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S_N2 Ring Opening of β-Lactones: An Alternative to Catalytic Asymmetric Conjugate Additions

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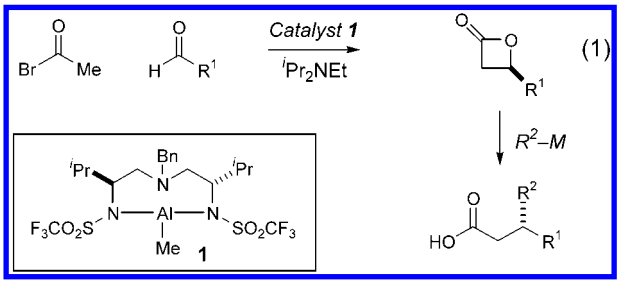
Merging catalytic asymmetric acyl halide-aldehyde cyclocondensation (AAC) reactions with ensuing Grignard-mediated ring opening of the derived enantiomerically enriched β-lactones is presented as a generally useful asymmetric synthesis of β-disubstituted carboxylic acids. Enantiomerically enriched β-lactones are subject to efficient S_N2 ring opening with a variety of copper-modified alkyl Grignard reagents, including highly branched nucleophiles. Considerable structural variation in the lactone electrophile is also tolerated. Phenyl- and vinyl-derived organometallics are not efficient nucleophiles for the ring-opening reactions.

Introduction

Conjugate nucleophilic additions to enone electrophiles constitute fundamentally important transformations in organic synthesis.[1] The strategic nature of these bond constructions has resulted in the development of a number of highly successful strategies for effecting catalytic asymmetric conjugate hydride, heteroatom, and carbon nucleophile addition reactions.[2,3] Each of these transformations successfully achieves catalyst-based stereocontrol during the conjugate addition of various nucleophiles to achiral enone electrophiles. The ready availability of the requisite achiral enone electrophiles from the olefination of simple carbonyl starting materials renders these transformations especially attractive bond constructions. A mechanistically distinct approach to effecting identical bond constructions emerges from an analysis of S_N2 ring opening of β-lactone electrophiles with carbon-based nucleophiles (Figure 1). In comparison to prototypical conjugate additions, this reaction design reconstitutes the enone electrophile as an optically active β-lactone with S_N2 ring opening providing a surrogate for the conjugate nucleophilic addition. This report describes the successful implementation of this reaction design as a versatile asymmetric synthesis of β-disbustituted carboxylates relying on catalytic asymmetric acyl halide-aldehyde cyclocondensations as the source of the requisite β-lactone electrophiles (eq 1). This reaction strategy allows a variety of differentially substituted organocuprates to be employed in the ring opening of structurally diverse 4-substituted 2-oxetanones resulting in a highly general synthesis of enantiomerically enriched β-disubstituted carboxylic acids.



Results and Discussion

β-Lactones offer considerable versatility as intermediates for synthesis enterprises.[4] Ring opening via nucleophilic addition at the carbonyl residue affords access to a variety of ester and amide aldol-type adducts depending on the choice of nucleophile (eq 2).[5] However, ring strain within the β-lactone nucleus can elicit electrophilic

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(4) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441.
(5) Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883.

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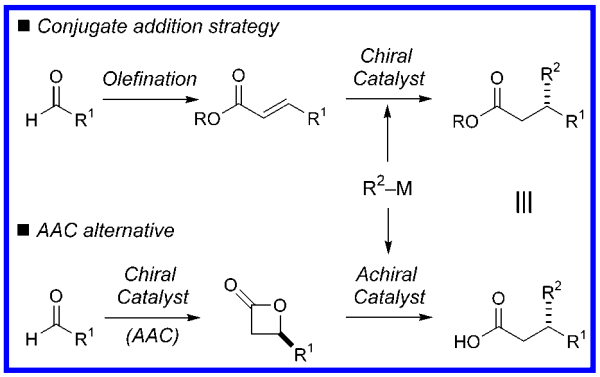
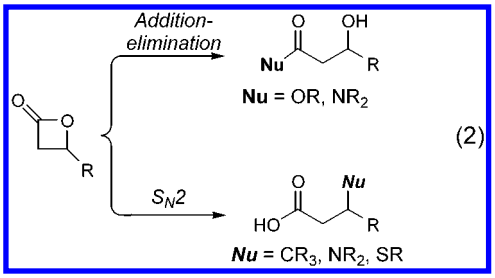


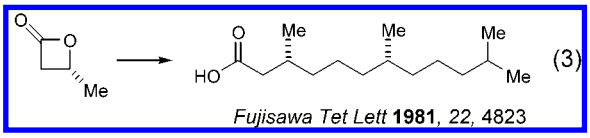
FIGURE 1. Strategies for asymmetric catalytic conjugate additions

character reminiscent of that expressed by epoxides. Appropriate tuning of the nucleophile reactivity can lead to scission of the C_{alkyl}–O bond in an S_N2 reaction pathway.[6,7,8]

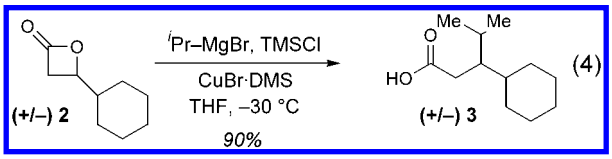


On the basis of the bifunctional electrophilic character expressed by β-lactones, we have been interested in developing optically active 4-substituted 2-oxetanones as generally useful platforms for asymmetric organic synthesis. Catalytic asymmetric acyl halide-aldehyde cyclocondensation (AAC) reactions have been developed as an operationally simple approach to highly enantiomerically enriched β-lactones.[9] This reaction technology provides convenient and economical access to the optically active electrophiles required as substrates for implementing the alternative "conjugate addition" reaction design. Indeed, from an operational perspective, the AAC β-lactone synthesis closely resembles the one-step aldehyde olefination processes used to prepare achiral enone electrophiles required for prototypical conjugate additions.[10]

The reactivity of simple β-lactones toward carbon-based nucleophiles was first recognized by Fujisawa.[7] Optically active β-butyrolactone was found to undergo regioselective S_N2 ring opening with alkyl Grignard reagents in the presence of a Cu(I) catalyst (eq 3). Despite Fujisawa's findings in this area, the development of this reaction design as a generally useful alternative to conjugate addition reactions had previously been hampered by the limited availability of optically active β-lactone electrophiles. Optically active β-lactones had previously been available only by resolution of racemic β-butyrolactone, asymmetric diketene dihydrogenation, multistep synthesis, or modestly enantioselective ketene-aldehyde cycloadditions.[11]



The convenient availability of highly enantiomerically enriched 4-substituted 2-oxetanones provided by the AAC reactions prompted us to explore β-lactone ring opening as a realistic and general alternative to prototypical conjugate additions. To evaluate the generality of the organocuprate-mediated S_N2 β-lactone ring opening, we selected the copper-mediated addition of isopropyl Grignard, a branched nucleophile, and 4-cyclohexyl-2-oxetanone, an α-branched electrophile, as a stringent test reaction (eq 4). Reacting lactone **2** with the Gilman reagent derived from isopropylmagnesium bromide and CuBr·DMS afforded exclusive S_N2 ring opening in yielding the β-disubstituted acid **3** (90%). The success of this test reaction suggested that the cuprate-mediated ring openings would be relatively insensitive to steric perturbations within the reaction components and foreshadowed our ultimate success in establishing their general utility.



Examining the scope of cuprate-mediated S_N2 lactone ring openings was initiated by preparing the requisite enantiomerically enriched β-lactone electrophiles. Asymmetric AAC reactions of acetyl bromide and various aldehydes catalyzed by Al(III) complex **1** delivered the enantioenriched β-lactones **4a**–**f** (eq 1).[9a] In accord with the preliminary test reaction, reacting the optically active β-lactones **4a**–**f** with various alkyl Grignard reagents and a stoichiometric quantity of CuBr·DMS and chlorotrimethylsilane (TMSCl) elicited efficient S_N2 lactone ring-

(6) The S_N2 ring-opening pathway provides entry to a variety of versatile synthesis building blocks, including β-amino acids, β-dialkyl carboxylates, and β-thiocarboxylic acids: (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105. (b) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1326. (c) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237. (d) Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Meloni, D.; Tinti, M. O. *J. Org. Chem.* **1995**, *60*, 8318. (e) Bernabei, I.; Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Muck, S.; Scafetta, N.; Tinti, M. O. *Chem. Eur. J.* **1996**, *2*, 826. (f) Nelson, S. G.; Spencer, K. L. *Angew. Chem.* **2000**, *39*, 1323.

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(10) Heathcock, C. H. The Aldol Reaction: Group I and II Enolates. In *Comprehensive Organic Synthesis: Additions to C–C π-Bond Part 2*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.6, p 181.

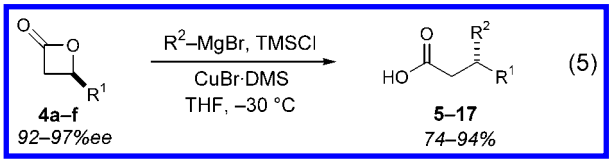
(11) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403.

TABLE 1. Cuprate-Mediated Ring-Opening Reactions of β-Lactones 4

entry	lactone **4**	Grignard[b]	% yield (**5**−**17**)[c]	config-uration[d]
	R^1 (%ee)[a]	R^2-MgBr		
a	CH_2CH_2Ph **4a** (*S*, 97)	CH_3	88 (**5**)	*R*
b	**4a**	$CHMe_2$	88 (**6**)	*R*
c	**4a**	CMe_3	80 (**7**)	*R*
d	**4a**	CH_2Ph	94 (**8**)	*S*
e	CH_2CHMe_2 **4b** (*S*, 95)	CH_2Ph	91 (**9**)	*S*
f	$^cC_6H_{11}$ **4c** (*S*, 98)	CH_2Ph	87 (**10**)	*R*
g	CH_2OCH_2Ph **4d** (*R*, 92)	CH_3	84 (**11**)	*S*
h	**4d**	$CHMe_2$	78 (**12**)	*R*
i	**4d**	CH_2Ph	88 (**13**)	*S*
j	$CH_2CH_2OCH_2Ph$ **4e** (*R*, 93)	CH_3	82 (**14**)	*S*
k	**4e**	$CHMe_2$	84 (**15**)	*S*
l	**4e**	CMe_3	74 (**16**)	*S*
m	$CH_2CH_2OTBDPS$ **4f** (*S*, 92)	CH_3	84 (**17**)	*R*

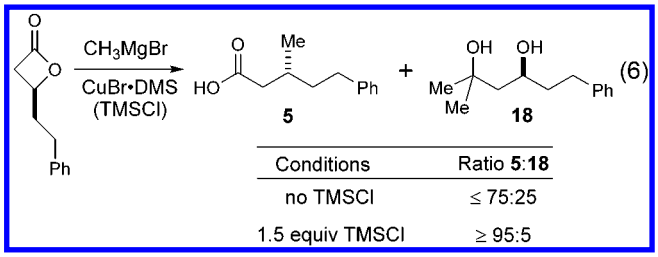
[a] Lactones **4a**,**b**,**d**−**f** were prepared as described in ref 9a; lactone **4c** was prepared as described in ref 9b. [b] Commercially available organomagnesium bromide reagents were used as cuprate precursors. [c] Values are for chromatographically purified materials. [d] Absolute configurations of acids **11** and **13** were unambiguously established; see ref 16. Configurations of the remaining β-disubstituted acids were assigned by analogy to these determinations.

opening to afford the enantiomerically enriched β-disubstituted acids **5**−**17** in 74−94% yield (eq 5).



The efficiency of these Grignard-mediated ring-opening reactions exhibited considerable sensitivity to the stoichiometry of the copper-modified Grignard reagents. High yields of the methyl-addition adducts **5** (Table 1, entries a, g, j, and m) were achieved only using the putative methyl Gilman reagent derived from a stoichiometric quantity of CuBr·DMS and 2 equiv of methylmagnesium bromide. Ring-opening reactions employing substoichiometric Cu(I) additives were not generally effective in providing clean S_N2 addition for the range of alkyl Grignard and 4-substituted β-lactones evaluated in this study.[12] Nucleophilc addition of larger alkyl Grignard reagents (isopropyl- or *tert*-butylmagnesium bromide) could be accomplished using 5 mol % CuBr·DMS with no apparent deleterious effects on the reaction yield. These results are consistent with the observation that alkyl Grignard reagents react with β-lactone electrophiles only slowly at low temperatures (<−30 °C); at higher reaction temperatures, unmodified alkyl Grignard reagents add exclusively to the lactone carbonyl.[13] Despite these observations, reactions employing stoichiometric amounts of the CuBr additive provided the greatest substrate generality and reproducibility. As a result, stoichiometric CuBr additive was typically utilized in the standard alkyl Grignard-mediated β-lactone ring-opening procedures.

Regardless of the copper stoichiometry used in these β-lactone ring openings, conducting the reactions in the presence of trimethylsilyl chloride was imperative for achieving consistently high reaction yields. For example, reacting lactone **4a** with the methyl Gilman reagent derived from MeMgBr and CuBr provided up to 25% of the tertiary alcohol **18** derived from carbanion addition to the carbonyl function (eq 6). However, the same reaction incorporating a stoichiometric amount of TMSCl afforded the desired S_N2 addition adduct **5** (88% yield) as the exclusive reaction products. This effect becomes even more dramatic for more sterically hindered organometallics that, in the absence of the TMSCl additive, afford predominately carbonyl addition. While the beneficial effects of added TMSCl on a variety of organocopper-mediated addition reactions is well-documented,[14] the precise role the TMSCl additive is playing in these reactions, and, indeed, the present lactone ring openings remains unclear.



Alkyl Grignard-mediated β-lactone ring opening is virtually insensitive to the steric environment of both the lactone electrophile and the nucleophilic carbon atom under the optimized reaction conditions. Copper-mediated Grignard additions involving β-lactones bearing branched alkyl substituents or highly branched nucleophiles, including *tert*-butylmagnesium bromide, were subject to equally efficient lactone ring opening (Table 1, entries b, c, f, and l). Considerable structural variation is also tolerated in the electrophilic reaction component, including β-lactones possessing oxygen functionality incorporating several common ether protecting groups (entries g−m). Cis-3,4-disubstituted 2-oxetanones **19**[8] also participated in efficient Grignard-mediated ring opening, providing a strategy for stereoselectively introducing vicinal tertiary carbon stereocenters (eq 7). Precedent indicated that each of these S_N2 ring-opening reactions would proceed with rigorous inversion of the 2-oxetanone stereocenter;[15] the veracity of this prediction was unambiguously confirmed for the β-chiral carboxylic

(12) The addition of geranyl Grignard to β-butyrolactone has been achieved using 5 mol % Li_2CuCl_4. See ref 7.

(13) Alkyl Grignard reagents participate in nucleophilic addition to β-lactone electrophiles only slowly at temperatures below −30 °C.

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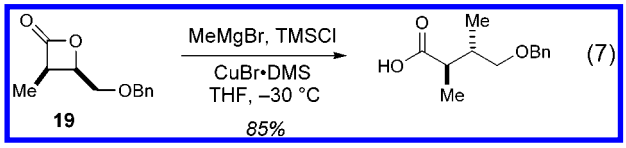
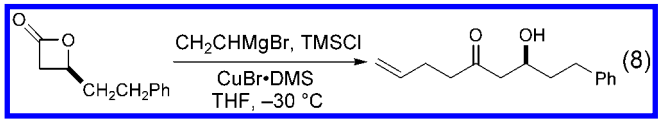
(15) For S_N2 β-lactone ring opening with inversion of configuration, see refs 6b,f and 7b−f. The ring opening of lactone **19** to afford exclusively the anti diastereomer of 2,3-dimethyl-4-benzyloxybutanoic acid (eq 7) provides additional evidence for configurational inversion upon S_N2 β-lactone ring opening.

acids **11** and **13** by comparing their optical rotations with reported values.[16]



In contrast to the successful ring-opening reactions employing sp^3-hybridized carbanions, sp^2-hybridized nucleophiles, including vinyl- and phenyl-derived organometallics, do not provide efficient S_N2 lactone ring opening. Vinyl Grignard, with either substoichiometric or stoichiometric Cu(I) additives, adds predominately to the lactone carbonyl providing, ultimately, the product of conjugate addition to the intervening vinyl ketone (eq 8).[7e] Aryl Grignard reagents afford poor yields of the β-disubstituted carboxylates (<50%) contaminated with significant amounts of the aryl ketone adduct resulting from nucleophilic attack at the carbonyl residue. In this regard, these lactone ring-opening reactions that function most efficiently with alkyl nucleophiles complement existing asymmetric conjugate additions of aryl and alkenyl boronic acids.[3b−e] Moreover, the utility of commercially available Grignard reagents in these conjugate addition surrogates extends the range of functional nucleophiles relative to those conjugate additions requiring organozinc nucleophiles.



Emerging from this two-step AAC-cuprate addition sequence is a general and highly versatile alternative to asymmetric conjugate addition reactions for generating optically active β-disubstituted carboxylic acids. Utilizing the catalyzed asymmetric AAC methodology as the stereochemically defining event provides access to the derived β-disubstituted carboxylates in either enantiomeric series via the readily available catalyst **1**. This methodology also allows the introduction of a considerable variety of structurally diverse alkyl groups at the incipient β-stereocenter. As a result, this reaction technology represents a useful complement to traditional asymmetric conjugate addition reactions.

(16) Schmid, R.; Hansen, H. J. *Helv. Chim. Acta* **1990**, *73*, 1258.

Experimental Section

General. The catalyst complex **1** was prepared according to the published procedure.[9a] Lactones **4a**,**b**,**d**−**f**,[9a] **4c**,[9b] and **19**[5] were prepared according to published procedures.

General Procedure for S_N2 CuprateAddition to β-Lactones 4. In a flame-dried 25 mL flask was weighed 215 mg of CuBr·DMS (1.5 mmol). Dimethyl sulfide (0.5 mL) and THF (15 mL) were added, and the resulting mixture was cooled to −50 °C. A solution of the alkyl Grignard reagent (3.0 mmol) was added, and the reaction mixture was stirred for 30 min at −50 °C. The reaction mixture was then warmed to −30 °C, and stirring was continued for another 30 min to allow complete formation of the cuprate. The reaction mixture was cooled to −50 °C, and a solution of the β-lactone **4** (1.0 mmol) in 2 mL of THF was added. After stirring for 30 min at −50 °C, TMSCl (1.5 mmol) was added and the reaction was then allowed to warm to ambient temperature over approximately 3 h; stirring was continued until all the lactone was consumed (as monitored by TLC). The reaction mixture was poured into a mixture of saturated NH_4Cl (30 mL) and 1 M HCl (10 mL), and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic portions were washed with saturated NH_4Cl and brine and dried over $MgSO_4$. After evaporation of the solvent, the product mixture was purified by flash chromatography.

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Supporting Information Available: Characterization data and proton and carbon NMR spectra are provided for compounds **5**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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