V. *Tetrahedron Lett.* **1996**, *37*, 8651−6852. (d) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabla, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268−272.

(3) For recent reports concerning other stereoselective reactions on solid support, see: (a) Reference 1c. (b) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724−8725. (c) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586−1587.

(4) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594−6600. (b) Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755−5758. (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.

(5) Our studies concerning the reactions of (*E*)-crotylsilane with achiral and chiral acetals and aldehydes (through *in situ* generated oxocarbenium ions) show universal *syn*-selectivity in homoallylic ether generation. For examples of chiral acetals/aldehydes see: (a) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587−10588. (b) Beresis, R. T. Ph.D. Thesis, Boston University, 1997; Chapter II.

(6) For the preparation of (*R*)- and (*S*)-(*E*)-crotylsilane reagent **1**, see: (a) Panek, J. S.; Yang, M. G.; Solomon, J. S. *J. Org. Chem.* **1993**, *58*, 1003−1010. (b) Beresis, R. T.; Solomon, J. S.; Yang, M. J.; Jain, N. F.; Panek, J. S. *Org. Synth.* In press.

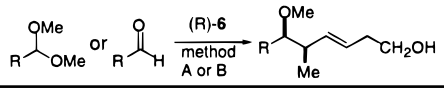
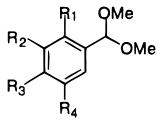
(7) Panek, J. S.; Garbaccio, R. M.; Jain, N. F. *Tetrahedron Lett.* **1994**, *35*, 6453−6456.

(8) Satisfactory spectroscopic data (^1H NMR, ^{13}C NMR, CIMS, CIHRMS, and IR data) were obtained for all new compounds. Ratios of diastereomers were determined by ^1H NMR analysis.

(9) Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790−5792.

S0002-7863(97)02877-1 CCC: $14.00

Table 1. Reactions of Polymer-Supported (*E*)-Crotylsilane Reagent (*R*)-**6** with Acetals and Aldehydes

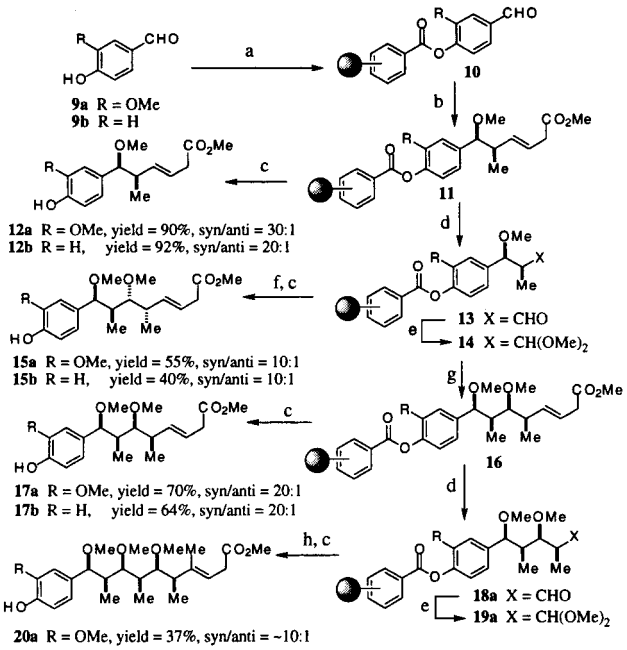
Acetal/Aldehyde	Method	Major Diastereomer	Yield[c]	syn/anti[d] selectivity
				
	A	**8a** R_1, R_2, R_3, R_4 = H	79%	20:1
	A	**8b** R_1, R_4 = OMe; R_2 = NO_2, R_3 = H	87%	20:1
	A	**8c** R_1, R_2 = OMe; R_3, R_4 = H	87%	30:1
	A	**8d** R_1, R_2, R4 = H; R_3 = Cl	90%	15:1
	A	**8e** R = $PhCH_2$	74%	7:1
	A	**8f** R = $BnOCH_2CH_2$	70%	7:1
	B	**8g** R = $(CH_3)_2CH$	87%	9:1
	B	**8h** R = $(CH_3)_3C$	92%	30:1
	B	**8i** R = cyclohexyl	90%	30:1

Method A: Silane **6**, acetal (2 equiv), TMSOTf (1 equiv), CH_2Cl_2, −78 → −55 °C, 72 h. Method B: Silane **6**, aldehyde (2 equiv), TMSOMe (2 equiv), TMSOTf (1 equiv), CH_2Cl_2, −78 → −55 °C, 72 h. [c] The yield is based on the initial loading level of carboxylic acid on the polymer support (4 steps overall). [d] The ratio is determined by ^{1}H NMR (400 MHz) analysis of the crude products.

the addition products **8** was also measured by ^{1}H NMR analysis to be greater than 90% (*syn* + *anti*). The yields reported for the four-step process were based on the initial loading level of carboxylic acid on the polymer support **4**. The results show that solid phase reactions gave similar or higher (for **8a**, *syn/anti* is 20:1 in solid phase reaction and 13:1 in solution phase reaction[4a]) level of diastereoselectivity compared to the solution phase reactions.

Gratifyingly, we have successfully extended this methodology to the synthesis of polypropionate-like subunits through an iterative crotylation sequence (Scheme 2). Aldehydes **9** were loaded on to the polymer support **5** through an ester linkage. The polymer-supported aldehyde **10** with excess TMSOMe and chiral silane reagent (*R*)-**1** in CH_2Cl_2 was treated with TMSOTf at low temperature to afford resin-bound homoallylic ether **11**. The expected homoallylic ether **12** could be hydrolytically cleaved from the polymer support (K_2CO_3, THF/MeOH) in good yield and high diastereoselectivity (Scheme 2). To perform the iterative crotylation reaction, polymer-supported homoallylic ether **11** was subjected to ozonolysis to generate the chiral aldehyde **13**. A two-step sequence which included the formation of acetal **14** from aldehyde **13** [cat. pyridinium *p*-toluenesulfonate (PPTS), $CH(OMe)_3$][11] followed by the crotylation reaction with silane reagents (*S*)-**1** or (*R*)-**1** in the presence of

Scheme 2



(a) Resin **5**, Et_3N, DMAP, CH_2Cl_2, rt; (b) Silane (*R*)-**1**, TMSOMe, TMSOTf, CH_2Cl_2, -78 → -55 °C, 72 h; (c) K_2CO_3, THF/MeOH 2:1, rt, 16 h; (d) O_3, CH_2Cl_2/MeOH 3:1, Me_2S, -78 °C to rt, 16 h; (e) $CH(OMe)_3$, PPTS, CH_2Cl_2, r.t.; (f) silane (*S*)-**1**, BF_3•Et_2O, CH_2Cl_2, -30 → -20 °C, 36 h; (g) Silane (*R*)-**1**, BF_3•Et_2O, CH_2Cl_2, -30 → -20 °C, 36 h; (h) Silane (*R*)-**2**, BF_3•Et_2O, CH_2Cl_2, -15 → −10 °C, 36 h.

BF_3·OEt_2 gave **15** or **17** after cleavage from the polymer support. In order to conduct the third crotylation, the double bond of the resin bound homoallylic ether **16a** was oxidatively cleaved (O_3, Me_2S, CH_2Cl_2/MeOH). The resulting resin bound aldehyde **18a** was then transformed to the dimethyl acetal **19a**. This material was mixed with silane reagent (*R*)-**2**[12] and treated with BF_3·OEt_2 at low temperature, followed by linker cleavage (K_2CO_3, THF/MeOH), to afford the final product **20a**. It is worth noting that this compound contains three propionate units and six stereogenic centers, and the overall yield is 37% for 10 steps (based on the initial loading level of carboxylic acid on the polystyrene support **4**).

In conclusion, we have successfully applied the chiral (*E*)-crotylsilane reagent-based asymmetric crotylation reaction in a solid phase format. The reaction provides functionalized chiral homoallylic ethers with high yield and diastereoselectivity. A new and useful procedure has been developed for the preparation of stereochemically well-defined polypropionate-like subunits on solid support. The methodology shall be a powerful tool in constructing complex molecules on solid support.

Acknowledgment. Financial suppport was obtained from the Community Technology Fund of Boston University.

Supporting Information Available: General experimental procedure and spectral data for all intermediates and final products (56 pages). See any current masthead page for ordering and Internet access instructions.

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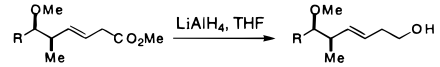
(10) The *syn/anti* ratio refers to the stereochemical relationship of the newly formed C−C bond. The stereochemistry was assigned by correlation with authentic material derived from solution phase chemistry: For example, the homoallylic ethers reported in ref 4a and 9 were reduced with $LiAlH_4$ to their primary alcohols, which had identical spectroscopic properties with the products from the solid phase reactions.



From solution phase reactions reported in ref 4a and 9 — Identical with the products from solid phase reactions

(11) No change of the *syn/anti* ratio was observed by ^{1}H NMR analysis in the acetalization step under the described reaction conditions.

(12) Jain, N. F.; Cirillo, P. F.; Shaus, J. V.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8723−8726.