Asymmetric Chlorination

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Catalytic Asymmetric Synthesis of Tertiary Alkyl Chlorides**

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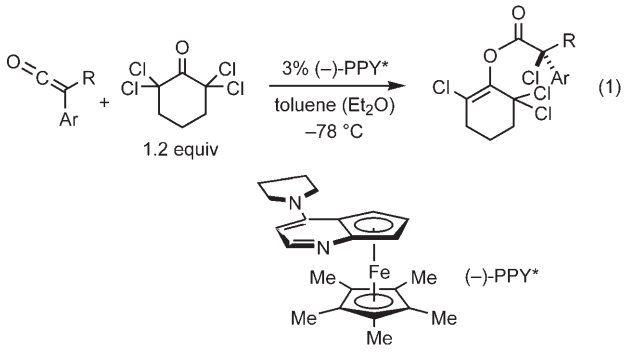
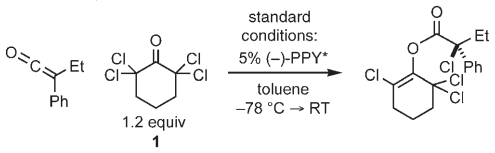
The bioactivity and the synthetic utility of enantioenriched alkyl halides provide a strong impetus for the development of stereoselective methods for their synthesis.[1] In recent years, a number of reports have described remarkable progress in the discovery of catalytic asymmetric approaches to this family of compounds (particularly, α-halocarbonyls[2,3]); nearly all of these processes generate secondary alkyl halides.[1] In contrast, there has been limited success in the development of catalysts for the enantioselective synthesis of tertiary halides.[4–6] Here, we describe progress toward addressing this challenge, specifically, a method for the catalytic asymmetric synthesis of tertiary α-chloroesters[7–9] from ketenes [Eq. (1)].[10,11]



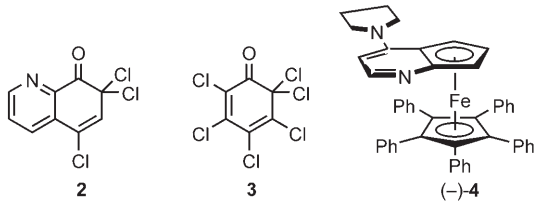
(1)

Table 1: Effect of reaction parameters on the catalytic asymmetric synthesis of tertiary α-chloroesters.[a]



Entry	Deviation from standard conditions	Yield [%]	*ee* [%]
1	*N*-chlorosuccinimide or **2**, instead of **1**	< 5	–
2	**3**, instead of **1**	40	8
3	hexachloroacetone, instead of **1**	96	57
4	–	86	94
5	**4**, instead of (–)-PPY*	46	88
6	benzoylquinine, instead of (–)-PPY*	< 5	–
7	RT, instead of −78 °C→RT	45	26
8	CH_2Cl_2, instead of toluene	17	11
9	THF, instead of toluene	< 5	–

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



In early studies, we examined the reaction of phenyl ethyl ketene with various chlorinating agents under a range of conditions (e.g., entries 1–4 of Table 1). In the presence of PPY*, a planar-chiral derivative of 4-(pyrrolidino)pyridine (PPY),[12] additions of reagents such as *N*-chlorosuccinimide,[3b] **2**,[5d] and **3**[10a] to the ketene proceed in poor yield and/or enantioselectivity (entries 1 and 2, Table 1). On the other hand, reaction with hexachloroacetone[13] cleanly furnishes the desired enol ester with promising enantioselectivity (57% *ee*; entry 3, Table 1). We hypothesized that a conformationally constrained relative of hexachloroacetone might afford improved stereoselection, and this has proved to be the case. Thus, PPY* catalyzes the addition of 2,2,6,6-tetrachlorocyclohexanone to phenyl ethyl ketene in very good yield and enantioselectivity (86% yield and 94% *ee*; entry 4, Table 1). To the best of our knowledge, this is the first example of the use of 2,2,6,6-tetrachlorocyclohexanone as a chlorinating reagent in asymmetric catalysis.

Catalyst **4**, which is related to PPY*, furnishes lower yield and enantioselectivity (entry 5), whereas benzoylquinine[14] affords essentially none of the desired product (entry 6, Table 1). If the chlorinations are conducted at higher temperature (entry 7) or in other solvents (entries 8 and 9, Table 1), then poor yield and enantioselectivity are observed. In the absence of a catalyst, there is no reaction between phenyl ethyl ketene and 2,2,6,6-tetrachlorocyclohexanone.

We have examined the scope of this method for the catalytic asymmetric synthesis of tertiary α-chlorocarbonyl compounds, and we have determined that the best enantioselectivities are obtained when the ketene substituents are less bulky (Table 2). Thus, reactions of phenyl alkyl ketenes in which the alkyl group is Me, Et, or *i*Bu proceed with good

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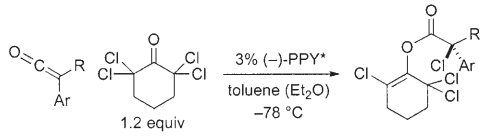
Table 2: Catalytic asymmetric synthesis of tertiary α-chlorocarbonyl compounds.[a]

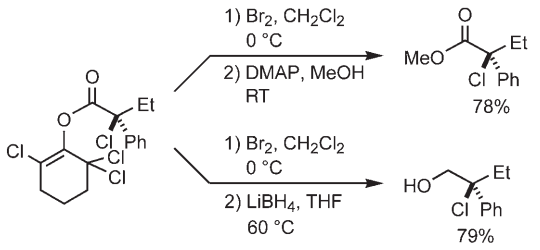


Entry	Ar	R	*ee* [%]	Yield [%]
1	Ph	Me	91	74
2	Ph	Et	94	86
3	Ph	*i*Bu	85	76
4[b]	Ph	cyclopentyl	65	79
5	*o*-tolyl	Et	67	90
6	*m*-tolyl	Et	95	88
7	3-(MeO)C_6H_4	Et	86	82
8	4-ClC_6H_4	Et	82	82
9	thiophen-3-yl	*i*Bu	83	62

[a] All data are the average of two experiments. [b] Reaction conducted at −78 °C→RT.

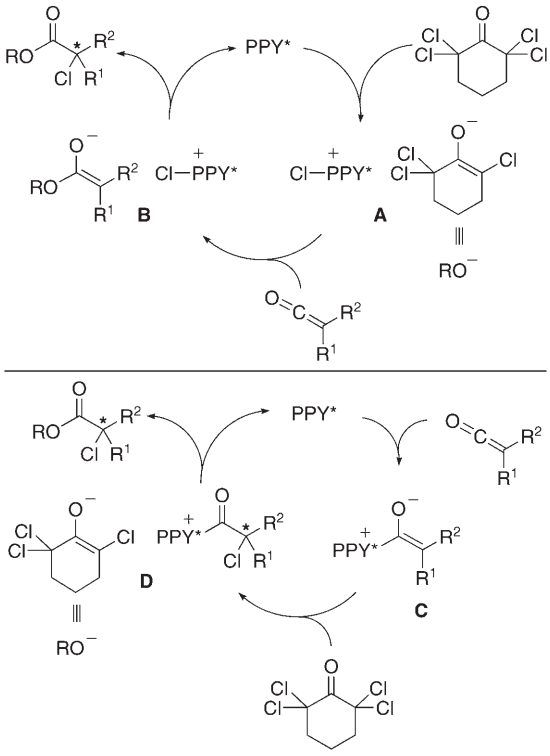
enantiomeric excess (entries 1–3), whereas modest *ee* is observed in the case of α-branched alkyl substituents (entry 4, Table 2). Similarly, if the aryl group is hindered (e.g., *ortho*-substituted), chlorination occurs with only moderate enantioselectivity (entry 5, Table 2). On the other hand, reactions of *meta*- and *para*-substituted aryl (entries 6–8) and of heteroaryl (entry 9, Table 2) ketenes generally proceed with acceptable levels of asymmetric induction.

Acyl transfer reactions of the sterically demanding enol ester can be accomplished through activation by bromine. Thus, treatment with Br_2 and then a nucleophile furnishes a methyl ester or an alcohol [Eq. (2), DMAP = dimethylaminopyridine] without a decrease in the enantiomeric excess of the tertiary alkyl chloride.



(2)

A variety of mechanisms, two of which are illustrated in Scheme 1, can be envisioned for the PPY*-catalyzed coupling of ketenes with 2,2,6,6-tetrachlorocyclohexanone to afford tertiary α-chlorocarbonyl compounds. In the upper pathway, a key intermediate is a chiral chlorinating agent (N-chlorinated PPY*; see ion pair **A**), which is formed by reaction of the catalyst with 2,2,6,6-tetrachlorocyclohexanone.[15] Then, a new ion pair (**B**) is produced by addition of RO^- to the ketene. Finally, Cl transfer occurs from the chiral N-chlorinated PPY* to the achiral enolate to furnish a new stereocenter and regenerate the catalyst.[16]



Scheme 1. Two of the possible mechanisms for asymmetric chlorinations catalyzed by PPY*. Top: By means of a chiral chlorinating agent; bottom: by means of a chiral enolate.

In an alternative mechanism (bottom of Scheme 1), PPY* adds as a nucleophile to the ketene to afford chiral enolate **C**, which reacts with the achiral chlorinating agent to furnish a new stereocenter (see ion pair **D**). Acyl transfer then produces the tertiary α-chloroester and regenerates the catalyst.[17,18]

We have made several observations that are useful in thinking about the mechanism, but which do not rule out either pathway. First, according to ^{1}H NMR spectroscopy, the resting state of the catalyst during the reaction is the catalyst itself (i.e., not N-chlorinated or N-acylated PPY*). Second, when PPY* is mixed with 2,2,6,6-tetrachlorocyclohexanone at −78 °C or at room temperature (in the absence of a ketene), no reaction is observed by ^{1}H NMR spectroscopy. Third, the *ee* value of the product correlates linearly with that of the catalyst, consistent with the presence of one catalyst molecule in the stereochemistry-determining step of the reaction.[19,20]

In summary, we have developed a catalytic asymmetric method for the synthesis of tertiary α-chloroesters that complements recent impressive progress in the generation of secondary α-halocarbonyl compounds. In future studies, we hope to elucidate the mechanism and origin of enantioselectivity of this process.

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

[13] Hexachloroacetone (hexachloro-2-propanone) is an attractive chlorinating agent owing to its relatively low cost ($71 kg^{-1} from Aldrich). As far as we are aware, there are no reports of its use in catalytic asymmetric chlorination reactions.

[14] See reference [10]. When we apply Lectka's method to the chlorination of phenyl ethyl ketene, the desired ester is produced in 30% yield and 5% *ee*.

[15] *N*-Chloropyridines are known. For example, see: J. R. L. Smith, L. C. McKeer, J. M. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1533–1537.

[16] This mechanism resembles the Brønsted acid pathway that we have proposed for certain asymmetric additions to ketenes that are catalyzed by planar-chiral derivatives of DMAP (i.e., Cl takes the place of H). For example, see: S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176–6177.

[17] We have suggested that PPY* and related compounds serve as nucleophilic catalysts for several reactions that involve ketenes.[12]

[18] Lectka favors a chiral-enolate pathway for his benzoylquinine-catalyzed asymmetric synthesis of secondary α-chloroesters from ketenes.[10]

[19] 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**, chap. 4.1.

[20] Although we have not ruled out reaction by mean of a chiral chlorinating agent (top of Scheme 1), on the basis of circumstantial evidence (the stereochemical outcome, the reactivity profile, and the effect of concentration on *ee*), we favor the chiral-enolate pathway (bottom of Scheme 1).

