

Facile enantioselective synthesis of a key homoallylic alcohol building block for polyketide synthesis: TiF₄-BINOL catalyzed allylsilylation with allyl trimethylsilane

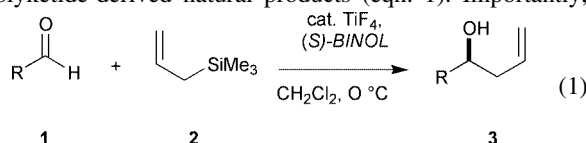
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The titanium fluoride-BINOL catalyzed asymmetric allylsilylation of α,α -disubstituted aldehydes provides facile access to highly functionalized, chiral building blocks, which following simple recrystallization affords a key versatile starting material for polyketide synthesis in 96% ee.

Polyketides constitute a large class of naturally occurring structures with diverse, biological activities of importance to human medicine. As a consequence of the common biosynthetic pathways through which these structures are assembled there are often a number of recurring structural patterns in the form of 1,3-dicarbonyls, 1,3-hydroxy carbonyls, and 1,3-diols derived from acetate, propionate, or isobutyrate. Access to fragments that function as building blocks for the synthesis of these structures has resulted in many useful asymmetric synthetic enantioselective and diastereoselective methods.¹ The majority of these address the construction of acetate and propionate derived subunits, while many fewer are available for the preparation of isobutyrate derived subunits. We have recently reported the enantioselective TiF₄-BINOL catalyzed allylsilylation of aldehydes employing allyltrimethylsilane to afford adducts in useful selectivities and yields.² In our initial communication, the catalytic, enantioselective allylsilylation of ⁱPr₃Si-protected 2,2-dimethyl-3-hydroxypropanal furnished the adduct in 93% yield, albeit in only 84% ee. The importance of such building blocks led us to initiate a program of study aimed at developing methods that would provide for their ready access. Herein we report investigations of this process furnishing fragments possessing the isobutyrate structural motif found in polyketide-derived natural products (eqn. 1). Importantly,



the approach described herein furnishes optically active, crystalline adducts from commercially available reagents, and as such should find use in the ongoing studies towards the development of efficient routes and strategies to polyketide-derived natural products, such as aplasmomycin³ byrostatin⁴ epothilones,⁵ mycalamides,⁶ and boromycin.⁷

Among the critical advantages offered by the allylation reaction we have developed are: (1) the commercial availability of the ligand ((*R*)- or (*S*)-BINOL), metal (TiF₄), and allyltrimethylsilane; (2) the single step, *in situ*, preparation of the active catalyst from BINOL, TiF₄; (3) the low toxicity of allylsilane as compared to the alternative and often utilized allylstannane reagents; and (4) the volumetric efficiency of the process. In our preliminary laboratory screening of substrate scope for this transformation it was noted that the method was particularly effective for the enantioselective allylation of hindered, aliphatic non-enolizable aldehydes, affording adducts consistently in useful levels of enantiopurity.

The specific use of protected 2,2-dimethyl-3-hydroxypropionaldehyde in the allylation reaction provides access to the

recurring structural isobutyrate motif found in polyketide-derived natural products. In an effort to identify the appropriate protecting group strategy that would provide crystalline material in high optical purity, we prepared a number of aldehyde substrates possessing a variety of protecting groups. Preparation of the necessary aldehydes was readily achieved by monoprotection of the 2,2-dimethylpropane-1,3-diol, an inexpensive commodity chemical, followed by oxidation with either catalytic TEMPO⁸ or catalytic TPAP.⁹

The allylation reaction of these substrates afforded adducts in 55–97% yield and 84–91% ee as shown in eqn. (2) and Table 1.^{10,11} It is interesting to note that *O*-silyl, *O*-benzyl, and ester protecting groups all proved to be stable to and compatible with the allylation reaction. Also noteworthy is the ability to utilize both acetate (entry 6) and nitro (entry 5) moieties without complication by potentially competing reactions. Of the various adducts isolated, the 2-naphthoate protected adduct **5g** was isolated as a white crystalline solid in 91% ee and in 97% yield, following desilylation of the adduct. Importantly, after simple recrystallization, product was isolated enriched to 96% ee, as determined by chiral HPLC analysis. Additionally, the same reaction could be carried out with 5 mol% of the titanium catalyst on an 80 mmol scale, with the product isolated in 92% ee and in 72% yield.

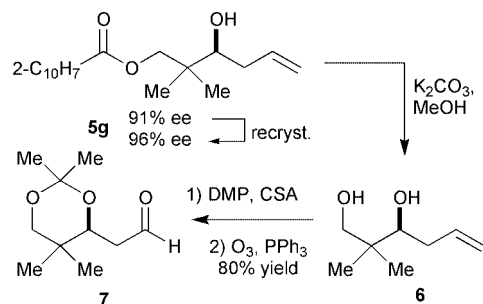


In an effort to demonstrate the versatility of these adducts, we have carried out a number of facile, high yielding transformations. Hydrolysis of the naphthoate esters with potassium carbonate in methanol led to diol **6**, which following protection

Table 1 TiF₄-BINOL catalyzed allyl silylation of **5a–g**

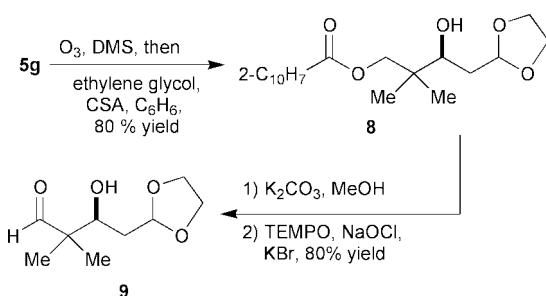
Entry	Substrate	Product	% ee	Yield
1	R = ⁱ Pr ₃ Si 4a	5a	84% ^a	93%
2	R = ^t BuMe ₂ Si 4b	5b	86% ^a	48%
3	R = PhCH ₂ 4c	5c	89% ^b	55%
4	R = PhCO 4d	5d	88% ^a	85%
5	R = <i>p</i> -NO ₂ C ₆ H ₄ CH ₂ 4e	5e	88% ^c	69%
6	R = MeCO 4f	5f	90% ^c	85%
7	R = 2-Naphthoyl 4g	5g	91% ^c (96%) ^d	97%

^a Determined by GC analysis of the Mosher ester. ^b Determined by ¹H NMR analysis of the Mosher ester. ^c Determined by chiral HPLC analysis (Chiradex OD). ^d Following recrystallization.



Scheme 1 Elaboration of adduct **6g** to diol **7**.

as the corresponding acetone and ozonolytic cleavage of the olefin afforded chiral aldehyde **7** in 80% overall yield (Scheme 1). Alternatively, ozonolysis could be performed directly on the allyl adduct and the resulting aldehyde protected *in situ* as dioxolane **8** in 80% yield. Following saponification and selective oxidation of the primary hydroxy moiety, aldehyde **9** was obtained in 80% yield (Scheme 2).



Scheme 2 Elaboration of adduct **6g** to aldehyde **9**.

In summary, the TiF_4 -BINOL catalyzed allylsilylation of protected aldehydes provides facile access to highly functionalized building blocks in high enantiopurity. These results demonstrate the possibility of employing this reaction for the preparation of significant quantities of chiral starting materials and attests to the tolerance of this catalyst towards a number of potentially reactive functionalities. Importantly, the synthesis study described herein furnishes optically active, crystalline adducts from commercially available reagents, and as such should find applications in the development of increasingly efficient strategies to polyketide-derived natural products.

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Notes and references

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- Experimental procedure for naphthalene-2-carboxylic acid (3*S*)-hydroxy-2,2-dimethylhex-5-enyl ester. To a suspension of TiF_4 (0.25 g, 2.0 mmol, 5.0 mol%) in 10 ml CH_3CN was added (*S*)-BINOL (1.15 g, 4.00 mmol, 10.0 mol%) and the mixture stirred 15 min before the solvent was removed under reduced pressure. After 10 min at 1.0 torr, the residue was dissolved in 10 ml CH_2Cl_2 and cooled to 0 °C. To this solution was added allyltrimethylsilane (12.7 ml, 80.0 mmol, 2.00 equiv.) and stirred 1 h to give a dark precipitate to which aldehyde **4g** (10.3 g, 40.0 mmol, 1.00 equiv.) was added neat in two portion to give a dark red-orange solution. This solution was allowed to stir 5 days at 0 °C at which time analysis by ^1H NMR showed the reaction to be complete. The reaction mixture was diluted with 2:1 pentane:ether (500 ml), filtered over silica gel and eluted with 2:1 pentane:Et₂O (500 ml). Following rotary evaporation, the resulting residue was treated with 5:95:1.5 HF:MeCN:H₂O (80 ml) for 0.5 h, dissolved in Et₂O (200 ml), washed with 2 M NaOH (2 × 50 ml), brine (100 ml), dried over Na_2SO_4 , and concentrated to give a yellow oil (11.65 g, 98% yield). Purification by crystallization from hexanes provided **5g** (8.30 g, 72% yield) as a white solid in 92% ee. (Determined by chiral HPLC analysis Chiraldex OD), 98:2 hexanes-*i*PrOH. $[\alpha]_D^{25}$ (c 0.950, CHCl_3) = +11.9; mp 46.5 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.61 (s, 1H), 8.06 (dd, J = 8.7, 1.6, 1H), 7.97 (d, J = 7.78, 1H), 7.92 (d, J = 8.7, 1H), 7.60–7.53 (m, 2H), 5.97–5.83 (m, 1H), 5.19 (d, J = 8.6, 1H), 5.14 (s, 1H), 4.48 (d, J = 10.9, 1H), 4.13 (d, J = 10.9, 1H), 3.59 (td, J = 8.4, 3.4, 1H), 2.45–2.39 (m, 1H), 2.20 (d, J = 3.4, 1H), 2.17–2.12 (m, 1H), 1.10 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): 167.0, 136.1, 135.6, 132.5, 131.1, 129.4, 128.3, 128.2, 127.8, 127.5, 126.7, 125.2, 118.0, 74.1, 71.2, 38.7, 36.2, 21.8, 19.4; IR (KBr) 3493, 3068, 2971, 2892, 1683, 1475, 1373, 1274, 1230, 1198, 905, 776; EI-MS: 298.1 (M)⁺; Anal. Calcd. for (C₁₉H₂₂O₃) C, 76.48; H, 7.43%; found, C, 76.64; H, 7.26%.
- At the current level of development the process works optimally with non-enolizable aldehydes. Enolizable aldehydes furnish adducts, albeit in reduced yields and selectivities.