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Catalytic Asymmetric Assembly of Stereodefined Propionate Units: An Enantioselective Total Synthesis of (−)-Pironetin

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The importance of aldol-based bond constructions in modern asymmetric synthesis has generated considerable interest in developing catalytic asymmetric reaction variants. Catalyzed aldol additions eliminate the requirement for installing and recycling, or destroying, a chiral auxiliary used to affect asymmetric bond constructions. A number of highly successful catalytic asymmetric aldol addition reactions have been developed involving both direct aldol processes and additions of pregenerated latent enolates.[1] However, examples of these catalytic asymmetric aldol reactions being used in an iterative fashion to assemble repeating propionate or acetate networks are rare.[2] Herein, we describe the utility of alkaloid-catalyzed acyl halide−aldehyde cyclocondensation (AAC) reactions for the catalytic asymmetric synthesis of extended propionate networks (Figure 1).[3] The utility of this reaction technology in synthesis activities is exemplified in a catalytic asymmetric total synthesis of (−)-pironetin.

As one solution to catalytic asymmetric aldol additions, we developed acyl halide−aldehyde cyclocondensations that provide enantioenriched β-lactones **1** as *syn* propionate aldol equivalents.[4] Extending these reactions to AAC-based strategies for assembling repeating propionate units was predicated on engaging the enantioenriched β-lactone-derived *syn* aldehyde **2** in further AAC homologation (Figure 1). Ensuing AAC reactions of **2** with correct selection of alkaloid catalyst (**3** or **4**) would then deliver the stereochemically complementary propionate dimers **5** or **6**. A central issue to be addressed in this context would be the catalyst's ability to reliably and predictably complement or override the intrinsic facial bias expressed by the chiral aldehyde substrates.[5]

Iterative AAC homologation of α-substituted aldehyde **7** provided a representative test sequence for evaluating this polypropionate synthesis design (Scheme 1). Reacting (*S*) aldehyde **7** with propionyl chloride using 10 mol % of **4a** as catalyst (2 equiv of LiI, ^{i}Pr$_2$NEt) afforded the anticipated *syn*,*anti* β-lactone **8** in 78% yield (*syn*,*anti*:Σ_{others} = 92:8).[6] Reformatting lactone **8** as the corresponding *syn* aldehyde **9** proceeded by amine-mediated lactone ring opening, alcohol silylation, and Weinreb amide reduction (55% yield for three steps). Ensuing TMS*Qd* (*O*-trimethylsilylquinidine; **3a**)-catalyzed AAC homologation of **9** afforded β-lactone **10** (94% de, 84%) as a surrogate for the corresponding *syn*,*anti*,*syn* propionate trimer.[7] The magnitude of double diastereoselection operative in these reactions became apparent upon AAC homologation of **9** employing the pseudoenantiomeric quinine-derived catalyst **4b** (10 mol %, EtCOCl, ^{i}Pr$_2$NEt, 3 equiv of LiI) that afforded lactone **11** with excellent diastereoselection albeit with the unanticipated C_2-C_3/C_3-C_4 *anti*,*anti* stereochemistry. Our failure to isolate the all-*syn* lactone expected from catalyst-dominated stereocontrol suggested that mismatched substrate/catalyst chirality was responsible for the *anti* diastereoselection across the β-lactone, an observation previously unprecedented for the AAC reactions. Nevertheless, this observation suggested a strategy for realizing *syn*- or *anti*-selective-catalyzed aldol additions via the AAC reaction design.

Examining the generality of the AAC-based propionate synthesis revealed the conditions under which matched and mismatched diastereoselection was manifested. Under the ostensibly matched AAC reaction conditions, the β-lactone-derived *syn* aldehydes **12a**/**b**

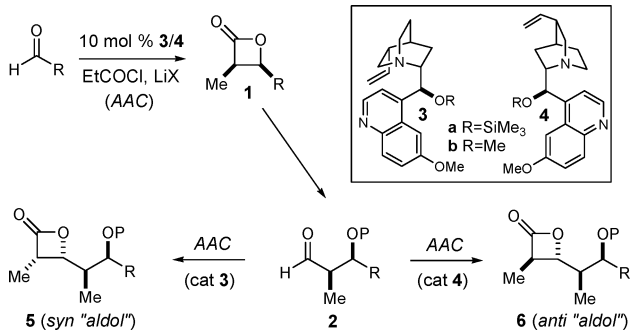
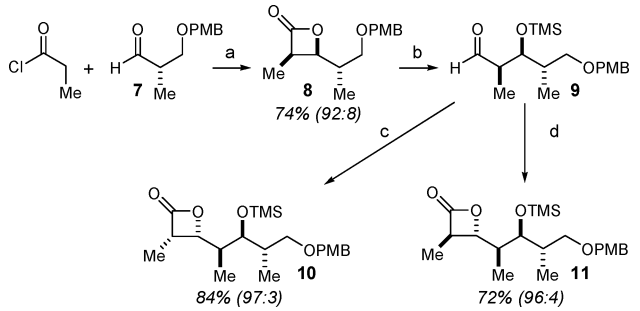


Figure 1. Iterative application of asymmetric catalytic AAC reactions.

Scheme 1 [a]



[a] Conditions: (a) 10 mol % of **4a**, $LiClO_4$, ^{i}Pr$_2$NEt, −78 °C (74%); (b) (i) (MeO)MeNH$_2$Cl, Me$_2$AlCl (80%); (ii) TMSOTf, 2,6-lutidine (86%); (iii) ^{i}Bu$_2$AlH, THF (80%); (c) 10 mol % of **3a**, LiI, ^{i}Pr$_2$NEt (84%); (d) 10 mol % of **4b**, LiI, ^{i}Pr$_2$NEt (72%).

delivered the anticipated *syn*,*anti*,*syn* β-lactones **13a**/**b** with complete stereocontrol (Table 1, entries a and b). The mismatched quinine-catalyzed AAC homologations of *syn* aldehydes **12a**/**c** faithfully produced the *anti*,*anti*,*syn* β-lactones **14a**/**c** with high diastereoselectivity (≥90% de) (entries c and d). Matched AAC homologation (quinine catalyst) of *anti* aldehyde **15** afforded the *syn*,*anti*,*anti* β-lactone **16** with equally high diastereoselection (entry e).[8] However, in contrast to the *syn* aldehyde electrophiles, the *anti* aldehyde **15** does not undergo the mismatched AAC reaction. To evaluate these reactions as potential conduits to extended propionate networks, the *syn*,*anti*,*syn* aldehyde **17**, obtained from β-lactone **13a**, was engaged in TMS*Qn* (*O*-trimethylsilylquinine; **4a**)-catalyzed (matched) cyclocondensation with propionyl chloride to afford the propionate trimer equivalent **18** as a single diastereomer (entry f, 79% yield).

A catalytic asymmetric total synthesis of (−)-pironetin (**19**) highlights this reaction technology's utility in the context of a representative polyketide-derived target.[9,10] The AAC-derived β-lactone **20** (99% ee, 89:11 *syn*:*anti*) was subjected to the three-step lactone-to-aldehyde conversion to afford *syn* aldehyde **21** (Scheme 2).[11] TMS*Qn*-catalyzed (matched) homologation of **21** then provided the *syn*,*anti*,*syn* β-lactone **22** (≥95% de). Lactone reduction to the corresponding diol preceded selective primary alcohol tosylation and installation of the C_9 methyl ether to afford the protected tetraol **23**. Tosylate substitution by Cu(I)-mediated allyl Grignard addition

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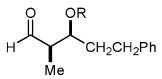
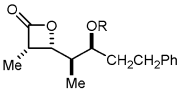
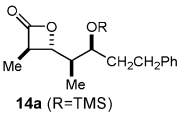
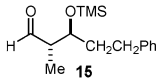
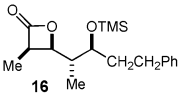
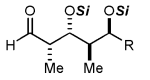
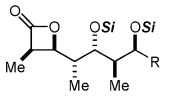
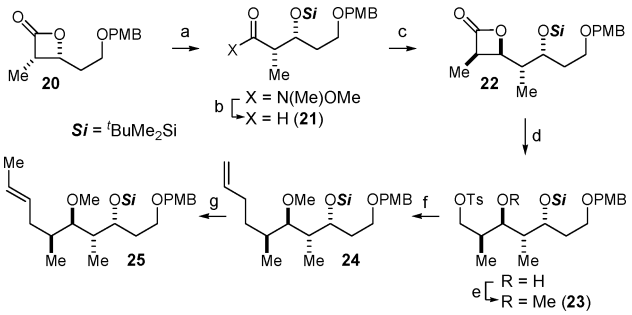
Table 1. Matched and Mismatched AAC Reactions

entry	aldehyde[a]	β-lactone[b]	% de (% yield)[c]
a	 **12a** (R=TMS)	 **13a** (R=TMS)	≥95 (83)
b	**12b** (R=Bn)	**13b** (R=Bn)	≥95 (78)
c	**12a**	 **14a** (R=TMS)	91 (81)
d	**12c** (R=PMB)	**14c** (R=PMB)	92 (81)
e	 **15**	 **16**	≥95 (81)
f	 **17** (***Si*** = TMS, R=CH_2CH_2Ph)	 **18**	≥95 (79)

[a] Catalyst (10 mol %) **3a**, entries a, b; **4a**, entries c−f. [b] Stereochemical assignments based on X-ray structure determinations of derivatives of **14c** and **16** and comparison of ^{1}H coupling constants. [c] Diastereomeric ratios determined by HPLC or ^{1}H NMR analysis of crude reaction mixtures.

Scheme 2 [a]



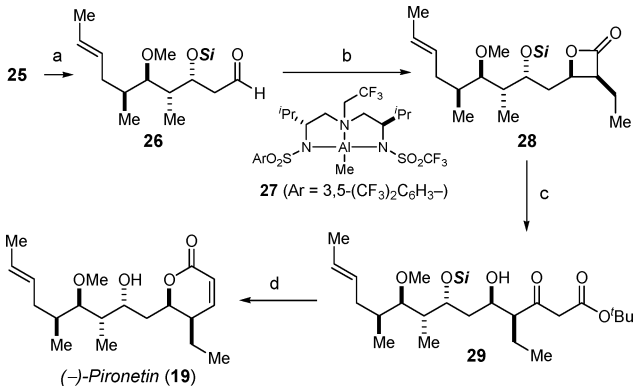
[a] Conditions: (a) (i) (MeO)MeNH$_2$Cl, Me$_2$AlCl; (ii) TBSCl, imidazole (97%); (b) ^{i}Bu$_2$AlH (96%); (c) 10 mol % of **4a**, EtCOCl, LiI, ^{i}Pr$_2$NEt (91%); (d) ^{i}Bu$_2$AlH, THF; (ii) TsCl, pyr (83%); (e) Me$_3$OBF$_4$, proton sponge (81%); (f) C$_3$H$_5$MgBr, CuBr (85%); (g) 2 mol % of Ir(PCy$_3$)$_3^+$, 50:1 CH_2Cl_2:acetone (98%).

provided the terminal alkene **24** with ensuing Ir(I)-catalyzed olefin isomerization delivering the requisite *E* propenyl unit in the complete C_5-C_{14} synthon **25**.[12]

From the C_5-C_{14} synthon **25**, completing the pironetin synthesis proceeded by routine alcohol deprotection and oxidation to give aldehyde **26** (Scheme 3). Engaging **26** in Lewis acid-catalyzed AAC homologation (50 mol % of **27**) employing butyryl bromide as a butanoate enolate equivalent afforded β-lactone **28** (≥95% de, 65% yield) possessing all of the (−)-pironetin stereocenters.[3b,13] β-Keto ester **29** emerged from ring opening **28** with the magnesium enolate of *tert*-butylacetate. Ketone reduction ($NaBH_4$) and reacting the resulting diol with TsOH elicited *tert*-butyl ester cleavage, lactonization, and dehydration to generate the requisite 2-pyranone unit, as well as silyl ether removal to directly furnish synthetic (−)-pironetin (**19**) (56% over two steps).

Alkaloid-catalyzed AAC reactions provide a uniform strategy for executing asymmetric *syn*- or *anti*-selective aldol additions on enantioenriched aldehyde substrates. Iterative application of these AAC reactions provides an entry to stereodefined polypropionate building blocks. The AAC-based catalytic asymmetric total synthesis of (−)-pironetin provides evidence for this methodology's utility in synthesis efforts directed toward polyketide-derived materials.

Scheme 3 [a]



[a] Conditions: (a) (i) DDQ, aq. CH_2Cl_2 (81%); (ii) Swern (88%); (b) ^{n}PrCOBr, ^{i}Pr$_2$NEt, 50 mol % of **27**, BTF, −25 °C (65%); (c) *t*-BuOAc, KHMDS then $MgBr_2$ (66%); (d) (i) $NaBH_4$, EtOH; (ii) TsOH, toluene, 110 °C (56% for two steps).

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Supporting Information Available: Experimental procedures, stereochemical proofs, and representative ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) α-Branched aldehydes generally require 1.5−3 equiv of lithium salt ($LiClO_4$ or LiI) for complete conversion. See ref 4.

(7) Control experiments confirmed that α-substituted aldehydes are not subject to epimerization under the AAC reaction conditions.

(8) For *anti* aldehyde substrates, a solvent system composed of 10:1 CH_2Cl_2/DMF provided superior reaction rates and yields as compared to the standard CH_2Cl_2/Et_2O system.

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(13) The alkaloid-catalyzed AAC variant failed for this transformation, a result attesting to the complementary nature of the Lewis acid- and alkaloid-catalyzed AAC reactions.

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