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Catalytic Asymmetric Propionate Aldol Reactions via Acyl Halide−Aldehyde Cyclocondensations

Scott G. Nelson* and Zhonghui Wan

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

sgnelson@pitt.edu

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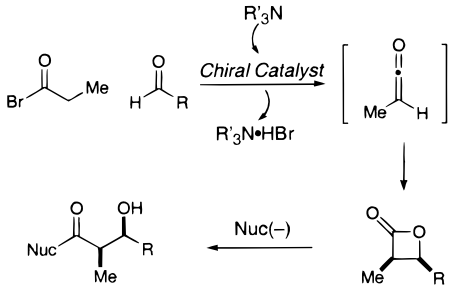
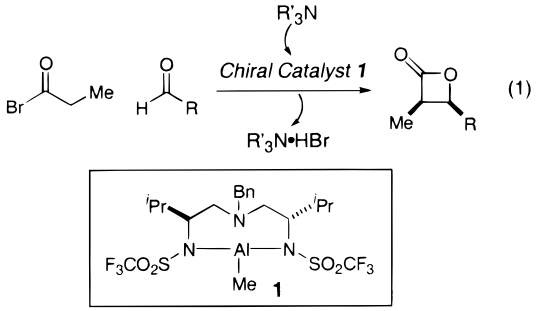
ABSTRACT



Catalyzed asymmetric acyl halide−aldehyde cyclocondensation (AAC) reactions afford highly enantiomerically enriched 3,4-disubstituted-2-oxetanones. These reactions constitute catalytic asymmetric propionate aldol additions. An optically active Al(III)-triamine complex (10 mol %) catalyzes the di(isopropyl)ethylamine-mediated cyclocondensation of propionyl bromide and a variety of aldehydes to afford *β*-lactone adducts with uniformly high enantioselection (90 → 98% ee), diastereoselection (74 → 98% de), and chemical yields (78−90%). Lactone ring opening reveals that the enantiomerically enriched *β*-lactones act as surrogates for *syn* propionate aldol adducts.

Asymmetric aldol bond constructions continue to be an essential tool for complex molecule synthesis.[1] Addressing the issues of cost and operational simplicity that pervade industrial-scale synthesis enterprises has generated significant impetus for developing catalyzed asymmetric variants of these important C−C bond-forming reactions. Reaction designs based on the catalyzed addition of latent enolate equivalents have provided a number of extremely successful solutions to this problem.[2] As an alternative to these Mukaiyama-type aldol reactions, reaction designs that integrate enolate generation and bond construction in the same catalytic cycle would impart further experimental simplification to these processes.[3] Catalyzed acyl halide−aldehyde cyclocondensation (AAC) reactions have recently been developed as equivalents of asymmetric acetate aldol additions by adhering to this reaction design principle.[4] Extending these reaction processes to the development of highly diastereo- and enantioselective propionate-type aldol bond constructions is described herein (eq 1).



Asymmetric propionate-type aldol additions must incorporate mechanisms for defining both relative and absolute stereocontrol during C−C bond construction. This constraint adds to the complexity associated with designing catalytic

(1) For an overview of a number of total syntheses incorporating asymmetric aldol bond constructions, see: (a) Mukaiyama, T. *Tetrahedron* **1999**, *55*, 8609−8670. (b) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44−122.

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asymmetric variants of these reactions. Prototypical aldol additions successfully relay enolate geometry to the relative stereochemistry at the two incipient stereogenic centers (Figure 1). The mechanism operative in the AAC reactions

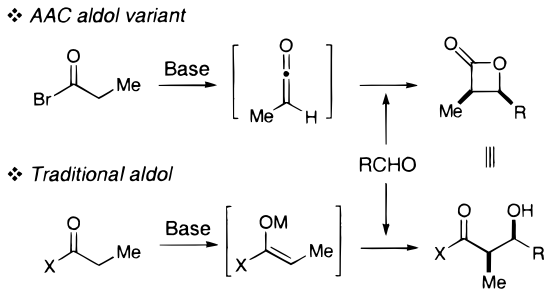
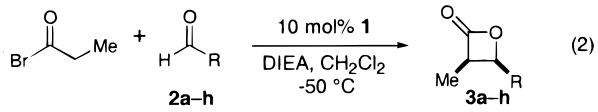


Figure 1. Strategies for propionate aldol bond constructions.

suggested that these processes were uniquely suited to addressing the issues of relative as well as absolute stereocontrol in developing stereoselective-catalyzed propionate aldol additions. Acyl halide−aldehyde reactions cast ketene generation as a surrogate for the enolization event common to prototypical aldol reactions with ensuing ketene−aldehyde cycloaddition representing the addition event.[5] The orbital requirements for concerted thermal ketene−aldehyde cycloaddition would ensure that substituted ketenes would afford the contrasteric *cis*-substituted 4-oxetanones, thereby providing the equivalent of a *syn*-selective propionate aldol.[6] The homology existing between the reaction transition states operative for substituted ketenes and ketene itself suggested that the optically active Al(III)-triamine catalyst **1** developed for catalyzed acetate aldol-type reactions would be equally effective in providing high levels of absolute stereocontrol in the propionate analogues. Constituting asymmetric aldol bond constructions in this fashion offered the additional advantage that the β-lactone nucleus provides a conduit to a variety of traditional aldol adducts, including ester and amide aldols, through nucleophilic ring opening.[7]

Propionyl bromide provides an effective propionate enolate equivalent under the catalytic asymmetric cyclocondensation reaction conditions using the Al(III)-triamine **1** as the reaction catalyst (eq 2).[8] Propionyl bromide undergoes cycloconden-



(2)

sation with benzyloxyacetaldehyde (**2a**) using 10 mol % of **1** and diisopropylethylamine (DIEA) to afford the *syn* propionate aldol equivalent masked as β-lactone **3a** with excellent absolute and good relative stereocontrol (94% ee, 88:12 *cis*:*trans*) (Table 1, entry a).[9] In addition to benzyloxyacetaldehyde, AAC reactions render a number of conjugated acetylenic aldehydes (**2b**−**f**) as effective substrates for the cyclocondensation reactions; α-methyl-β-alkynyl propiolactones are obtained with uniformly high enantio- and diastereoselection while accommodating a large degree of structural variation at the alkyne terminus (Table 1, entries b−h).[10] Ynal AAC reactions, therefore, provide convenient access to synthetically valuable optically active propargylic alcohol derivatives.[11]

Table 1. Asymmetric Propionyl Bromide−Aldehyde Cyclocondensation Reactions

entry	aldehyde **2** (R)[a]	% ee of **3**	*cis*:*trans*	% yield of **3**[d]
a	CH_2OBn	94	88:12	78
b	$C{\equiv}CCH_2OBn$	94	91:9	85
c	$C{\equiv}CCH_2CH_2OPMB$	90	87:13	86
d	$C{\equiv}CC_5H_{11}$[b]	93	98:2	85
e	$C{\equiv}CCMe_3$[c]	90	>99:1	90
f	$C{\equiv}CSiMe_3$[c]	93	>99:1	90
g	$C{\equiv}CPh$	91	>99:1	83
h	4-$(NO_2)C_6H_4$	>98	>99:1	90

[a] Stereoisomer ratios assayed by chiral HPLC (Chiralcel OD-H) unless otherwise indicated. [b] Stereoisomer ratios determined by chiral HPLC (Chiralcel OD-H) of the corresponding benzyl amide. [c] Stereoisomer ratios determined by chiral GC (Chiraldex G-TA). [d] Values are for purified materials.

(2) For recent asymmetric catalyzed additions of latent enolates, see: (a) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837−838. (b) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032−10039. (c) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685 and references therein. (d) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699 and references therein. For reviews, see: (e) ref 1a. (f) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389.

(3) For catalyzed asymmetric intermolecular aldol reactions, see: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. For other examples of catalytic asymmetric aldol-type reactions, see: (c) Shibasaki, M.; Sasi, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256 and references therein. (d) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.

(4) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743.

(5) Nelson, S. G.; Peelen, T. J.; Wan, Z. *Tetrahedron Lett.* **1999**, *40*, 6541−6543.

(6) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; VCH: Weinheim, 1970.

(7) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−459.

(8) Acid bromides are superior to acid chlorides as ketene precursors in the catalyzed AAC reactions.

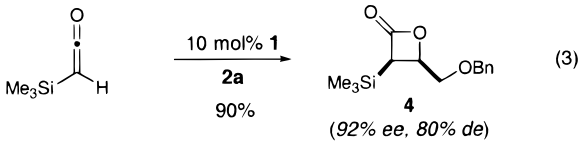
(9) **Typical experimental procedure:** under a N_2 atmosphere, to a solution of 58 mg of aluminum complex **1** (0.10 mmol) in 5 mL of CH_2Cl_2 at −50 °C was added 280 mL of di(isopropyl)ethylamine (1.6 mmol), 140 mL of propionyl bromide (1.5 mmol), and aldehyde (1.0 mmol) in succession via syringe. The reaction was stirred until complete as monitored by TLC (~2−72 h; typically 30 h). The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic portions were dried (Na_2SO_4) and concentrated, and the crude product mixture was purified by flash chromatography (hexanes:ethyl acetate) or by bulb-to-bulb distillation.

(10) The absolute and relative stereochemistry of β-lactone **3a** was established by conversion to the corresponding β-hydroxy acid (LiOH, 30% H_2O_2, THF−H_2O) and comparing the spectral and optical properties to those reported for the authentic material, see: Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171−7174. The stereochemistry of lactones **3b**−**h**, **4**, and **5** was assigned by analogy to this determination and to the stereochemical outcome of the analogous acetyl bromide AAC reactions. See ref 4.

Electron-deficient conjugated aromatic aldehydes are also effective electrophiles for the catalyzed AAC reactions. Cataylzed asymmetric AAC reaction yields had previously been below synthetically useful levels for aromatic aldehyde electrophiles due to the facile ionization of the C_{alkyl}−O bond.[12,13] Reasoning that inductive destabilization of the putative carbocation intermediate would render the derived β-lactones less susceptible to unwanted ionization, we explored 4-nitrobenzaldehyde as a suitable aromatic aldehyde substrate (Table 1, entry h). Indeed, 4-nitrobenzaldehyde (**2h**) undergoes clean cyclocondensation with propionyl bromide under the standard reaction conditions to afford the α-methyl-β-aryl β-lactone in high yield (90%, >98% ee).

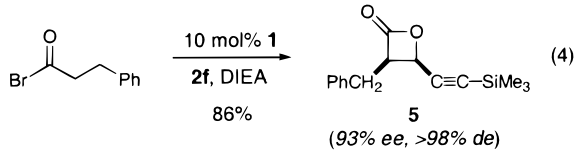
Propionyl bromide-based AAC reactions do not, however, exhibit the generality of the analogous acetyl bromide reactions. Aliphatic aldehydes or conjugated enals presently afford low reaction yields and variable levels of enantioselectivity. It appears that the Al(III)-triamine reaction catalyst **1** imposes stringent requirements on substrate structure and any deviation from these constraints, including increased steric bulk in the aldehyde electrophile, render the reaction inoperative.

Effective asymmetric cycloaddition of other substituted ketene derivatives can also be achieved under the catalyzed AAC reaction conditions. The catalyzed [2 + 2] cycloaddition of commercially available trimethylsilylketene and benzyloxyacetaldehyde (**2a**) affords α-trimethylsilyl-β-lactone **4** with enantioselectivity and diastereoselectivity paralleling that obtained for methylketene (92% ee, 90:10 *cis:trans*) (eq 3).[14] The potential for engaging other substituted



(3)

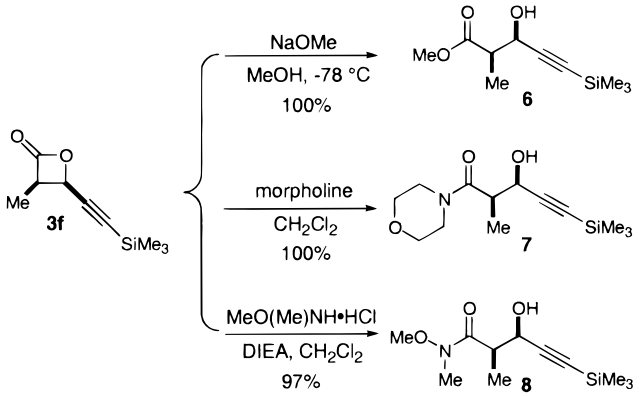
ketenes in the standard asymmetric AAC reactions was demonstrated using hydrocinammoyl bromide as the ketene precusor (eq 4); the benzyl ketene intermediate undergoes asymmetric cycloaddition with ynal **2f** to afford *cis* α-benzyl-substituted lactone **5** in 95% ee (>99:1 *cis:trans*, 86% yield).



(4)

Revealing the *cis*-3,4-disubstituted-2-oxetanones emerging from the AAC reactions as direct precursors to structurally diverse *syn* propionate aldol units exploits the reactivity of the β-lactone unit toward nucleophilic ring opening (Scheme 1). The *syn* ester aldol adduct **6** was obtained from the

Scheme 1 β-Lactone Ring-Opening Reactions



sodium methoxide-mediated ring opening of lactone **3f** at −78 °C (100%).[15] Secondary amines are also very effective in ring opening the optically active β-lactones, providing access to amide aldol adducts. Aldol synthon **3f** undergoes ring opening with morpholine (1.0 equiv) at ambient temperature in THF to afford the *syn* amide aldol adduct **7** (100%) with relative and absolute stereochemistry directly reflecting that of the lactone substrate.[16] The Weinreb amide-derived aldol adduct **8** was obtained from *N*,*O*-dimethylhydroxylamine-mediated opening of lactone **3f** (97%); the β-lactone electrophile is sufficiently reactive that amide formation is achieved with the amine free base and does not require the ubiquitous aluminum amide reagent.[17]

Catalyzed asymmetric AAC reactions successfully address the issues of relative and absolute stereochemical control in catalytic variants of crossed aldol addition reactions. The β-lactone aldol surrogates emerging from these reactions are obtained with high enantiomeric purity employing an operationally simple experimental procedure. The versatility of the enantiomerically enriched β-lactones is expected to render asymmetric AAC reactions as valuable reaction technology useful for asymmetric organic synthesis.

(11) For recent examples of asymmetric catalytic syntheses of optically active propargylic alcohols, see: (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (b) Tao, B.; Ruble, J. C.; Diego A. Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091−5092. (c) Frantz, D. E.; Roger Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807.

(12) Moyano, A.; Pericas, M. A.; Valenti, E. *J. Org. Chem.* **1989**, *54*, 573−582.

(13) Cyclocondensations employing aromatic aldehydes previously afforded cinnamic acid derivatives in good yield: Nelson, S. G.; Wan, Z. Unpublished results.

(14) For previous asymmetric cycloadditions utilizing trimethylsilylketene, see: (a) Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K.; Yang, H. W.; Zhao, C.; Wright, G. D. *Bioorg. Med. Chem.* **1998**, *6*, 1255−1272 and references therein. (b) Yang, H. W.; Romo, D. *Tetrahedron Lett.* **1998**, *39*, 2877−2880. (c) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *Synthesis* **1998**, 1655−1661.

(15) The low-temperature ring opening of alkynyl lactones using stoichiometric quantities of the metal alkoxide affords superior yields relative to the previously reported lanthanum(*tert*-butoxide)-catalyzed lactone alcoholysis, see: Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535−6539.

(16) For the conversion of morpholine amides to ketones, see: Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414−1416.

(17) Garigipati, S. G.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790.

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

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