Catalytic, Asymmetric α-Halogenation

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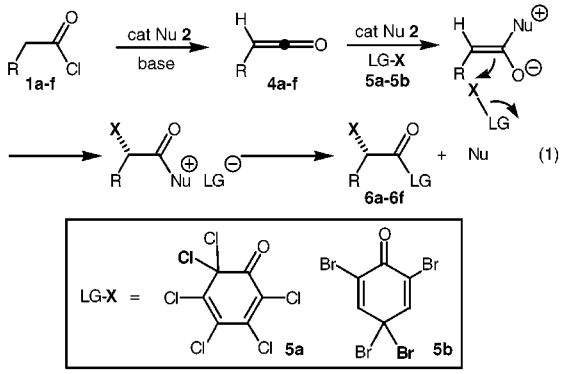
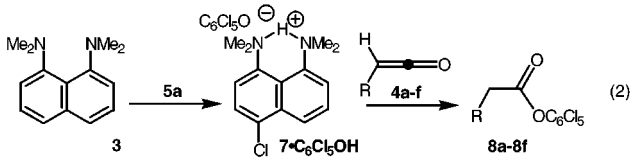
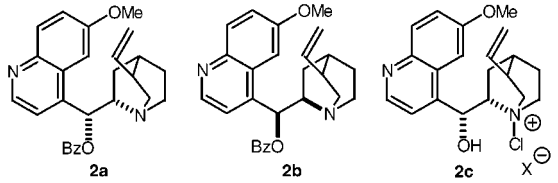
The central importance of halogenation reactions, in which organic molecules are formally oxidized, is a widely accepted fact in synthetic organic chemistry. Halocarbon products are useful chemical intermediates, serving as branch points in the synthesis of numerous functionalized molecules.[1] Within this context, α-halogenations of carbonyl compounds have played a particularly notable role.[2] For over 100 years, the most commonly used halogenation reagents for this purpose have been diatomic halides, which are known to be highly reactive and in some cases very nonselective. For this reason α-halogenation reactions are not often deliberately catalyzed, and the chemical control and selectivity derived from a finely tuned catalytic process is not brought to bear. Similarly, the full utility of chiral, optically active α-carbonyl halides[3] could be extended by suitable catalytic, asymmetric halogenation reactions.[4] The products would serve as useful precursors for optically active amines, ethers, and sulfides. We report herein a tandem asymmetric halogenation/esterification process of inexpensive acyl halides that successfully addresses the twin problems of catalysis and enantioselectivity to yield highly optically enriched α-haloesters as versatile products (eq 1).



The first problem we addressed concerned catalysis. We envisioned a strategy wherein chiral nucleophiles would attack in situ generated ketenes **4a**−**f** to form zwitterionic enolates. In our initial attempts, we generated ketenes through our previously reported "relay" deprotonation strategy,[5] in which protons are shuttled from the chiral amine catalyst to a thermodynamically strong, but kinetically weak base. An electrophilic halogenating reagent then reacts at the α-position of the enolate to afford an acylammonium salt, which undergoes transacylation with the leaving group (LG^-) to regenerate the catalytic nucleophile (eq 1). The primary goal here is to employ a less reactive halogenating reagent that possesses minimal background rate with the substrate of interest under the reaction conditions. Along these lines, mild sources of electrophilic halogen such as *N*-halosuccinimides (NCS, NBS) and alkylhypochlorites[6] were screened, employing easy-to-prepare, inexpensive benzoylquinine (BQ) **2a** as the catalyst.[7] Phenylacetyl chloride **1a** was used as a test substrate to screen the various halogenating agents using 10 mol % alkaloid catalyst in toluene at −78 °C in the presence of 1.1 equiv of **3**. Unfortunately, the *N*-halosuccinimides and alkylhypochlorites yielded only small amounts of product, and they were not investigated further.



At this point we were attracted by the electrophilic perhaloquinone-derived reagents **5a**[8] and **5b**,[9] in which "positive" halogen is transferred to release aromatic phenolate anions in a thermodynamically more favorable process. The safe, commercially available perchlorinated quinone **5a** gave good results, affording product in moderate yield and high enantioselectivity (ee). To our surprise, we found that derivatives of cinchona alkaloids such as BQ (**2a**) are significantly more catalytically active than typical tertiary amines in this halogenation reaction. For example, **1a** was treated with 1.1 equiv of **3** in toluene at −78 °C in the presence of 10 mol % **2a** and 1 equiv of halogenating reagent **5a** to form a dark red solution at −78 °C. After 2 h, quenching the reaction with saturated $NaHCO_3$ and chromatography yielded product ***(S)*-6a** in 40% yield and 95% ee.[10] We detected achiral ester **8a** (∼30%) as the product of the reaction of phenylketene with pentachlorophenol, implying that under certain conditions **3** becomes an unwanted participant in the halogenation.



We found that **3** is very easily ring-chlorinated by **5a** under reaction conditions to yield proton sponge derivative **7**,[11] in a process that not only consumes chlorinating agent but liberates pentachlorophenol that can engage in competitive ketene alcoholysis (eq 2). When **7** was used as a base in the reaction of **1a**

(1) (a) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: New York, 1992. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum: New York, 1990.

(2) (a) House, H. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972; pp 459−478. (b) De Kimpe, N.; Verhé, R. *The Chemistry of* α*-Haloketones,* α*-Haloaldehydes, and* α*-Haloimines*; John Wiley & Sons: New York, 1988.

(3) (a) Togni recently reported an elegant Lewis acid-catalyzed asymmetric fluorination of α-keto esters: Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359−4362. (b) Evans has developed an auxiliary-based route to α-chloroimides: Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123−1126.

(4) It is useful to distinguish between asymmetric processes in which halogen adds as either an electrophile or a nucleophile. The latter category includes the enantioselective opening of meso epoxides: Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.

(5) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(6) For example, *tert*-butyl hypochlorite was prepared by Walling's method: Walling, C.; Padwa, A. *J. Org. Chem.* **1963**, *27*, 2976−2977.

(7) For other timely uses of cinchona alkaloids in catalytic asymmetric synthesis see ref 5 and others contained therein. Cinchona alkaloid derivatives have recently been used as stoichiometric reagents for asymmetric halogenation: (a) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699−3701. (b) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728−10729.

(8) Guy, A.; Lemaire, M.; Guette, J.-P. *Synthesis* **1982**, *12*, 1018−1020. Compound **5a** can be purchased from Aldrich Chemicals.

(9) For a recent use of **5b,** see: Tanaka, A.; Oritani, T. *Biosci. Biotechnol. Biochem.* **1995**, *34*, 516−517.

(10) See Supporting Information for experimental details.

(11) Pietrzak, M.; Stefaniak, L.; Pozharskii, A. F.; Ozeryanskii, V. A.; Nowicka-Scheibe, J.; Grech, E.; Webb, G. A. *J. Phys. Org. Chem.* **2000**, *13*, 35−58.

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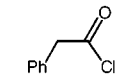
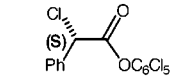
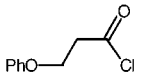
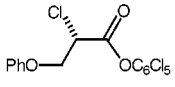
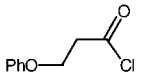
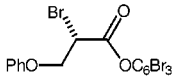
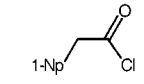
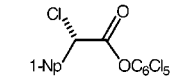
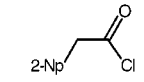
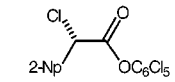
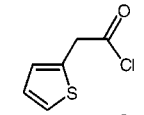
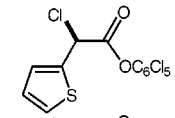
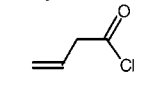
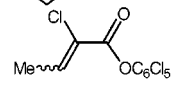
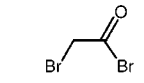
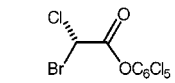
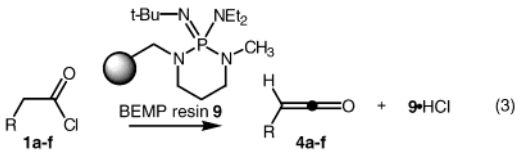
Table 1. Alkaloid Catalyzed Reactions of Acyl Halides **1** with Halogenating Agents **5a** and **5b** to Form α−Haloesters **6**

entry[a]	acid chloride		product		% ee	% yield[b]
1		**1a**		**(S)-6a**	95	40[c]
2				**(S)-6a**	99	80
3				**[(R)-6a**	99	81[d]]
4		**1b**		**(S)-6b**	97	57
5				**[(R)-6b**	96	60[d]]
6		**1b**		**(S)-6c**[e]	99	50
7		**1c**		**(S)-6d**	95	57
8		**1d**		**(S)-6e**	94	63
9		**1e**		**(S)-6f**	80	66[d]
10		**1f**		**6g**	--	65
11		**1g**		**(S)-6h**[f]	97	51

[a] Reactions run with 10 mol% catalyst (0.15 mmol ketene, 0.15 mmol **5**) in THF at -78 °C for 3 h then allowed to warm to room temperature overnight. [b] Isolated yields after column chromatography. [c] Proton sponge used as the ketene forming base. [d] Benzoylquinidine **2b** used as the catayst. [e] Brominating agent **5b** was used with standard conditions (C_6Br_3 = 2,4,6-tribromophenyl). [f] No racemization of **6h** ocurred even after several weeks of storage.

and **5a** catalyzed by **2a**, the amount of alcoholysis product was reduced by ∼50%, confirming that in situ chlorination of proton sponge can pose a problem. Given the potential byproducts of the proton sponge reaction, we sought another method of ketene generation using a solid-phase base that obviated the presence of byproduct salts (eq 3).



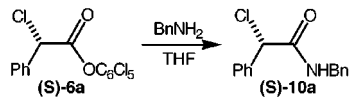
(3)

The basic resin BEMP (**9**), a triaminophosphonamide imine bound to a polymeric support,[12] produces many ketenes rapidly and virtually quantitatively when a THF solution of **1a**−**f** is passed through an addition funnel at −78 °C containing the polymer.[13] The ketene solution is added dropwise to a flask (−78 °C) containing catalyst **2a** (10 mol %) to which **5a** (1 equiv) was added. After stirring at −78 °C for 4 h, quenching was followed by chromatography, and the product **(*S*)-6a** was isolated in 99% ee and 80% yield, *free from alcoholysis product **8a*** (Table 1, entry 2). When we used "psuedoenantiomeric" benzoylquinidine **2b** as catalyst, the opposite enantiomer **(*R*)-6a** was obtained in comparable yield and ee (entry 3).

A number of other acid chlorides were screened in the reaction. For instance, the α-chloroester **(*S*)-6b** derived from 3-phenoxypropionyl chloride **1b** was obtained in 57% yield and 97% ee (entry 4). This substrate also performed well with catalyst **2b**, yielding the enantiomer **(*R*)-6b** in high ee (entry 5). We undertook a preliminary study with brominating agent **5b** (entry 6) that shows its viability as a halogenating reagent for a challenging monoketene. Under standard conditions, the reaction provides α-bromide **(*S*)-6c** in 50% yield and 99% ee. 1-Naphthylacetyl chloride **1c** (entry 7) affords product in fair yield and high ee (95%) as does 2-naphthylacetyl chloride **1d** (63% yield, 94% ee). 2-Thienylacetyl chloride leads to **(*S*)-6f** in good yield (66%) and fair ee (80%). Entry 10 shows a α-chlorination in the presence of C=C bond that migrated under the basic reaction conditions to afford the achiral product **6g**. Although **9** is exemplary at forming solutions of many monoketenes, especially aromatic ones, bromoacetyl bromide **1g** (which generates the intermediate bromoketene) affords the α,α-bromochloroester **(*S*)-6h** in high ee but low yield. Poor mass recovery for the reaction suggests that **9** reacts with bromoketene.[14] High ee (97%) and moderate yield (51%, entry 11) can be attained in this reaction by the use of 1.1 equiv of **2a**. In this instance **2a** is a substoichiometric catalyst, but also a stoichiometric dehydrohalogenating agent. This result makes it clear that, in view of the large reactivity spectrum of ketenes, each must be optimized on a case-by-case basis.

In conjunction with a solid-phase base, we investigated the reaction employing a solid-phase catalyst of resin-bound quinine.[13] Solutions of ketene **4a** and chlorinating agent **5a** were added to a jacketed addition funnel cooled to −78 °C packed with the catalyst-loaded beads. To our surprise, the reaction failed due to apparent rapid catalyst deactivation. The quinine moiety was cleaved from the polymeric support ($NaBH_4$, EtOH) and recharacterized. The spectroscopic data (NMR, MS) are consistent with the unusually stable putative *N*-chloro species **2c**.[15] Isolation and resubmission of **2c** to reactions in solution show that it is completely inactive under a spectrum of different conditions.[16] In this experiment, we inadvertently shed light on a mechanistic point—namely whether chlorine is transferred from the reagent to a zwitterionic enolate, or through an intermediary such as **2c**. The inactivity of **2c** seems to disfavor transfer of chlorine from catalyst to ketene.

As an illustration of the utility of the chlorinated products we generated from our asymmetric reaction, we found that mixing 1 equiv of benzylamine with product **(*S*)-6a** at room temperature in THF for 2 h produces a virtually quantitative yield of optically pure derivatized amide **10a** (eq 4). The racemic form of **10a** is known to exhibit powerful anticonvulsant activity.[17] Further studies on the asymmetric halogenation of organic molecules, including catalytic fluorination processes, are underway and will be reported in due course.



(4)

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Supporting Information Available: Experimental procedures, compound characterization, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA005791J

(12) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454.

(13) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963−3965.

(14) In this case, the color of the BEMP turned purple, an unusual occurrence not witnessed when any other ketene was generated.

(15) Similar *N*-chloro amines have been investigated: Lindsay Smith, J. R.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans.* **1987**, 1533−1537.

(16) The probable existence of BQ-Cl^+ was based upon standard experimental data; see Supporting Information for details.

(17) Choi, D.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **1996**, *12*, 2105−2114.