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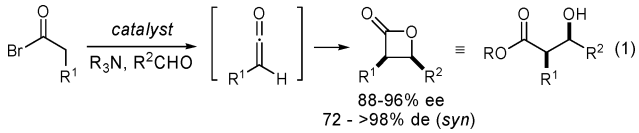
Catalytic Asymmetric Acyl Halide−Aldehyde Cyclocondensation Reactions of Substituted Ketenes

Scott G. Nelson,* Cheng Zhu, and Xiaoqiang Shen

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

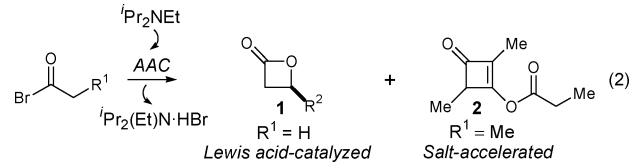
Received October 18, 2003; E-mail: sgnelson@pitt.edu

Recent success in developing de novo asymmetric syntheses of enantioenriched β-lactones has created renewed interest in these heterocycles as versatile platforms for asymmetric organic synthesis.[1,2] β-Lactones are direct progenitors of numerous useful building blocks, including enantioenriched β-amino acids,[3] allenes,[4] and β,β-disubstituted carboxylic acids.[5] β-Lactones are also functional equivalents of ester enolate aldol addition products.[6] In this latter context, we developed acyl halide−aldehyde cyclcondensation (AAC) reactions that deliver enantioenriched β-lactone acetate aldol surrogates from commercially available starting materials (eq 1).[2c,7] However, these first-generation AAC reactions proved to be generally useful only for reactions involving unsubstituted ketene.[8] Herein, we report generally applicable catalytic asymmetric AAC reactions of alkyl-substituted ketenes with structurally diverse aldehydes as a functional solution to highly enantio- and diastereoselective substituted ester enolate aldol additions.



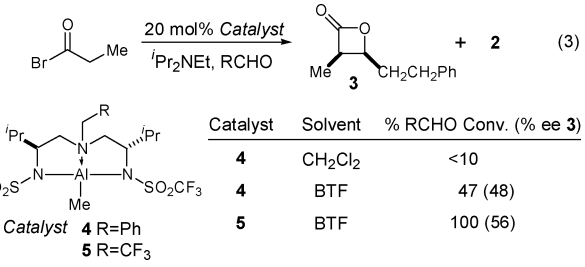
(1)

Mechanistic investigations of the catalyzed AAC reactions revealed these reactions to be kinetically complex processes.[9] First-generation AAC reactions successfully mediate up to four competing reaction pathways to deliver the desired [2 + 2] ketene−aldehyde cycloadduct (β-lactone) **1** in high yield (eq 2). This reaction fidelity is notable considering that ketene dimerization, ketene trimerization, and aldehyde homoaldol addition are all accessible processes under the AAC reaction conditions. While AAC reactions employing acetyl bromide-derived ketene faithfully generate the β-lactone cycloadducts, substituted ketenes exhibited substantially suppressed reactivity toward aldehydes, allowing competing reaction manifolds to interfere with the desired [2 + 2] pathway. For example, reacting propionyl bromide (methylketene precursor) with various aliphatic aldehydes affords methylketene trimer **2** as the major reaction product, while analogous acetyl bromide AAC reactions deliver exclusively β-lactone **1**. These observations highlight the significant differences existing between AAC reactions involving ketene and those employing substituted ketenes despite the superficial similarity of these transformations.



(2)

Attempted AAC reactions of substituted ketenes with aliphatic aldehydes employing first-generation reaction conditions (10−20 mol % **4**, CH_2Cl_2) afforded primarily ketene trimer **2** and <10% of the desired β-lactone **3** (eq 3). Kinetic evidence indicated that while ketene trimerization was Lewis acid (catalyst)-independent, this reaction manifold was accelerated substantially by the ammonium bromide byproduct of amine-mediated ketene generation.[10] This analysis suggested that elucidating reaction conditions that would effectively remove the ammonium halide salts would slow unproductive methylketene homocoupling. We discovered that pseudo-salt-free conditions could be achieved by substituting benzotrifluoride (BTF) for CH_2Cl_2 as the AAC reaction solvent.[11] In BTF, the ammonium bromide salts are insoluble and AAC reaction conversions improved considerably in the standard propionyl bromide−hydrocinnamaldehyde test reaction (<10% → 47%) due to extended ketene lifetimes.



Catalyst	Solvent	% RCHO Conv. (% ee **3**)
4	CH_2Cl_2	<10
4	BTF	47 (48)
5	BTF	100 (56)

(3)

Although solvent modification assisted in improving AAC reaction conversions, the need for improved catalysts that would further accelerate the desired ketene−aldehyde cross-coupling remained evident. Designs for more reactive reaction catalysts were predicated on structural investigations of the first-generation Al-triamine catalyst **4**.[12] Crystallographic studies revealed complex **4** to adopt a four-coordinate, trigonal monopyramidal (tmp) geometry; this Al(III) coordination geometry and the central Al−N Lewis acid−base contact that defines the tmp geometry were demonstrated to be crucial to catalyst activity. Thus, new catalyst designs evolved from Al(triamine)-based structures that retain the essential metal coordination geometry while delivering enhanced metal electrophilicity. For example, the *N*-2,2,2-trifluoroethyl-substituted catalyst **5** expressed significantly enhanced reactivity relative to the analogous *N*-benzyl catalyst **4** (eq 3). We speculate that inductive electron withdrawal from nitrogen decreases electron density at aluminum, thereby enhancing Lewis acidity, while retaining sufficient central nitrogen Lewis basicity to maintain the integrity of the catalytically active tmp coordination geometry.[13] Propionyl bromide AAC reactions employing catalyst **5** in conjunction with BTF solvent combined to define ketene−aldehyde cross-coupling as the dominant reaction pathway, affording the desired β-lactone "propionate" aldol adduct **3** as the sole reaction product.

The next phase of our investigation focused on identifying modified Al-triamine catalysts that would provide the requisite levels of enantioselectivity at reaction temperatures above the freezing point of BTF (−29 °C). Various Al(III) catalysts derived from C_2-symmetric triamine ligands differing in sulfonamide

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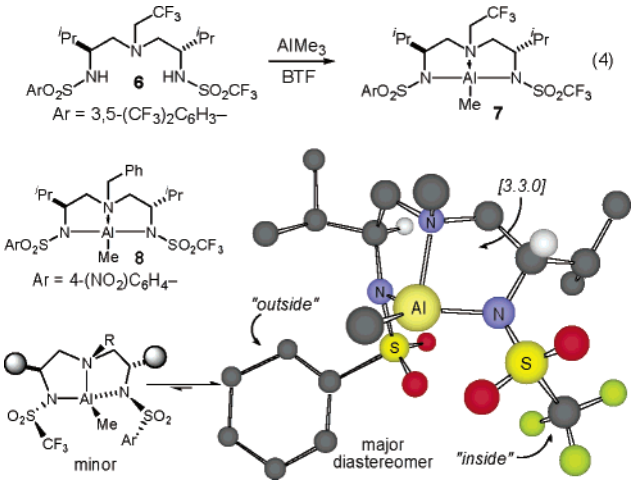
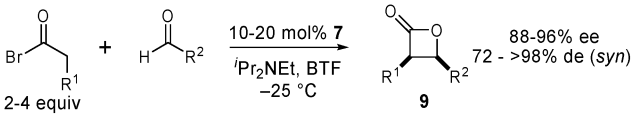


Figure 1. Second-Generation AAC Catalyst Structure (from X-ray **8**).[14]

Table 1. Asymmetric AAC Reactions of Substituted Ketenes



entry	R^1	R^2	%ee **9**[a]	syn:anti[b,c]	% yield **9**[d]
a	Me	CH_2CH_2Ph	90	95:5	71
b	Me	$(CH_2)_8CHCH_2$	88	94:6	77
c	Me	CH_2CH_2OBn	91	86:14	75
d	Me	C_6H_5	96	>98:2	80
e	Me	C≡$CSiMe_3$	95	98:2	76[e]
f	Et	CH_2CH_2Ph	91	95:5	81
g	Et	CH_2CH_2OBn	91	88:12	83
h	Et	CH_2OBn	93	89:11	78
i	Et	C_6H_5	94	>98:2	83
j	^{n}Pr	CH_2CH_2OBn	91	91:9	88
k	^{n}Pr	C_6H_5	96	>98:2	85
l	^{i}Pr	C≡$CSiMe_3$	94	>98:2	71[e]
m	^{i}Pr	C_6H_5	96	>98:2	84

[a] Enantiomeric ratios determined by chiral GLC or HPLC. [b] Diastereomeric ratios determined by ^{1}H NMR of crude product mixtures except for entries b and e (GLC). [c] Relative and absolute stereochemical assignments based on prior literature precedent; see ref 2d. [d] Yields for diastereomerically pure materials except entries g and j (diastereomers were inseparable). [e] Yield for the amide derived from amine-mediated ring opening of the crude β-lactone. See Supporting Information for details.

structure and backbone alkyl groups provided little improvement in enantioselectivity relative to **4**. However, the catalyst derived from unsymmetrical triamine **6** provided an Al(III)-derived complex **7** exhibiting substantially improved competency in the substituted ketene AAC reactions (eq 4). Although unsymmetrical ligands offered the potential for generating diastereomeric tmp Al(III) complexes, NMR analysis of the closely related complex **8** revealed a significant bias favoring one diastereomer (~14:1, 23 °C). X-ray analysis of **8** revealed the major diastereomer to orient the larger aryl sulfonamide in the sterically less congested "outside" position relative to the [3.3.0] ring system defined by the Al-coordinated triamine ligand (Figure 1). A similar conformational bias expressed in **7** would position the large aryl residue ideally to block the *Si* diastereoface of an apically coordinated aldehyde.

The second-generation Al(triamine) catalyst **7** in conjunction with pseudo-salt-free reaction conditions (BTF, −25 °C) combined to deliver substituted ketene AAC reactions exhibiting consistently high levels of enantioselection (Table 1). The standard test reaction involving propionyl bromide and hydrocinnamaldehyde under the optimized reaction conditions (10−20 mol % **7**, 2−4 equiv of RCOBr, 2 equiv of ^{i}Pr$_2$NEt) afforded the *syn*-propionate aldol surrogate **9a** in 90% ee (syn:anti = 95:5) (entry a). Methylketene seems to be uniquely disposed toward trimerization; as a result, slow-reacting aliphatic aldehydes require 20 mol % catalyst to ensure that ketene−aldehyde cycloaddition competes effectively with ketene homocoupling (entries a−c). However, unsaturated aldehydes provide sufficiently accelerated [2 + 2] reaction rates such that efficient AAC cross-coupling is achieved with 10 mol % **7** (entries d and e). Similarly, ethylketene trimerization is sufficiently retarded relative to the AAC process that 10 mol % **7** affords efficient cross-coupling for both enolizable aliphatic and unsaturated aldehydes (entries f−i). Propylketene and *i*-propylketene, derived from valeryl bromide and isovaleryl bromide, respectively, also participate in highly stereoselective AAC reactions under the second-generation reaction conditions, although *i*-propylketene reactions are currently limited to relatively reactive, nonenolizable aldehydes (entries j−m).[15]

The structural homology existing between traditional aldol adducts and β-lactones reveals the second-generation AAC reactions to be effective surrogates for syn-selective asymmetric aldol additions. In this context, the AAC reactions deliver enantioenriched ester enolate "aldols" free of the requirement for pre-enolization or special substrate derivatization beyond preparation of the requisite acyl bromide. These reaction attributes coupled with the array of transformations available to the AAC-derived β-lactones portend considerable utility for this reaction technology in a variety of synthesis enterprises.

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Supporting Information Available: Experimental procedures 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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(14) Phenyl and NO_2 groups have been omitted from Figure 1 for clarity.
(15) α-Branched aldehydes and conjugated enals are not effective substrates for the AAC reactions, affording substantially attenuated enantioselection (60−70% ee) or no reaction, respectively.

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