# Catalytic Asymmetric Acyl Halide−Aldehyde Cyclocondensations. A Strategy for Enantioselective Catalyzed Cross Aldol Reactions

Scott G. Nelson,* Timothy J. Peelen, and Zhonghui Wan

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

Considerable interest currently exists in developing catalyzed asymmetric variants of aldol addition reactions. Despite elegant solutions to this problem, examples of asymmetric catalyzed cross aldol reactions that require no pre-enolization[1] or special substrate derivatization are relatively rare.[2,3] The considerable homology existing between traditional aldol addition reactions and ketene−aldehyde cycloadditions implicates these transformations as alternative platforms for developing catalyzed asymmetric variants of cross aldol bond constructions.[4,5] Catalyzed asymmetric acyl halide−aldehyde cyclocondensation (AAC) reactions presented herein successfully integrate in situ ketene formation and aldehyde cycloaddition in realizing catalyzed aldol-type bond constructions employing commercially available reaction partners (eq 1).
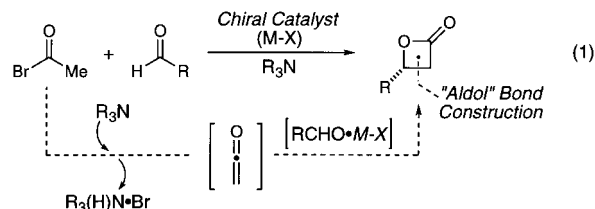
We have recently described Al(III)-catalyzed cyclocondensations of acyl halides and enolizable aldehydes as a strategy for effecting catalyzed cross aldol reactions.[6] These investigations identified the reactive Lewis acid−aldehyde complex responsible for mediating the operative [2 + 2] ketene−aldehyde cycloaddition as the strategic construct for inducing asymmetry during C−C bond formation.[7,8] In designing asymmetric variants of these reactions, we were aware that cycloaddition reaction variants and accompanying catalyst systems that merged in situ ketene

formation with ensuing enantioselective aldehyde addition had not been reported.[9] During preliminary development of the Al(III)-catalyzed AAC reactions, the optically active Al(III)− triamine complex **1** (10 mol %) was found to catalyze the cyclocondensation of acetyl bromide (AcBr) and benzyloxyacetaldehyde (**2a**), employing di(isopropyl)ethylamine (DIEA) as the base, to afford the optically active β-lactone **3a** as a 71:19 [4(R):4(S)] mixture of enantiomers (eq 2).

Catalyst	ketene source	%ee
1	AcBr, DIEA	42
5b	AcBr, DIEA	92
5b	CH₂CO	92
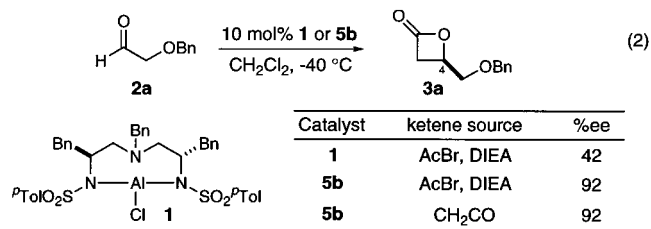
The success of this initial Al(III)[triamine]-catalyzed AAC reaction implicated optically active triamine ligands as platforms for further refinement of the Al(III)-derived cyclocondensation catalysts. Evaluating catalyst efficiency as a function of the triamine ligand's terminal amine functionality and alkyl group structure led to the L-valine-derived ligand **4** being identified as providing catalyst complexes exhibiting optimum enantioselection and turnover numbers in the catalyzed AAC reactions.[10] Catalyst systems were generated by reacting triamine **4** with AlMe₃ or Me₂AlCl to afford Al(III) complexes **5a** and **5b**, respectively (eq 3); these two catalyst systems function nearly equivalently in the
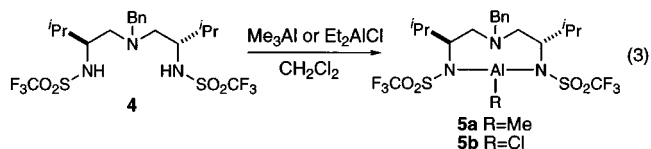
AAC reactions.[11] Substoichiometric quantities of the Al(III) complex **5a** (or **5b**) (10 mol %), in concert with DIEA (1. 7 equiv), catalyze the cyclocondensation of acetyl bromide (1.9 equiv) and benzyloxyacetaldehyde (**2a**) to afford the β-lactone "cross aldol" adduct **3a** as the exclusive reaction product with an enantiomer ratio of 4(R):4(S) = 96:4 (91% yield) (eq 2). No background reaction of acetyl bromide and the aldehyde was observed in the absence of the Al(III)−triamine catalyst. Remarkably, the trialkylammonium·HBr salt generated during the cyclocondensation process has no deleterious effect on reaction

(1) 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 a review, see: (e) Nelson, S. G. *Tetrahedron: Asymmetry* **1998,** *9,* 357−389.

(2) For highly enantioselective catalyzed aldol addition reactions involving commercially available reagents, see: Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995,** *117,* 3649−3650.

(3) For a recent example of catalyzed asymmetric intermolecular aldol reactions, see: (a) 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 aldol-type reactions, see: (b) Shibasaki, M.; Sasi, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 1236−1256 and references therein. (c) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986,** *108,* 6405− 6406.

(4) Optically active 4-methylene-2-oxetanones have been developed as propionate aldol synthons, see: Calter, M. A.; Guo, X. *J. Org. Chem.* **1998,** *63,* 5308−5309.

(5) For the utility of aldol adducts as precursors to β-lactones, see: (a) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991,** *56,* 1176−1185. (b) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997,** *62,* 4−5. (c) Wedler, C.; Ludwig, R.; Schick, H. *Pure Appl. Chem.* **1997,** *69,* 605−608. (d) Yang, H. W.; Romo, D. *J. Org. Chem.* **1998,** *63,* 1344−1345.

(6) Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999,** *40,* 6535−6539.

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

(8) Asymmetric catalyzed ketene additions to chloral and related aldehydes: (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982,** *104,* 166− 168. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985,** *50,* 1977−1979. Asymmetric ketene-aldehyde additions: (c) Tamai, Y.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994,** 1549−1550. (d) Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1994,** 2281−2282. Asymmetric catalyzed cycloadditions using trimethylsilylketene: (e) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *J. Chem. Soc., Chem. Commun.* **1996,** 1053−1054. (f) 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. (g) Yang, H. W.; Romo, D. *Tetrahedron Lett.* **1998,** *39,* 2877−2880. (h) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *Synthesis* **1998,** 1655−1661. For catalyzed asymmetric ketene dimerization, see: (i) Calter, M. A. *J. Org. Chem.* **1996,** *61,* 8006−8007.

(9) For a comprehensive review of syntheses of optically active β-lactones, see: Yang, H. W.; Romo, D. *Tetrahedron* **1999,** *55,* 6403−6434.

(10) Triamine **4** was prepared according to the published procedure: Cernerud, M.; Skrinning, A.; Bérgère, I.; Moberg, C. *Tetrahedron: Asymmetry* **1997,** *8,* 3437−3441.

(11) For structural investigations of related Al(III)−triamine complexes, see: (a) Emig, N.; Réau, R.; Krautscheid, H.; Fenske, D.; Bertrand, G. *J. Am. Chem. Soc.* **1996,** *118,* 5822−5823. (b) Jegire, J. A.; Atwood, D. A. *Inorg. Chem.* **1997,** *36,* 2034−2039.

Communications to the Editor

J. Am. Chem. Soc., Vol. 121, No. 41, 1999 9743

Table 1. Asymmetric Acetyl Bromide−Aldehyde Cyclocondensations[a]

| entry	Aldehyde 2 (R)	catalyst [time (h), temp (°C)]	% yield[b]	% ee 3[d] (configuration)
a	BnOCH$_2$—	5b (8, -40)	91	92 (R)
b	PhCH$_2$CH$_2$—	5a (16, -50)	93	92 (S)
	PhCH$_2$CH$_2$—	5a (72, -78)	89	95 (S)
c	CH$_2$CH(CH$_2$)$_8$—	5b (16, -50)	91	91 (S)
d	Me$_2$CHCH$_2$—	5a (24, -50)	80[c]	93 (S)
e	BnOCH$_2$CH$_2$—	5b (16, -40)	90	91 (S)
f	TBDPSOCH$_2$—	5b (16, -40)	74	89 (R)
g	BnOCH$_2$—≡—	5a (16, -50)	86	93 (R)
h	Me$_3$C—≡	5a (16, -50)	91	85 (R)
i	C$_6$H$_{11}$—	5b (24, -40)	56	54 (R)

[a] Reactions were carried out using the conditions given in ref 12. [b] Reported values are for chromatographically purified materials. [c] Isolated yield is reflective of product volatility. [d] Enantiomer ratios for entries a, b, e and g were determined by HPLC (chiral Chiralcel OD-H column); enantiomer ratios for entries c, d, h, and i were determined by capillary GC (chiral Chiraldex G-TA column).

efficiency or enantioselectivity. The catalyzed addition of pre-formed ketene to benzyloxyacetaldehyde using 10 mol % **5b**, a process that is free of any ammonium halide salts, afforded the β-lactone **3a** with chemical yield and enantioselection directly paralleling those values obtained from the cyclocondensation reaction (89% yield, 92% ee).

Catalyst complexes **5a** and **5b** render a variety of structurally diverse, enolizable aldehydes as effective electrophiles for the catalyzed asymmetric AAC reactions.[12] Straight-chain, β-branched, and alkoxy-substituted aldehydes afford the derived β-lactone adducts **3a−f** with uniformly high enantioselection (89−95% ee) and chemical yields using 10 mol % **5a/b** at −40 to −50 °C (eq 4; Table 1).[13] Further enhanced β-lactone enantiomer ratios are

(4)
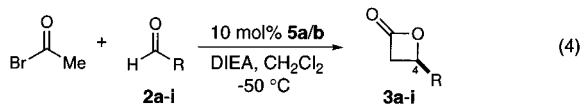
obtained at lower reaction temperatures at the expense of extended reaction times (entry b). Catalyzed AAC reactions are also compatible with certain silyl ether protecting groups encountered widely in organic synthesis. Attempted cyclocondensation of aldehydes incorporating primary *tert*-butyldimethylsilyl (TBS)

ethers afforded significant quantities of desilylated aldehyde and correspondingly low reaction yields. Incorporating the less acid-sensitive *tert*-butyldiphenylsilyl (TBDPS) protecting group in the α-alkoxyaldehyde **2f** alleviated silyl ether cleavage, affording the β-lactone **3f** in high yield and enantiomeric excess (entry f). Conjugated ynals are also very reactive electrophiles in the asymmetric AAC reactions, delivering the corresponding β-lac-tones with enantiomeric purities and chemical yields consistent with those obtained for aliphatic aldehydes (entries g and h). Conjugated aldehydes are not, however, generally effective electrophiles in the catalyzed AAC reactions; conjugated enals afford little to no β-lactone product under the optimized reaction conditions. Aldehydes possessing branching at the α-carbon, represented by cyclohexanecarboxaldehyde (entry i), presently are also not functional electrophiles in the asymmetric cycloconden-sation reactions.

The preparative utility of the asymmetric AAC reactions was documented in a reaction using 10 mmol (1.5 g) of benzyloxy-acetaldehyde (**2a**). Using the typical experimental procedure, 10 mol % of the enantiomeric form of the preformed Al(III) catalyst **5a** afforded β-lactone *ent*-**3a** in 89% isolated yield and 92% ee, values that are nearly identical for those obtained on 1 mmol reaction scale.[14]

Ring-opening alcoholysis reveals the optically active β-lactone adducts derived from the asymmetric AAC reactions as direct progenitors of prototypical acetate aldol adducts. We have previously disclosed that 4-substituted 2-oxetanones undergo rapid lanthanum alkoxide-catalyzed ring-opening with alcohols to afford the corresponding β-hydroxy esters.[6] The La(O*t*-Bu)$_3$-catalyzed (5 mol %) ring-opening of the enantiomerically enriched β-lac-tones **3c−f,i** with benzyl alcohol affords the optically active benzyl acetate aldols **6c−f,i** in nearly quantitative yield (eq 5).

(5)
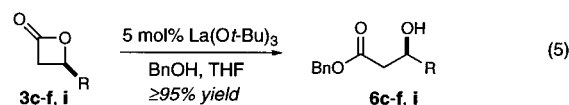
Catalyzed asymmetric AAC reactions provide an effective strategy for executing enantioselective C−C bond constructions that constitute surrogates for typical cross aldol addition reactions. These catalyzed aldol variants are characterized by their opera-tional simplicity and their use of inexpensive, commercially available reaction components. The access to enantiomerically enriched β-lactones afforded by this methodology is expected to accelerate the exploitation of these intermediates both as masked aldol adducts and as versatile intermediates for asymmetric organic synthesis.

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

JA992369Y

(12) Typical experimental procedure: Under a N$_2$ atm, a solution of 54 mg of triamine ligand **4** (0.10 mmol) in 8 mL of CH$_2$Cl$_2$ is treated with 100 μL of a 1 M hexanes solution of dimethylaluminum chloride (0.10 mmol) at ambient temperature. The resulting homogeneous, colorless solution was stirred at room temperature for 1 h, whereupon 300 μL of di(isopropyl)ethylamine (1.7 mmol) was added via syringe. The reaction was cooled to −50 °C, and 140 μL of acetyl bromide (1.9 mmol) and the aldehyde (1.0 mmol) were added via syringe. The reaction was stirred until complete as monitored by TLC (~8−72 h). The reaction mixture was eluted through a silica gel pad with CH$_2$Cl$_2$, and the filtrate was concentrated *in vacuo*. If necessary, crude reaction mixtures were purified by flash chromatography (hexanes:ethyl acetate). For an experimental procedure using preformed Al(III) complex **5a**, see the Supporting Information.

(13) The absolute configuration of β-lactones **3a,b,i** was established by reduction to the corresponding 1,3-diol derivatives (LiAlH$_4$, Et$_2$O, 0 °C) and correlation of their optical rotation to those of authentic samples of known configuration; see the Supporting Information for full procedural details. The configuration of the remaining β-lactones (**3c−h**) was assigned by analogy to these determinations.

(14) As part of synthesis studies underway in our laboratories, the enantiomeric form of lactone **3a** was required. Thus, this large-scale reaction was conducted with the enantiomer of catalyst **5a**.