Asymmetric Catalysis

Catalytic Asymmetric Couplings of Ketenes with Aldehydes To Generate Enol Esters**

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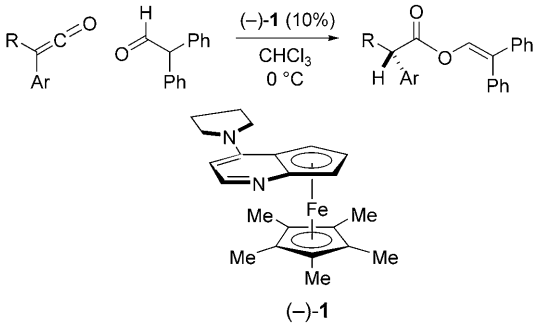
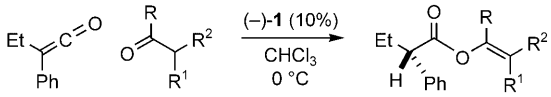
The synthesis of enantiopure α-arylalkanoic acids is an objective of significant interest, due in part to the bioactivity and commercial importance of this family of compounds.[1] One approach that has been pursued in industry is the asymmetric addition of alcohols to aryl alkyl ketenes to generate chiral esters (which can then be hydrolyzed to α-arylalkanoic acids).[2–5] Herein, we report a new method for the enantioselective synthesis of esters: the catalytic asymmetric coupling of a ketene with an aldehyde [Eq. (1)].

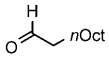
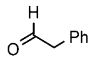
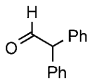
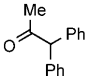


(1)

In the presence of planar-chiral dimethylaminopyridine (DMAP) derivative **1**,[6] we observed no reaction between phenyl ethyl ketene and *n*-decanal (Table 1, entry 1). In contrast, phenylacetaldehyde coupled with the ketene to furnish an enol ester in modest yield and with very good enantioselectivity (entry 2). Diphenylacetaldehyde was an excellent reaction partner (entry 3: 91% *ee*, 84% yield), whereas a related ketone was not (entry 4).[7,8]

Table 1: Survey of carbonyl compounds: Catalytic asymmetric couplings with ketenes.[a]



Entry	Carbonyl compound	*ee* [%]	Yield [%][b]
1		–	0
2		92	55
3		91	84
4		–	0

[a] All data are the average of two experiments. [b] Isolated product.

As illustrated in Table 2, we achieved the catalytic asymmetric synthesis of a wide array of enol esters of α-arylalkanoic acids through couplings of ketenes with diphenylacetaldehyde.[9–11] Thus, reactions of phenyl alkyl ketenes, in which the alkyl group ranges in size from methyl to *tert*-butyl, proceeded with moderate to excellent enantioselectivity (Table 2, entries 1–6). Furthermore, the addition occurred with very good stereoselectivity regardless of whether the aromatic group of the ketene was bulky (Table 2, entries 7 and 8), electron-rich (entries 8 and 9), or electron-poor (entry 10).

Enol esters are attractive targets in synthetic organic chemistry, in part as a result of the ease with which they can be

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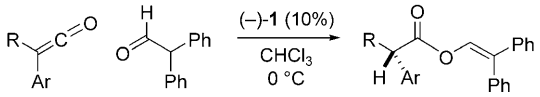
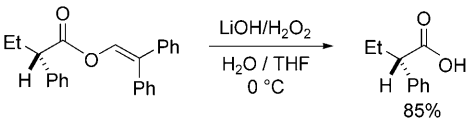
Table 2: Catalytic asymmetric couplings of aldehydes with ketenes to generate enol esters.[a]



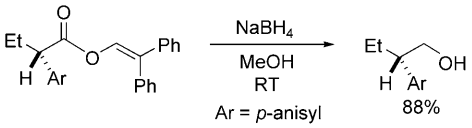
Entry	Ar	R	*ee* [%]	Yield [%][b]
1	Ph	Me	78	74
2	Ph	Et	91	84
3	Ph	*i*Bu	77	81
4	Ph	*i*Pr	98	95
5	Ph	cyclopentyl	97	99
6	Ph	*t*Bu	88	96
7	*o*-tolyl	Et	98	99
8	*o*-anisyl	Me	97	95
9	*p*-anisyl	Et	92	89
10	4-chlorophenyl	Et	88	96

[a] All data are the average of two experiments. [b] Isolated product.

converted into other useful families of compounds. We have established that our diphenyl-substituted enol esters can be hydrolyzed and reduced under mild conditions without racemization [Eqs. (2) and (3)].[12]



(2)



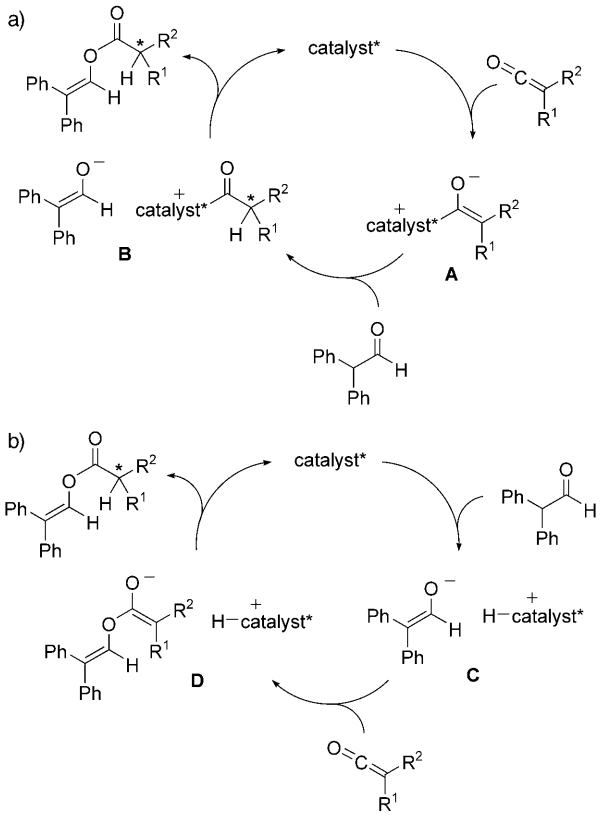
(3)

A number of mechanisms, two of which are illustrated in Scheme 1, can be envisioned for this new catalytic asymmetric coupling of ketenes with aldehydes to generate enol esters. In one possible pathway (Scheme 1a), catalyst **1** serves as a nucleophile and adds to the ketene to afford chiral enolate **A**,[13] which undergoes diastereoselective protonation by the aldehyde to furnish the ion pair **B**. Acylation of the enolate by the acylpyridinium ion then produces the enantioenriched enol ester and regenerates the catalyst.

Alternatively, the role of catalyst **1** may be to serve as a Brønsted base/acid (Scheme 1b). According to this hypothesis, the catalyst deprotonates the aldehyde to furnish an achiral enolate **C**. This nucleophilic enolate then adds to the electrophilic ketene to produce a new achiral enolate **D**,[14] which undergoes enantioselective protonation by its counterion (protonated **1**, a chiral Brønsted acid) to thereby generate the enol ester.[15]

To date, we have made the following observations with respect to the reaction pathway:

- The *ee* value of the product correlates linearly with that of the catalyst;[16]
- When catalyst **1** is mixed with one equivalent of diphenylacetaldehyde, there is no evidence for deprotonation of the aldehyde to form an ion pair;[17]



Scheme 1. Two of the possible mechanisms for the coupling of ketenes with aldehydes to form enol esters: a) nucleophilic catalysis and b) Brønsted acid/base catalysis.

- In the presence of catalyst **1**, the α proton of diphenylacetaldehyde exchanges rapidly with D_2O at 0 °C (in the absence of **1**, there is essentially no exchange after 3 days at room temperature);
- A small primary kinetic isotope effect is observed ($k_H/k_D \approx 2$ for the reaction of diphenylacetaldehyde relative to α-*d*-diphenylacetaldehyde).[18]

These data can be accommodated by either of the pathways illustrated in Scheme 1, as well as by others. A detailed mechanistic investigation will be required in order to gain improved insight into this interesting process.

In summary, we have developed a new method for the synthesis of enantioenriched esters: the catalytic asymmetric coupling of ketenes with aldehydes. We have established that this approach provides access to a wide array of α-arylalkanoic acid derivatives. Future studies will build upon our preliminary mechanistic observations to elucidate the reaction pathway for this intriguing transformation.

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[6] For leading references, see: G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542–547.

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[8] In contrast, treatment of a ketene with catalyst **1** and a non-enolizable aldehyde (e.g., PhCHO) leads to [2+2] cycloaddition to generate a β-lactone with good stereoselectivity: J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518–6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358–6360.

[9] Interestingly, under these conditions, catalyst **1** does not rearrange the enol ester to a 1,3-dicarbonyl compound. For example, see: I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051–4054; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924.

[10] General procedure: Under argon, a solution of the ketene (1.0 equiv) in $CHCl_3$ was added by syringe over 7 min to a solution of the catalyst (10%) and diphenylacetaldehyde (1.1 equiv) in $CHCl_3$ at 0 °C. The resulting solution was stirred at 0 °C, and then the reaction was quenched by the addition of MeOH (1 mL). The solvent was removed by rotary evaporation, and the residue was purified by column chromatography.

[11] Notes: a) The reaction of phenyl ethyl ketene with diphenylacetaldehyde proceeds in moderate to excellent enantioselectivity in a variety of solvents (e.g., toluene, Et_2O, EtOAc, 1,2-dimethoxyethane, THF, and CH_2Cl_2; however, not *N*-methylpyrrolidone); b) Slightly lower *ee* values were observed at room temperature; c) Typically, ca. 85% of catalyst **1** can be recovered at the end of the reaction.

[12] These enol esters are more reactive than the aryl esters produced by the addition of 2-*tert*-butylphenol to ketenes (see ref. [4b]).

[13] For other processes catalyzed by **1** that are believed to proceed through chiral enolate **A**, see: a) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579; b) Ref. [8].

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[15] For a process catalyzed by **1** that is believed to proceed through an analogous chiral Brønsted base/acid pathway, see ref. [4b].

[16] For a review of nonlinear effects in asymmetric catalysis, see: H. B. Kagan, T. O. Luukas in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, chapt. 4.1.

[17] This behavior contrasts with enantioselective additions of 2-*tert*-butylphenol to ketenes catalyzed by **1** in which the catalyst deprotonates the phenol; the mechanism is likely a chiral Brønsted acid catalyzed pathway (see ref. [4b]).

[18] Owing to the rapidness of the reaction at 0 °C, this experiment was conducted at −90 °C ($t_{1/2} \approx 1$ h).

